Journal Publication of International Research for Engineering and Management (JOIREM)
Volume: 05 Issue: 06 | June-2025

Nanocarriers for Gene Therapy: Progress and Challenges

Manoj Shetty

Manoj Shetty

Abstract- Gene therapy has emerged as a revolutionary approach in modern medicine, aiming to treat, prevent, or even cure a wide range of genetic, acquired, and infectious diseases by introducing therapeutic nucleic acids into patient cells. Despite its potential, one of the foremost challenges remains the effective and safe delivery of these genetic materials, which are inherently unstable and susceptible to degradation in biological environments. Nanocarriers—engineered nanoscale delivery vehicles—have been increasingly recognized as promising platforms for gene delivery because of their ability to encapsulate, protect, and transport nucleic acids efficiently to targeted cells or tissues while minimizing off-target effects and toxicity. This paper provides an in-depth review of the various types of nanocarriers currently utilized in gene therapy, including lipid-based nanoparticles, polymeric carriers, inorganic nanoparticles, and hybrid systems. It also explores key technological advances in nanocarrier design that enhance delivery efficiency, cellular uptake, and endosomal escape. Additionally, clinical applications and ongoing trials illustrate the translational progress of nanocarrier-mediated gene therapies. Challenges such as immunogenicity, off-target effects, large-scale production, and regulatory hurdles are critically analysed. Finally, future perspectives focusing on personalized nanocarriers, multifunctional platforms, and AI-driven optimization are discussed, emphasizing their potential to transform gene therapy into a mainstream therapeutic modality.

***Keywords*:** Nanocarriers, Gene Therapy, Targeted Delivery, Therapeutic Nucleic Acids

Introduction

Gene therapy represents a paradigm shift in treating diseases by directly targeting the genetic root causes rather than merely managing symptoms. The principle involves delivering functional nucleic acids—such as plasmid DNA encoding therapeutic genes, small interfering RNA (siRNA) for gene silencing, messenger RNA (mRNA) for transient protein expression, or components of the CRISPR-Cas9 system for genome editing—into target cells. However, the clinical implementation of gene therapy has been impeded by several biological and technological barriers. Naked nucleic acids are vulnerable to enzymatic degradation, exhibit poor cellular uptake, and often induce unintended immune responses, reducing therapeutic efficacy and safety. Viral vectors, including adenoviruses, lentiviruses, and adeno-associated viruses (AAV), have historically been the dominant gene delivery vehicles owing to their high transfection efficiency. Nonetheless, viral vectors suffer from safety concerns such as insertional mutagenesis, immunogenicity, limited packaging capacity, and complex production processes, motivating the exploration of non-viral alternatives. Nanocarriers, defined as nanoscale particles engineered to carry therapeutic agents, have gained significant attention as promising gene delivery systems. By virtue of their size, surface chemistry, and material composition, nanocarriers can encapsulate nucleic acids, protect them from degradation, facilitate cellular uptake via endocytosis, and release them intracellularly in a controlled manner. Furthermore, their surfaces can be functionalized with targeting ligands that enable selective delivery to specific cell types or tissues, thereby enhancing therapeutic specificity while reducing off-target toxicity [1-4]. This review aims to provide a comprehensive overview of the state-of-the-art nanocarrier systems used in gene therapy. It discusses the design principles, material platforms, targeting strategies, and mechanisms underlying successful gene delivery. Furthermore, it highlights key clinical successes and challenges faced in the translation of nanocarrier-mediated gene therapy. The review concludes by outlining future directions that may overcome current limitations and enable widespread clinical adoption.

Types of Nanocarriers in Gene Therapy

Among the variety of nanocarriers developed for gene delivery, lipid-based nanoparticles (LNPs) have emerged as the frontrunners. These particles typically consist of ionizable cationic lipids, phospholipids, cholesterol, and polyethylene glycol (PEG)-lipids that self-assemble into stable nanoscale structures capable of encapsulating nucleic acids through electrostatic interactions. The ionizable nature of the lipids allows them to acquire a positive charge in acidic environments (such as endosomes), facilitating endosomal escape of the cargo. The clinical success of LNPs in mRNA vaccines against COVID-19 has validated their potential as effective and safe gene delivery vehicles. Their modular composition allows for optimization of size, surface charge, and stability, while PEGylation reduces opsonization and clearance by the immune system.

