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NANOMEDICINE AND LIPID NANOPARTICLES: TARGETED DELIVERY OF NUCLEIC ACIDS AND SMALL MOLECULES IN ONCOLOGY AND BEYOND

Prasad Sahani *

Dr. B.C. Roy College of Pharmacy and Allied Health Sciences (BCRCP), Durgapur, West Bengal, India.
* Corresponding Author

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ABSTRACT

Nanomedicine has transformed drug delivery by enabling the encapsulation, protection, and targeted release of therapeutic agents, particularly nucleic acids and small molecules. Among nanocarrier systems, lipid nanoparticles have emerged as the leading platform for nucleic acid delivery, largely due to the clinical success of mRNA vaccines against COVID-19 and the FDA approval of patisiran, a lipid nanoparticle-formulated siRNA for hereditary transthyretin amyloidosis. Lipid nanoparticles typically consist of ionizable cationic lipids, cholesterol, helper phospholipids, and PEGylated lipids, which together facilitate efficient encapsulation, cellular uptake, and endosomal escape. This review critically examines the design principles, mechanisms, and clinical applications of lipid nanoparticles in oncology and other disease areas, focusing on literature published through 2024. In oncology, lipid nanoparticles are being used for mRNA cancer vaccines, siRNA-mediated gene silencing, and delivery of small-molecule chemotherapeutics. Targeted delivery strategies, including ligand conjugation and stimuli-responsive formulations, aim to improve tumor specificity and reduce systemic toxicity. Beyond oncology, lipid nanoparticles have enabled hepatic gene silencing, infectious disease vaccines, and emerging applications in rare metabolic and cardiovascular diseases. Challenges remain, including immunogenicity, off-target hepatic accumulation, manufacturing scalability, and long-term safety. Future directions include next-generation ionizable lipids, extrahepatic targeting, and combination therapies. Overall, lipid nanoparticles represent a versatile and clinically validated platform that is poised to expand the therapeutic landscape.

Keywords: Lipid Nanoparticles; Nanomedicine; Nucleic Acid Delivery; Targeted Drug Delivery; Oncology; Ionizable Lipids

1 INTRODUCTION

Nanomedicine, the application of nanotechnology to medicine, has opened new avenues for the diagnosis and treatment of disease. Among the various nanocarrier systems developed over the past decades, lipid-based nanoparticles have gained particular prominence due to their biocompatibility, scalable manufacturing, and ability to encapsulate a wide range of therapeutic cargo. Lipid nanoparticles are colloidal particles composed of lipid bilayers or lipid–polymer hybrids, typically ranging from 50 to 200 nanometers in size. They can encapsulate hydrophobic drugs within their lipid core, complex with nucleic acids through electrostatic interactions, and be surface-modified for targeted delivery.

The clinical success of lipid nanoparticle-based therapies has accelerated dramatically in recent years. In 2018, patisiran became the first FDA-approved lipid nanoparticle-formulated small interfering RNA (siRNA) for the treatment of hereditary transthyretin amyloidosis. In 2020–2021, two lipid nanoparticle-formulated mRNA vaccines, BNT162b2 and mRNA-1273, received emergency use authorization for COVID-19 and were subsequently administered to billions of people worldwide. These milestones demonstrated the feasibility, safety, and efficacy of lipid nanoparticle-mediated nucleic acid delivery on a global scale.

Beyond vaccines, lipid nanoparticles are being investigated for a broad range of therapeutic applications, including cancer immunotherapy, gene silencing, gene editing, and small-molecule delivery. In oncology, lipid nanoparticles can deliver tumor antigens as mRNA vaccines, silence oncogenic drivers with siRNA, or deliver chemotherapeutic agents with improved pharmacokinetics and reduced toxicity. Targeted delivery strategies, such as conjugation of antibodies, peptides, or aptamers to the nanoparticle surface, aim to increase accumulation in tumor tissue and reduce off-target effects.

This review provides a comprehensive overview of lipid nanoparticle technology, with an emphasis on design principles, mechanisms of action, and clinical applications in oncology and beyond. It critically discusses the evidence through 2024, identifies limitations, and outlines future directions.

