REVIEW article

Next-generation nucleic acid therapeutics: Breakthroughs in delivery and translational frontiers

Jay Nand [1], **Revathi S.** [2], and **Vanitha S** [2 *]

[1] Department of Pharmacy Practice, The Erode College of Pharmacy, Erode- 638112, Tamil Nadu, India
[2] Department of Pharmaceutics, The Erode College of Pharmacy, Erode - 638112, Tamil Nadu, India
[*] Author to whom correspondence should be addressed

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Abstract: Nucleic acid-based therapeutics have rapidly advanced from conceptual tools to frontline clinical modalities, reshaping the landscape of precision medicine. Key platforms, including antisense oligonucleotides, small interfering RNAs, messenger RNAs, aptamers, and CRISPR-based genome editors, demonstrate the versatility of nucleic acids in silencing, correcting, or reprogramming gene expression. Central to their success are delivery innovations, particularly lipid nanoparticles (LNPs) and bioconjugates, which provide stability, enable targeted uptake, and broaden tissue accessibility. Breakthroughs such as selective organ-targeting LNPs, chemical conjugation strategies like GalNAc, and machine learning-guided optimization are redefining delivery from empirical design to predictive engineering. Alongside these advances, chemical modifications enhance durability and mitigate immunogenicity, while computational and mechanistic modeling accelerate the translation of these findings into clinically viable formulations. Clinically, nucleic acid medicines now span rare genetic disorders, oncology, infectious disease vaccines, and emerging gene-editing trials, with mRNA-based COVID-19 vaccines serving as a landmark proof of concept. Looking ahead, the convergence of precision targeting, AI-driven design, and next-generation editing platforms positions nucleic acid therapeutics to evolve into one-time, potentially curative interventions across a wide spectrum of diseases.

Introduction

Therapeutics based on nucleic acids are among the most revolutionary developments in contemporary medicine, offering the ability to directly modulate genetic information to treat diseases at their root cause [1]. These therapies encompass synthetic or biologically engineered nucleic acids-DNA, RNA, or derivatives-that can alter, silence, replace, or regulate gene expression [1, 2]. Historically, the field evolved from early explorations of antisense oligonucleotides in the late 20th century to the breakthrough approval of mRNA-based vaccines during the COVID-19 pandemic, cementing nucleic acid therapeutics as a cornerstone of precision medicine [1]. Their ability to address previously “undruggable” targets underscores their unique promise for rare genetic disorders and personalized treatment paradigms, **Figure 1**, [1, 3].