Polymeric nanocarriers offer another versatile platform, utilizing biodegradable and biocompatible polymers such as poly(lactic-co-glycolic acid) (PLGA), polyethyleneimine (PEI), chitosan, and dendrimers. These polymers can form nanoparticles or polyplexes with nucleic acids, enabling sustained release and protection from enzymatic degradation. Certain polymers exhibit "proton sponge" effects that disrupt endosomal membranes, facilitating intracellular release. Moreover, polymers can be engineered to be stimuli-responsive, releasing their payload upon exposure to changes in pH, redox conditions, or enzymatic activity, allowing spatial and temporal control over gene delivery [4-6].

Inorganic nanoparticles, including gold nanoparticles, mesoporous silica nanoparticles, and magnetic nanoparticles, provide unique features such as facile surface functionalization, intrinsic imaging capabilities, and responsiveness to external stimuli (e.g., magnetic fields, light). Gold nanoparticles, functionalized with thiolate oligonucleotides, have been extensively studied for nucleic acid delivery and photothermal therapy. Magnetic nanoparticles enable magnetically guided delivery, potentially enhancing accumulation in target tissues [7-11].

Hybrid nanocarriers combine organic and inorganic components to integrate the advantages of both, yielding multifunctional platforms capable of simultaneous gene delivery, imaging, and therapeutic modulation.

Advances in Targeting and Delivery Efficiency

Achieving specific targeting and efficient intracellular delivery are critical for the success of nanocarrier-based gene therapies. Surface functionalization with targeting ligands such as antibodies, peptides, aptamers, or small molecules allows nanocarriers to bind to overexpressed receptors on target cells, enhancing cellular uptake and specificity. For example, folate-conjugated nanocarriers target folate receptors frequently overexpressed in certain cancers, while transferrin-modified particles exploit iron uptake pathways for brain targeting. Endosomal entrapment remains a significant barrier, as nucleic acids degraded in lysosomes fail to reach their site of action in the cytoplasm or nucleus. To overcome this, nanocarriers are engineered with materials capable of inducing endosomal escape. These include pH-sensitive lipids that become positively charged in acidic endosomes, facilitating membrane disruption, as well as Fuso genic peptides that mimic viral fusion proteins [12-16].

Multifunctional nanocarriers incorporating imaging agents (fluorescent dyes, contrast agents) permit real-time tracking of biodistribution, cellular uptake, and therapeutic response, enabling more precise treatment monitoring and optimization. Furthermore, efforts to develop stimuli-responsive nanocarriers that release their cargo in response to intracellular cues such as redox potential or enzymatic activity are advancing precision delivery and reducing systemic toxicity [12-16].

Clinical Applications and Case Studies

Nanocarrier-mediated gene therapies have transitioned from preclinical studies to several clinical applications. The approval of Onpattro® (patisiran), an LNP-formulated siRNA drug for hereditary transthyretin-mediated amyloidosis, marked the first clinically approved RNA interference therapy delivered via nanocarriers, demonstrating safety and efficacy in humans. This success has spurred interest in expanding nanocarrier platforms to a wider range of genetic and acquired diseases. The rapid development and deployment of LNP-based mRNA vaccines for COVID-19, including those by Pfizer-BioNTech and Moderna, exemplify the capability of nanocarriers to enable scalable and effective gene therapies with significant global health impact. These vaccines utilize LNPs to deliver mRNA encoding the SARS-CoV-2 spike protein, eliciting robust immune responses with a favourable safety profile. Other investigational nanocarrier gene therapies include CRISPR-Cas9 delivery systems designed for genome editing in genetic disorders such as sickle cell anemia and Duchenne muscular dystrophy. Early-phase clinical trials are evaluating polymeric and lipid-based nanocarriers for delivering gene editing components, with promising preliminary results regarding safety and on-target editing efficiency. Additionally, nanocarriers have been explored for oncological applications, delivering siRNA or mRNA to silence oncogenes or induce tumour-suppressor expression. These approaches aim to complement or replace conventional therapies, offering targeted, less toxic alternatives [17-21].

