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Current trends in delivery of non-viral nucleic acid-based therapeutics for improved efficacy

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Published in:
Advanced Drug Delivery Reviews

DOI:
[10.1016/j.addr.2022.114297](https://doi.org/10.1016/j.addr.2022.114297)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2022

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Avci-Adali, M., & A. Santos, H. (2022). Current trends in delivery of non-viral nucleic acid-based therapeutics for improved efficacy. *Advanced Drug Delivery Reviews*, 185, [114297].
<https://doi.org/10.1016/j.addr.2022.114297>

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Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/adr

Preface

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Keywords:

Drug delivery
Nanomedicine
Nucleic acid
RNA
CRISPR
Microfluidics

In recent years, the use of nucleic acid-based drugs to treat and prevent diseases has become increasingly important. Last year, two nanovaccines based on synthetic messenger RNAs (mRNAs) encoding viral proteins were approved by the FDA against COVID-19, successfully demonstrating the applicability of synthetic mRNAs for infectious disease prevention [1]. In addition to vaccination, synthetic mRNAs hold great potential for regenerative medicine and therapy by the expression of missing or defective proteins [2]. In contrast to synthetic mRNA, siRNA or shRNA can be applied to downregulate the expression of undesired proteins in cells [3]. miRNAs can be administered to restore metabolic health and re-establish a healthy environment in diseased tissue, such as inflamed or cancerous tissue [4]. In the future, CRISPR technology may offer new treatment options for patients to correct mutations or deletions [5]. Aptamers are short target-specific ssDNA or RNA molecules that can be used to functionalize vehicles loaded with drugs, such as siRNA or miRNA [6] to target the desired cell and tissue types for a specific and efficient treatment. Moreover, various types of vehicles, such as lipid nanoparticles and liposomes, and their fabrication using innovative technologies, such as microfluidics, are being investigated to enable the efficient production, delivery and uptake of nucleic acid molecules into the desired cells [7]. In addition, the introduction of new modifications in nucleic acids allows for increased stability, decreased activation potential of the innate immune system, and modulation of nucleic acid-based drugs [8], which increases the efficiency of nucleic acid-based therapy.

This special issue collects 10 amazing contributions and focuses on novel and innovative strategies for the delivery of non-viral nucleic acid-based therapeutics. Worldwide contributions from experts in the fields of chemistry, biology, biotechnology, and pharmaceuticals highlight the versatility of nucleic acid-based molecules for various applications in medicine and discuss translational challenges and required improvements for nucleic acid-based drugs.

The review article of Prof. Avci-Adali and co-workers highlights novel and innovative strategies for the delivery of synthetic mRNA-based therapeutics for tissue regeneration. The versatility of synthetic mRNA molecules for various applications in the field of regenerative medicine are presented and translational challenges and required improvements for mRNA-based therapeutics are discussed to show the auspicious potential of the synthetic mRNA in the field of tissue regeneration.

Prof. Remaut and colleagues describe the mechanisms behind the recognition of synthetic mRNA by the innate immune system and provide an extensive overview of strategies to control their innate immune-stimulating activity. These strategies range from modifications of the mRNA backbone to combination with inhibitors of the innate immune system to optimization of production and purification processes. In addition, the delicate balance of the self-adjuvant effect in mRNA vaccination strategies was discussed, which can be both beneficial and detrimental to therapeutic outcome.

In their review, Prof. Santos and co-workers summarize the general principles for the development of RNAi vectors and discuss the practical aspects that should be considered in the production of these vectors, as well as the critical aspects of the vehicle that affect RNA encapsulation, targeting yield, and successful cytosolic release of RNA. Finally, recent advances in RNAi vectors and their further prospects for resolving therapeutic obstacles and promoting clinical translation are discussed.