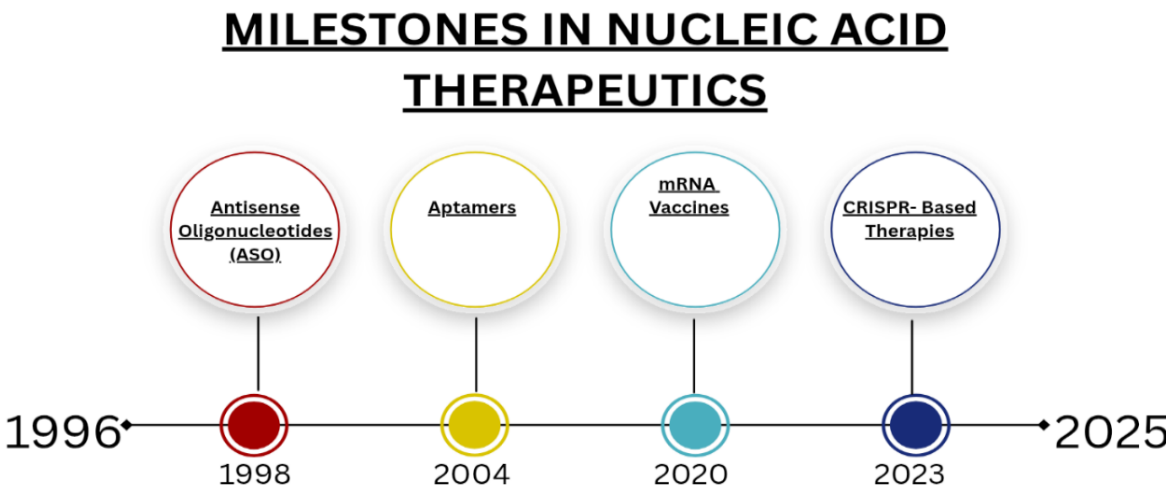

Figure 1: Timeline of major milestones in nucleic acid therapeutics (1998-2024) (Open access), showing early ASO and aptamer approvals through recent siRNA, mRNA vaccine, and CRISPR-based therapies

Materials and methods

A comprehensive literature search was conducted using databases including PubMed, Scopus, and Google Scholar. Keywords such as nucleic acid therapeutics, oligonucleotide delivery, lipid nanoparticle, gene editing, and bioconjugation were used to identify relevant publications. The search covered articles published up to mid-2025 in English. Reference lists of key reviews and primary research articles were also examined to ensure coverage of recent advances in delivery systems and translational development of nucleic acid medicines. Selection criteria focused on innovations in delivery technologies, chemical modifications, and clinical translation of nucleic acid therapies.

Results

Current classes and modalities: The therapeutic toolbox of nucleic acids is diverse: Antisense oligonucleotides (ASOs): Short, synthetic strands of DNA or RNA that bind to target mRNA, modulating splicing or inducing degradation [3]. Small interfering RNAs (siRNAs): Double-stranded RNAs harnessing RNA interference pathways to silence specific genes [1]. Messenger RNA (mRNA): Exogenous mRNAs that enable the transient expression of therapeutic proteins or vaccines [1]. Aptamers: Structured oligonucleotides with high binding affinity for proteins, functioning like nucleic acid-based antibodies [1]. CRISPR-based genome editing: RNA-guided nucleases enabling precise, programmable DNA modifications [1]. Each modality operates through distinct molecular mechanisms but converges on a unifying therapeutic principle: the reprogramming of genetic expression to restore homeostasis or correct pathogenic states [1-4].

Chemical and bioconjugate strategies: Despite their potency, naked oligonucleotides face challenges such as nuclease degradation, poor cellular uptake, and rapid clearance [1]. To address this, bioconjugation strategies have emerged, involving the chemical attachment of ligands, peptides, or polymers to nucleic acids [5]. These modifications enhance pharmacokinetics, facilitate receptor-mediated uptake, and improve tissue specificity [5]. Recent advances in conjugation chemistry, including GalNAc (N-acetylgalactosamine) targeting for hepatocyte delivery, exemplify clinically validated breakthroughs [5]. Broader applications extend to peptide and antibody-oligonucleotide conjugates, which expand delivery beyond the liver and open pathways for multi-organ targeting [5].

Lipid nanoparticle systems for delivery: The most clinically useful substances are lipid nanoparticles (LNPs) advanced and widely adopted carriers for nucleic acid delivery [6]. Their modular design-comprising ionizable lipids, helper lipids, cholesterol, and PEG-lipids-enables encapsulation, protection, and efficient endosomal escape of nucleic acids [5, 6]. Initially optimized for hepatic delivery, LNPs are now being engineered for extrahepatic targeting, a critical step toward expanding therapeutic applications [7]. However, stability during storage and circulation, as well as batch-to-batch variability in formulation, remain ongoing challenges (**Figures 2** and **3**) [6-8].