Challenges and Future Directions

Despite encouraging progress, several challenges impede the full clinical translation of nanocarrier-based gene therapy. The immune system can recognize and clear nanocarriers rapidly, reducing bioavailability and causing inflammatory responses. Designing stealth nanocarriers that evade immune detection without compromising targeting remains a formidable task. Off-target effects, including unintended gene modulation or toxicities, present safety concerns necessitating improved targeting specificity and controlled release mechanisms. The complexity of biological barriers such as the blood-brain barrier further complicates delivery to certain tissues. Manufacturing challenges include the scalable production of nanocarriers with uniform size, composition, and functionalization, while maintaining stability and reproducibility. Regulatory approval pathways are also evolving to address the unique features and risks associated with nanomedicines, requiring comprehensive preclinical and

clinical evaluations. Future perspectives emphasize the integration of artificial intelligence and machine learning to optimize nanocarrier design by predicting physicochemical and biological interactions. Personalized nanocarriers, tailored based on patient-specific genetics and disease characteristics, hold promise for improving efficacy and reducing adverse effects. The development of multifunctional nanocarriers capable of simultaneous gene delivery, imaging, and therapeutic modulation could enable real-time monitoring and adaptive treatment strategies. Advances in stimuli-responsive and self-assembling nanocarriers may further enhance delivery precision. Interdisciplinary collaborations bridging material science, molecular biology, immunology, and computational modelling are crucial to overcoming current limitations and accelerating clinical adoption [22-26].

Conclusion

Nanocarriers have established themselves as pivotal components in advancing gene therapy by enabling the safe and efficient delivery of therapeutic nucleic acids to target cells. Their modular and tunable nature allows overcoming many biological barriers, improving specificity, and reducing systemic toxicity. Clinical successes such as siRNA drugs and mRNA vaccines validate their potential, yet challenges in immunogenicity, targeting, manufacturing, and regulation remain to be addressed. Continued innovation in nanocarrier design, supported by emerging technologies like artificial intelligence and personalized medicine, is essential to fully realize the transformative promise of gene therapy for a broad spectrum of diseases. The ongoing interdisciplinary efforts will likely herald a new era of precision genetic medicine with enhanced patient outcomes and therapeutic possibilities.