Prof. Prassl and co-workers described the key regulatory activities of miRNAs in the adipose tissue, discussed various miRNA replacement and inhibition strategies, summarized promising delivery systems for miRNAs, and reflected on the future of novel miRNA-based therapeutics to target adipose tissue with the ultimate goal to combat metabolic disorders.

Dr. Hassan and colleagues discussed in their review article the opportunities offered by lipid nanoparticles (LNPs) for efficient and precise gene delivery. Furthermore, various synthesis strate-

gies via microfluidics used for high-throughput fabrication of non-viral gene delivery vehicles are discussed. In addition, the application of these vehicles for the delivery of RNA and CRISPR editors for different diseases ranging from cancer to rare diseases are discussed.

In their review article, Prof. Raemdonck and colleagues discuss both established and emerging techniques that can be used to evaluate the effects of different intracellular barriers on RNA transfection performance. They also demonstrate how various modulators, including small molecules but also genetic perturbation technologies, can promote RNA delivery by intervening at differing stages of the intracellular delivery process, such as cellular uptake, intracellular trafficking, endosomal escape, autophagy, and exocytosis. Gaining mechanistic insights into how RNA formulations are processed by cells is expected to fuel the rational design of the next generation of delivery carriers.

Prof. Wang and colleagues from Melbourne, VIC, Australia outlined the advances in clinical and preclinical ultrasound technologies and the development of ultrasonic particles for ultrasound targeted gene delivery (UTGD). The use of UTGD in a variety of diseases was highlighted to readers. Furthermore, the advantages, future perspectives, and translational limitations of UTGD were discussed.

Prof. Wang and colleagues briefly introduced the advantages and requirements of polymeric vectors for gene delivery into the skin. The incurable monogenic skin disease, recessive dystrophic epidermolysis bullosa (RDEB), and the main treatment methods and limitations were described. Then, the development of highly branched poly(β -amino ester)s (HPAEs) for *in vitro* evaluation and *in vivo* treatment of RDEB was summarized. In addition, the challenges, prospects, and favorable delivery routes of polymeric vectors for hereditary skin diseases were discussed. In the future, rapidly developing polymeric gene delivery systems could enable gene therapy for hereditary skin disorders.

Prof. Cui and colleagues presented biomaterial-based strategies for delivering nucleic acids for various tissue regeneration approaches. First, the classes of nucleic acids and their mechanisms in tissue regeneration were introduced. Recent advances in the design of biomaterial-based nucleic acid delivery for tissue regeneration, including bone, cartilage, skin, nerve, and heart were then explained. In addition, the impact of gene delivery methods, therapeutic genes, and biomaterial selection on tissue regeneration was reviewed. Finally, the application perspectives of biomaterial-based nucleic acid delivery and the challenges of clinical implementation were highlighted.

Prof. Zhang and his coworkers introduced the promising design of the nanocarriers and explained how they can enable the CRISPR/Cas9-based cancer therapy *in vivo* and how they can be used in the clinic in the future. First, the main features of the CRISPR/Cas9 gene-editing system were discussed and its applications in cancer therapy were summarized. Then, different types of nanocarriers for anticancer drug delivery were introduced. Finally, they focused on how to rationally design *in vivo* delivery systems for CRISPR/Cas9 to improve oncogene editing and cancer immunotherapy.

Overall, this special issue is intended to provide important background and new insights into recent advances in the delivery of non-viral nucleic acid-based therapeutics to improve efficacy. We believe that advances in delivery systems will expand the non-viral nucleic acid-based therapeutics and provide promising options to address challenging clinical needs.

Acknowledgments

The guest editors of this special issue are very grateful to all authors who accepted our invitation and contributed with their amazing works to this exciting issue on the topic "Current trends in delivery of non-viral nucleic acid-based therapeutics for improved efficacy". This special issue is dedicated to all scientists working in the field of nanomedicine and other related fields. Finally, our special thanks go also to the editors and staff of *Advanced Drug Delivery Reviews* for their continued support for this special issue and for making it possible.

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Available online 12 April 2022