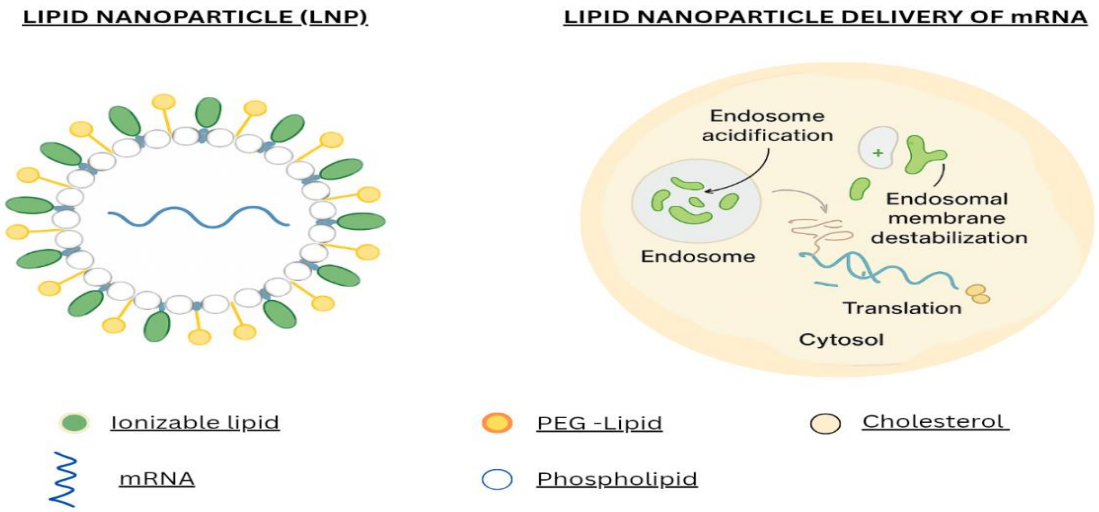

Figure 2: Example of lipid nanoparticle (LNP) delivery

(Left) The LNP's structure: ionizable lipid (green), phospholipid (tan), cholesterol (gray), and PEG-lipid (yellow) form a nanoscale vesicle encapsulating mRNA. (Right) After endocytosis by a target cell, acidification triggers ionizable lipid protonation, destabilizing the endosome and releasing mRNA into the cytosol
(Created by the authors)

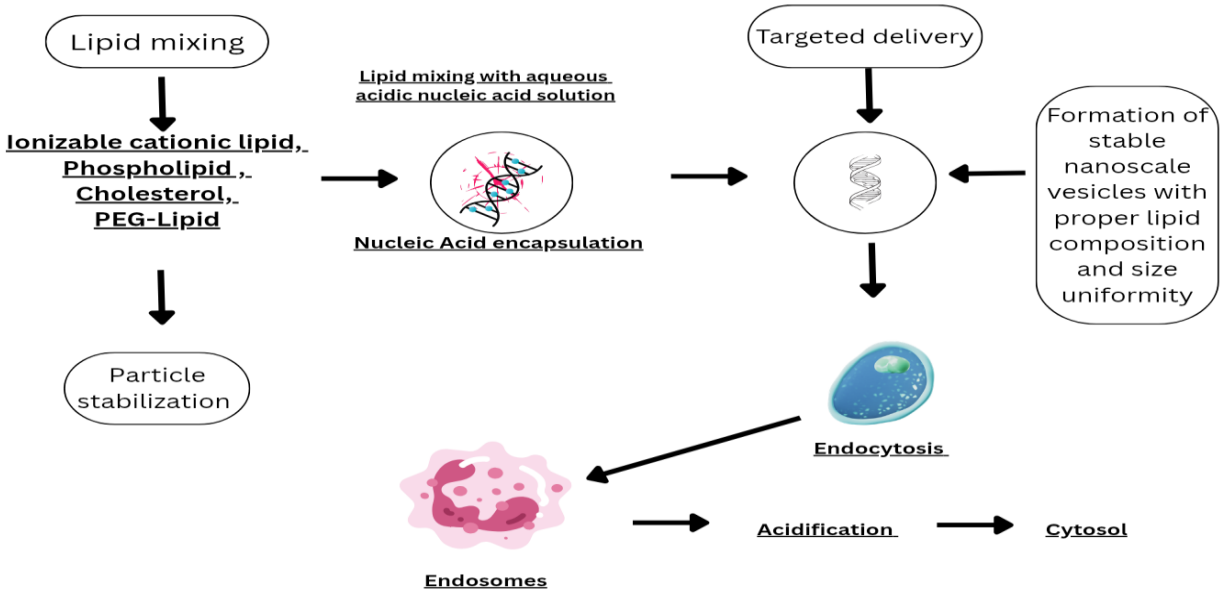

Figure 3: Flowchart illustrating LNP formulation: lipid mixing, nucleic acid encapsulation, particle stabilization, and targeted delivery pathways (Created by the authors)