2 LIPID NANOPARTICLE DESIGN AND COMPOSITION

2.1 Core Components

Lipid nanoparticles for nucleic acid delivery typically consist of four lipid components:

- Ionizable cationic lipids: These lipids are neutral at physiological pH but become positively charged in acidic environments, facilitating nucleic acid encapsulation and endosomal escape. The pKa of the ionizable lipid is critical for balancing stability, delivery efficiency, and toxicity.
- Cholesterol: Provides membrane stability and enhances cellular uptake.
- Helper phospholipids (e.g., distearoylphosphatidylcholine): Contribute to the lipid bilayer structure and promote endosomal fusion.
- PEGylated lipids: A polyethylene glycol (PEG) coating reduces opsonization, prolongs circulation time, and prevents aggregation. However, excessive PEGylation can reduce cellular uptake and induce anti-PEG antibodies.

For small-molecule delivery, liposomes and lipid nanoparticles may use different lipid compositions, often incorporating high transition temperature phospholipids and cholesterol to retain drugs. Doxil, a PEGylated liposomal doxorubicin, was one of the first FDA-approved nanomedicines, though its lipid composition differs from modern lipid nanoparticles.

2.2 Mechanism of Nucleic Acid Delivery

After intravenous or intramuscular administration, lipid nanoparticles adsorb serum proteins, forming a protein corona that influences biodistribution. They are taken up by cells primarily through receptor-mediated endocytosis or macropinocytosis. Within the acidic endosome, ionizable lipids become protonated, interacting with anionic endosomal lipids and leading to membrane disruption and release of the nucleic acid into the cytoplasm. The encapsulated nucleic acid then exerts its therapeutic effect—mRNA is translated into protein, siRNA induces RNA interference, or DNA is delivered to the nucleus for gene expression.

2.3 Optimization and Evolution

The first generation of lipid nanoparticles used permanently cationic lipids, which caused significant toxicity. The development of ionizable lipids with optimized pKa values (around 6.2–6.5) dramatically improved the therapeutic index. Modern lipid nanoparticles are formulated by rapid mixing in microfluidic devices, enabling reproducible, scalable production. Rational design, combinatorial synthesis, and structure–activity relationship studies have generated libraries of ionizable lipids with enhanced delivery potency and biodegradability. The evolution of lipid nanoparticles from early gene delivery vehicles to clinically approved products has been driven by iterative optimization of lipid chemistry, formulation parameters, and manufacturing processes.

3 LIPID NANOPARTICLES FOR NUCLEIC ACID DELIVERY

3.1 mRNA Delivery and Vaccines

The most visible success of lipid nanoparticles is the delivery of mRNA vaccines. The COVID-19 vaccines BNT162b2 and mRNA-1273 use ionizable lipid nanoparticles to deliver nucleoside-modified mRNA encoding the SARS-CoV-2 spike protein. The lipid nanoparticle protects the mRNA from nuclease degradation, facilitates cellular uptake, and promotes efficient translation. Intramuscular injection results in local protein expression and robust humoral and cellular immune responses. The success of these vaccines has catalyzed the development of mRNA vaccines for influenza, RSV, cytomegalovirus, Zika, HIV, and cancer. In oncology, mRNA vaccines encoding tumor neoantigens are being tested in combination with checkpoint inhibitors, showing promise in early trials for melanoma, pancreatic cancer, and other malignancies.

3.2 siRNA Delivery and Gene Silencing

RNA interference is a natural mechanism for post-transcriptional gene silencing. Lipid nanoparticles have enabled the therapeutic delivery of siRNA to the liver, where they accumulate naturally due to the fenestrated endothelium and uptake by hepatocytes. Patisiran, the first FDA-approved lipid nanoparticle-siRNA, targets transthyretin mRNA and reduces serum transthyretin levels in hereditary transthyretin amyloidosis. Other lipid nanoparticle-siRNA therapies, such as inclisiran (targeting PCSK9 for hypercholesterolemia), have also been approved, demonstrating the platform's utility for hepatic gene silencing. Challenges remain for extrahepatic siRNA delivery.