References

1. Mirza, Z., & Karim, S. (2021, February). Nanoparticles-based drug delivery and gene therapy for breast cancer: Recent advancements and future challenges. In *Seminars in cancer biology* (Vol. 69, pp. 226-237). Academic Press.
2. Zu, H., & Gao, D. (2021). Non-viral vectors in gene therapy: recent development, challenges, and prospects. *The AAPS journal*, *23*(4), 78.
3. Chinthala, L. K. (2022). Entrepreneurship in the digital age: New ventures and innovative business models. *International Journal of Scientific Research & Engineering Trends*, *8*(6). ISSN (Online): 2395-566X.
4. Dinesh, A., & Mandati, S. R. (2020). *Artificial intelligence on information services*. SSRN Electronic Journal.
5. Chinthala, L. K. (2022). Corporate social responsibility: How companies are integrating purpose with profit. *International Journal of Science, Engineering and Technology*, *10*(6). ISSN (Online): 2348-4098, ISSN (Print): 2395-4752.
6. Yu, C., Li, L., Hu, P., Yang, Y., Wei, W., Deng, X., ... & Ma, J. (2021). Recent advances in stimulus-responsive nanocarriers for gene therapy. *Advanced Science*, *8*(14), 2100540.
7. Keles, E., Song, Y., Du, D., Dong, W. J., & Lin, Y. (2016). Recent progress in nanomaterials for gene delivery applications. *Biomaterials science*, *4*(9), 1291-1309.
8. Wang, K., Kievit, F. M., & Zhang, M. (2016). Nanoparticles for cancer gene therapy: Recent advances, challenges, and strategies. *Pharmacological research*, *114*, 56-66.
9. Keeler, A. M., Elmallah, M. K., & Flotte, T. R. (2017). Gene therapy 2017: progress and future directions. *Clinical and translational science*, *10*(4), 242.
10. Mokhtarzadeh, A., Alibakhshi, A., Yaghoobi, H., Hashemi, M., Hejazi, M., & Ramezani, M. (2016). Recent advances on biocompatible and biodegradable nanoparticles as gene carriers. *Expert opinion on biological therapy*, *16*(6), 771-785.
11. del Pozo-Rodriguez, A., Solinís, M. Á., & Rodríguez-Gascón, A. (2016). Applications of lipid nanoparticles in gene therapy. *European Journal of Pharmaceutics and Biopharmaceutics*, *109*, 184-193.
12. Rai, R., Alwani, S., & Badea, I. (2019). Polymeric nanoparticles in gene therapy: New avenues of design and optimization for delivery applications. *Polymers*, *11*(4), 745.
13. Gavas, S., Quazi, S., & Karpiński, T. M. (2021). Nanoparticles for cancer therapy: current progress and challenges. *Nanoscale research letters*, *16*(1), 173.
14. Roma-Rodrigues, C., Rivas-García, L., Baptista, P. V., & Fernandes, A. R. (2020). Gene therapy in cancer treatment: why go nano?. *Pharmaceutics*, *12*(3), 233.
15. Chen, J., Guo, Z., Tian, H., & Chen, X. (2016). Production and clinical development of nanoparticles for gene delivery. *Molecular Therapy Methods & Clinical Development*, *3*.
16. Zhang, M., Zang, X., Wang, M., Li, Z., Qiao, M., Hu, H., & Chen, D. (2019). Exosome-based nanocarriers as bio-inspired and versatile vehicles for drug delivery: recent advances and challenges. *Journal of Materials Chemistry B*, *7*(15), 2421-2433.

17. Hill, A. B., Chen, M., Chen, C. K., Pfeifer, B. A., & Jones, C. H. (2016). Overcoming gene-delivery hurdles: physiological considerations for nonviral vectors. *Trends in biotechnology*, *34*(2), 91-105.
18. Bulaklak, K., & Gersbach, C. A. (2020). The once and future gene therapy. *Nature communications*, *11*(1), 1-4.
19. Chinthala, L. K. (2022). E-commerce 2.0: The evolution of online retail and consumer behavior post-pandemic. *Innovative Journal of Business and Management*, *11*(03). https://doi.org/10.15520/ijbm.v11i03.3539
20. Yelagandula, S. K., & Mandati, S. R. (2020). *Designing an AI expert system*. SSRN Electronic Journal.
21. Mandati, S. R. (2020). *Globalization in information technology trends*. SSRN Electronic Journal.
22. Chinthala, L. K. (2022). Nanotech startups and the future of high-tech entrepreneurship. *Nanoscale Reports*, *5*(3), 1-4. Retrieved from https://nanoscalereports.com/index.php/nr/article/view/71
23. Francia, V., Schiffelers, R. M., Cullis, P. R., & Witzigmann, D. (2020). The biomolecular corona of lipid nanoparticles for gene therapy. *Bioconjugate chemistry*, *31*(9), 2046-2059.
24. Behr, M., Zhou, J., Xu, B., & Zhang, H. (2021). In vivo delivery of CRISPR-Cas9 therapeutics: Progress and challenges. *Acta Pharmaceutica Sinica B*, *11*(8), 2150-2171.
25. Loh, X. J., Lee, T. C., Dou, Q., & Deen, G. R. (2016). Utilising inorganic nanocarriers for gene delivery. *Biomaterials science*, *4*(1), 70-86.
26. Gaber, M., Medhat, W., Hany, M., Saher, N., Fang, J. Y., & Elzoghby, A. (2017). Protein-lipid nanohybrids as emerging platforms for drug and gene delivery: challenges and outcomes. *Journal of Controlled Release*, *254*, 75-91.