Delivery engineering and targeting: Recent innovations are redefining the boundaries of LNP delivery [1]. Selective organ-targeting (SORT) LNPs enable preferential biodistribution to lungs, spleen, or other tissues by altering lipid composition [9]. Complementary strategies employ chemical targeting ligands and structural optimization to improve delivery efficiency [10]. In parallel, machine learning-guided design accelerates discovery by predicting LNP formulations that achieve desired biodistribution patterns [4, 12]. Mechanistic modelling further supports rational design, helping to understand how lipid composition and structural dynamics influence performance [13]. Together, these approaches signal a paradigm shift from empirical formulation toward computationally informed, precision-engineered delivery vehicles (**Figure 4**) [4, 11-13].

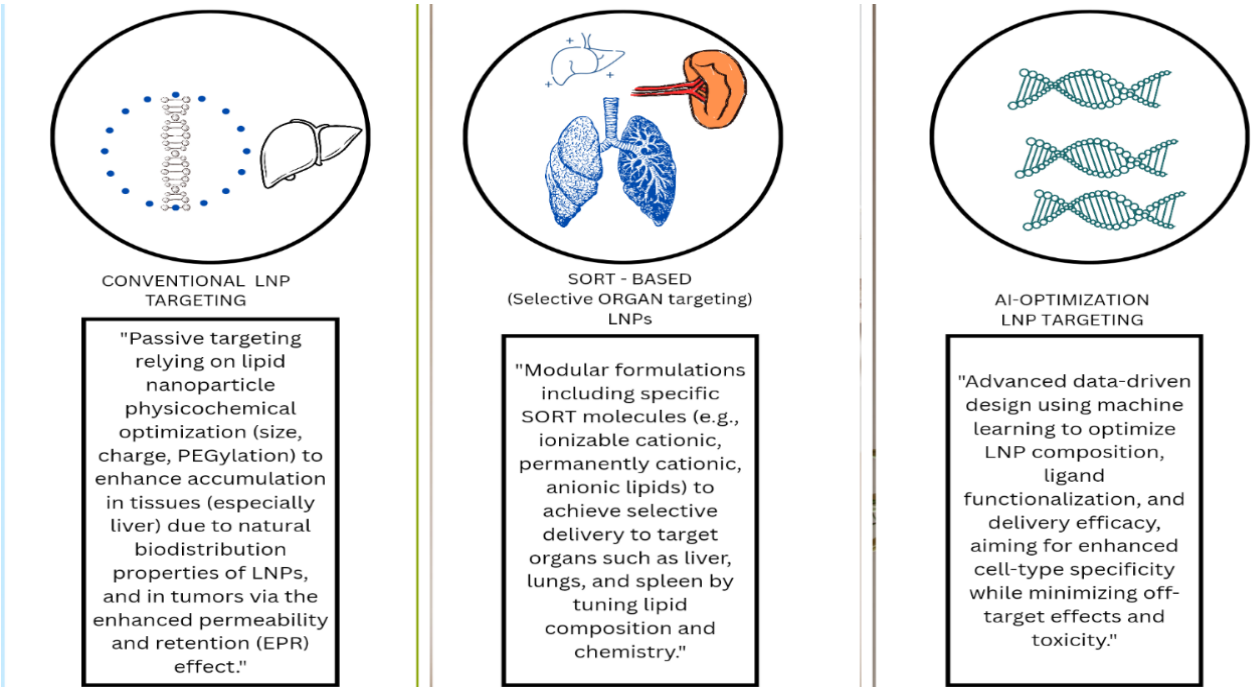

Figure 4: Infographic showing conventional vs SORT-based vs AI-optimized LNP targeting strategies (Created by the authors)