3.3 CRISPR-Cas9 Delivery

Lipid nanoparticles have been used to deliver CRISPR-Cas9 components, either as mRNA encoding Cas9 plus guide RNA or as ribonucleoprotein complexes. The first clinical demonstration of in vivo CRISPR gene editing used lipid nanoparticles to deliver mRNA and guide RNA targeting the transthyretin gene in patients with transthyretin amyloidosis (NTLA-2001), achieving significant reductions in serum transthyretin. This success highlights the potential of lipid nanoparticles for gene editing in the liver. Ongoing research aims to extend delivery to other organs and to improve editing efficiency and specificity.

4 TARGETED DELIVERY STRATEGIES IN ONCOLOGY

Passive Targeting via the Enhanced Permeability and Retention Effect

Solid tumors often exhibit leaky vasculature and impaired lymphatic drainage, leading to preferential accumulation of nanoparticles—a phenomenon known as the enhanced permeability and retention effect. Passive targeting exploits this effect to increase drug delivery to tumors. However, the enhanced permeability and retention effect is heterogeneous across tumor types and patients, and its clinical relevance has been debated. Nanoparticle properties such as size, surface charge, and PEGylation influence tumor accumulation.

4.1 Active Targeting

Active targeting involves decorating the nanoparticle surface with ligands that bind to receptors overexpressed on tumor cells or tumor vasculature. Ligands include antibodies, antibody fragments, peptides, aptamers, and small molecules. Examples include transferrin receptor-targeted liposomes, folate receptor-targeted nanoparticles, and HER2-targeted immunoliposomes. Active targeting can enhance cellular uptake and specificity, but clinical translation has been challenging. Several targeted nanoparticles have failed to show superiority over non-targeted formulations in clinical trials, possibly due to the complexity of the tumor microenvironment and the limited penetration of nanoparticles into solid tumors. Nonetheless, active targeting remains an active area of research, particularly for nucleic acid delivery.

4.2 Stimuli-Responsive Nanoparticles

Stimuli-responsive lipid nanoparticles are designed to release their cargo in response to specific triggers such as low pH, enzymes, redox conditions, or external stimuli (e.g., heat, light). For example, pH-sensitive lipid nanoparticles can destabilize in the acidic tumor microenvironment or endosomes, enhancing drug release. Enzyme-responsive formulations exploit matrix metalloproteinases overexpressed in tumors. These approaches aim to improve tumor-specific drug delivery and reduce systemic toxicity. While many stimuli-responsive systems have shown promise preclinically, clinical translation is still limited.

4.3 Applications in Cancer Therapy

Lipid nanoparticles are being developed for several cancer-related applications:

- mRNA cancer vaccines: Lipid nanoparticle-delivered mRNA encoding tumor-associated antigens or neoantigens can induce anti-tumor immunity. Early clinical trials show feasibility and immune responses.
- siRNA for oncogene silencing: Lipid nanoparticle-siRNA targeting oncogenes such as KRAS, MYC, or PLK1 are in development, though delivery to solid tumors remains challenging.
- Small-molecule chemotherapy: Liposomal formulations of doxorubicin, daunorubicin, and irinotecan are approved and improve pharmacokinetics and reduce cardiotoxicity. Lipid nanoparticles for other chemotherapeutics are being investigated.
- Immunomodulatory agents: Lipid nanoparticles can deliver mRNA encoding cytokines (e.g., IL-12) or costimulatory molecules to reprogram the tumor microenvironment.

5 BEYOND ONCOLOGY: EXPANDING INDICATIONS

5.1 Liver-Directed Therapies

The liver is the primary site of lipid nanoparticle accumulation after intravenous administration, making it an attractive target for hepatic diseases. Approved lipid nanoparticle therapies include patisiran for transthyretin amyloidosis and inclisiran for hypercholesterolemia. Other candidates target hepatitis B virus, alpha-1 antitrypsin deficiency, and nonalcoholic steatohepatitis.