Therapeutic applications and case studies: Clinical translation has rapidly followed technological innovation [3]. mRNA vaccines, notably against COVID-19, demonstrated the scalability and immunogenic potential of nucleic acid therapies, opening doors to vaccines against cancer and infectious diseases [13]. Similarly, siRNA-based drugs have achieved regulatory approval for diseases such as transthyretin amyloidosis and acute hepatic porphyria [3]. In rare genetic disorders, gene-editing therapies leveraging CRISPR-Cas9 are entering clinical trials, offering curative potential where conventional drugs fail [1, 3, 7]. Aptamers, though fewer in number, continue to progress in ophthalmology and oncology [3]. Collectively, these successes underscore the clinical versatility of nucleic acids across diverse therapeutic landscapes [1, 4, 9].

Recent advances in nucleic acid therapeutics highlight lipid-based delivery systems as transformative tools. Thakur and others. [3] stressed patient-specific oligonucleotide therapy, while Benizri and associates [4] discussed bioconjugation strategies. Saber and others [7] expanded LNP use beyond the liver, and Lüdtke et al. [7] standardized protocols for reproducibility. Farsani and others [4] showed cased LNPs in CRISPR-Cas9 editing, while Ding and others [12] and Kumar and Ardekani [13] applied machine learning for nanoparticle optimization. Together, these studies show a multidisciplinary shift toward next-generation nucleic acid delivery (**Table 1**).

Table 1: FDA-approved nucleic acid therapies (Open access)

Year	Drug (generic)-brand	Indication	Modality
1998	Fomivirsen - Vitravene	CMV retinitis (AIDS)	ASO (RNase H)
2004	Pegaptanib -Macugen	AMD (Wet age-related macular degeneration	RNA aptamer
2016	Eteplirsen - Exondys 51	Duchenne muscular dystrophy	ASO (exon skipping)
2017	Nusinersen -Spinraza	Spinal muscular atrophy	ASO (Splice modulation)
2018	Onasemnogene abeparvovec - Zolgensma	Spinal muscular atrophy	AAV gene therapy
2018	Patisiran - Onpattro	hATTR amyloidosis	siRNA (LNP)
2018	Inotersen - Tegsedi	hATTR amyloidosis	ASO (RNase H)
2019	Golodirsen - Vyondys 53	Duchenne muscular dystrophy	ASO (Exon skipping)
2019	Givosiran - Givlaari	Acute hepatic porphyria (AIP)	siRNA (GalNAc)
2020	Lumasiran - Oxlumo	Primary hyperoxaluria type 1	SiRNA (GalNAc)
2020	BNT162b2 - Comirnaty	COVID-19	mRNA vaccine
2020	mRNA - Spikevax	COVID-19	mRNA vaccine
2021	Casimersen - Amondys 45	Duchenne muscular dystrophy	ASO (Exon skipping)

Safety and stability considerations: Immune activation, cytokine release, and complement system responses are potential risks for nucleic acid drugs, particularly with LNP formulations [8, 14]. Strategies such as chemical modifications (e.g., 2'-O-methyl nucleotides), optimized lipid chemistries, and tailored dosing regimens mitigate these risks [5]. Stability studies have revealed the sensitivity of mRNA-LNPs to environmental conditions, necessitating rigorous cold-chain storage and controlled formulation practices [14]. Improving stability through novel excipients and lyophilization approaches continues to be a critical research priority [14].

Technical considerations and protocols: Strong formulation and manufacturing protocols are necessary for translation from bench to bedside. Standardized methods for nucleic acid purification, LNP characterization (size, charge, polydispersity), and release criteria underpin clinical-grade production [8]. Regulatory guidance emphasizes reproducibility, scalability, and adherence to Good Manufacturing Practice (GMP) standards. Specific considerations apply to oligonucleotide solution APIs, including sterility, excipient compatibility, and long-term stability testing [8, 15].

Data modeling and artificial intelligence: Computational tools are becoming indispensable in guiding experimental design [1]. Mechanistic modeling provides insights into LNP structure-function relationships, supporting rational optimization [13]. Simultaneously, artificial intelligence (AI) and machine learning approaches mine large experimental datasets to predict delivery efficiency and tissue distribution [4, 12, 16]. These methods reduce reliance on costly trial-and-error experimentation, accelerate the identification of lead formulations, and expand the ability to explore complex, multidimensional formulation spaces (**Figure 5**) [12,13].

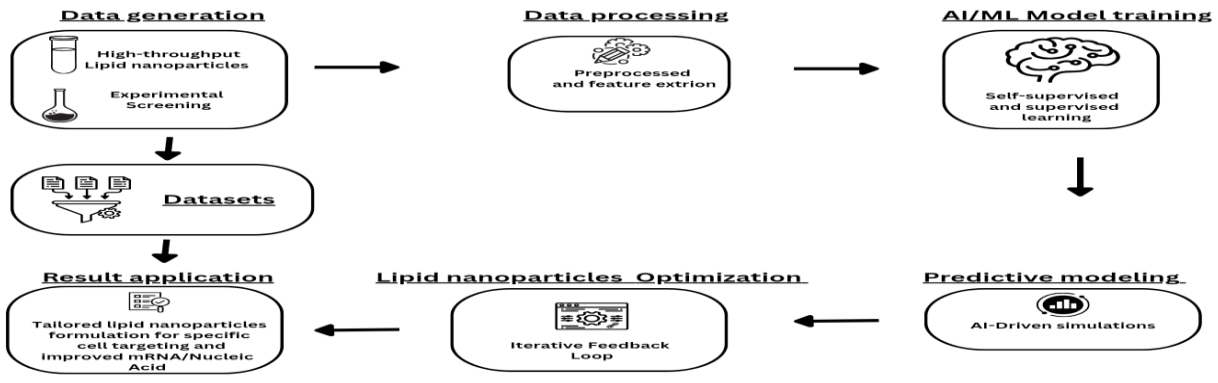

Figure 5: Schematic illustrating integration of AI/ML pipelines with LNP formulation optimization and predictive modeling (Created by the author)

Discussion

The next frontier of nucleic acid therapeutics lies in tissue-specific delivery beyond the liver, with cardiac, pulmonary, and central nervous system targeting as active areas of investigation [6, 7, 11]. Coupled with gene-editing platforms such as base editing and prime editing, delivery innovations could enable one-time curative therapies [4]. Moreover, the integration of API development pipelines and industrial-scale protocols will accelerate commercialization [15]. As computational modeling and AI-driven design mature, the field is poised to transition into a highly predictive and precision-focused discipline [1]. Ultimately, nucleic acid therapeutics hold the potential to reshape clinical practice, extending from rare diseases to widespread conditions such as cancer, metabolic disorders, and autoimmune diseases [1-18].

Conclusion: Nucleic acid-based therapeutics have transitioned from experimental concepts to clinically validated platforms, demonstrating the capacity to directly reprogram gene expression and address conditions previously considered untreatable. Progress in chemical modifications, lipid nanoparticles, and bioconjugation has not only enhanced stability and delivery efficiency but also enabled the expansion of therapeutic reach beyond hepatic targets. The incorporation of machine learning and mechanistic modeling is reshaping delivery design from trial-and-error toward predictive engineering, accelerating clinical translation. Collectively, these innovations are driving a shift toward more precise, durable, and potentially curative interventions across a spectrum of diseases ranging from rare genetic disorders to cancer and infectious diseases. As the field continues to integrate advanced delivery systems with next-generation editing tools, nucleic acid therapeutics are poised to redefine the future of personalized medicine and transform global healthcare.

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Author contribution: VS conceived and designed the study. JN collected data, performed data analysis, and drafted the manuscript. RS contributed to data analysis. All authors final version of the manuscript, and agreed to be accountable for its contents.
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Author declarations: The authors confirm that they have followed all relevant ethical guidelines and obtained any necessary IRB and/or ethics committee approvals.