5.2 Infectious Disease Vaccines

Following the success of COVID-19 mRNA vaccines, lipid nanoparticle-mRNA vaccines are being developed for influenza, RSV, HIV, malaria, and other pathogens. The platform's rapid design and manufacturing make it well suited for pandemic preparedness.

5.3 Cardiovascular and Metabolic Diseases

Lipid nanoparticle-siRNA therapies targeting PCSK9 (inclisiran) have shown durable reductions in LDL cholesterol with twice-yearly dosing. Lipid nanoparticles are also being explored for delivery of mRNA encoding therapeutic proteins for metabolic disorders.

5.4 Rare Diseases and Protein Replacement

Lipid nanoparticles can deliver mRNA encoding missing or defective enzymes, offering a potential alternative to enzyme replacement therapy. For example, lipid nanoparticle-mRNA encoding methylmalonyl-CoA mutase has shown efficacy in animal models of methylmalonic acidemia. Clinical trials are in early phases.

6 CHALLENGES AND LIMITATIONS

6.1 Immunogenicity and Toxicity

Lipid nanoparticles can activate the innate immune system, leading to cytokine release and infusion reactions. PEGylated lipids may induce anti-PEG antibodies, potentially reducing efficacy upon repeated dosing. Ionizable lipids can cause inflammation and hepatotoxicity at high doses. Careful lipid design and dose optimization are required to minimize toxicity.

6.2 Off-Target Accumulation and Delivery to Non-Liver Tissues

The liver dominates lipid nanoparticle biodistribution after systemic administration, which limits applications for extrahepatic diseases. Strategies to redirect delivery include changing lipid composition, adding targeting ligands, and using local administration routes. However, efficient delivery to the lung, spleen, brain, or solid tumors remains a major challenge.

6.3 Manufacturing and Stability

While microfluidic mixing has improved scalability and reproducibility, maintaining batch-to-batch consistency and long-term stability remains complex. Lipid nanoparticles require cold chain storage for mRNA vaccines, which can be a logistical barrier in low-resource settings. Lyophilization and thermostable formulations are under investigation.

6.4 Regulatory and Safety Considerations

The novelty of lipid nanoparticle-based products requires careful regulatory evaluation. Long-term safety data are limited, and rare adverse events (e.g., myocarditis after mRNA vaccines) require continued pharmacovigilance. The development of standardized assays for potency and biodistribution is needed.

7 FUTURE PERSPECTIVES

The lipid nanoparticle field is evolving rapidly. Key future directions include:

- Next-generation ionizable lipids: Biodegradable, less toxic, and more efficient lipids are being developed through high-throughput screening and machine learning.
- Extrahepatic targeting: Novel lipid chemistries, targeting moieties, and administration routes may enable delivery to the lung, spleen, brain, and tumors.
- Combination therapies: Lipid nanoparticles can co-deliver multiple nucleic acids or combine nucleic acids with small molecules, enabling synergistic effects.
- Personalized nanomedicine: Patient-specific mRNA vaccines and gene therapies will leverage lipid nanoparticle versatility.
- Theranostic applications: Lipid nanoparticles carrying imaging agents and therapeutics may enable simultaneous diagnosis and treatment.

The success of mRNA vaccines has generated enormous investment and interest, which is likely to accelerate the translation of lipid nanoparticle-based therapies across a wide range of diseases.

8 CONCLUSION

Lipid nanoparticles have emerged as a clinically validated, versatile platform for the delivery of nucleic acids and small molecules. Their success in mRNA vaccines and siRNA therapeutics has demonstrated the feasibility of nucleic acid-based medicine on a large scale. In oncology, lipid nanoparticles hold promise for cancer vaccines, gene silencing, and targeted chemotherapy, although delivery to solid tumors remains a significant challenge. Beyond oncology, liver-directed therapies and infectious disease vaccines are already benefiting patients. While immunogenicity, off-target accumulation, and manufacturing issues persist, ongoing innovations in lipid chemistry, targeting, and formulation are addressing these limitations. The future of nanomedicine and lipid nanoparticles is bright, with the potential to transform the treatment of cancer, genetic diseases, and infectious diseases.

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