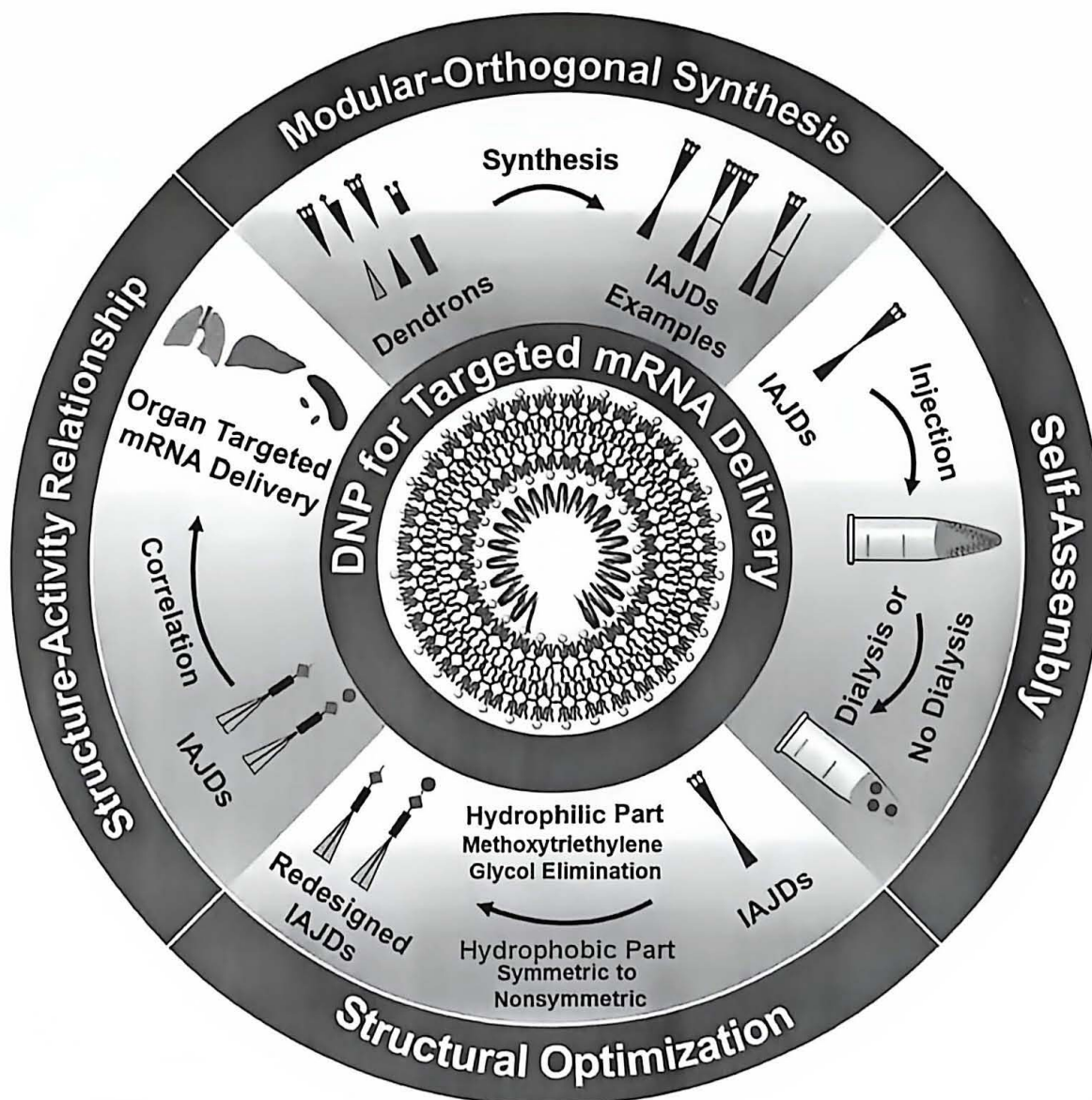


mRNA Delivery

One-Component Ionizable Amphiphilic Janus Dendrimers for Targeted mRNA Delivery

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Abstract: mRNA nanomedicine represents a new generation of therapeutics. However, how to deliver mRNA to the desired organs and cells effectively remains challenging. Common mRNA delivery vectors include viral and nonviral types such as four-component lipid nanoparticles (LNPs), polymer-based nanoparticles, lipid-polymer hybrid nanoparticles, and so on. One-component ionizable amphiphilic Janus dendrimers (IAJDs), are an emerging type of mRNA delivery vehicle displaying good stability and high delivery efficiency. In this review, we comprehensively present the design, synthesis, and mRNA delivery properties of IAJDs, with particular focus on the relationship between their molecular structures and organ targeted delivery properties. Other representative types of dendrimers for RNA delivery are also reviewed. Overall, this review summarizes the recent research progress on IAJDs systematically, aiming to guide the development of more efficient mRNA delivery platforms and next-generation mRNA nanomedicines.

1. Introduction

Messenger RNA (mRNA) is a type of single-stranded ribonucleic acid that is transcribed from one of the strands of the DNA double helix, carrying genetic information to guide protein synthesis. This pivotal molecule serves as a critical middleman in the central dogma of molecular biology—a cornerstone concept in life science. Its role is essential, as it mediates the translation of genetic information into functional proteins, including enzymes, antigens, antibodies, cytokines, and so on.^[1] Since scientists successfully extracted mRNA in 1961,^[2] mRNA has attracted tremendous interest in the fields of biology, biochemistry, and biomedicine. The application of mRNA extends to the treatment and prevention of an array of diseases characterized by protein expression abnormalities. Compared with DNA-related therapeutics, mRNA-based therapeutics present several compelling advantages. First, enhanced cytoplasmic translation: unlike DNA, mRNA does not necessitate entry into the cell nucleus; instead, it directly translates into proteins within the cytoplasm, thereby increasing efficiency. Second, mitigation of genomic integration risks: mRNA does not integrate into

the host genome, significantly reducing the likelihood of mutagenesis.^[3] Third, temporal control: mRNA undergoes rapid degradation post translation, ensuring transient therapeutic effects. Recently, the groundbreaking success of two mRNA vaccines against COVID-19, developed by Pfizer-BioNTech and Moderna respectively and achieved through efficient exogenous nucleic acid delivery, has exemplified one of the most fundamental principles of nanomedicine. This landmark achievement underscores the vast potential of mRNA technology in clinical applications.

Besides the predominant nucleoside-modified technology contributed by Drs. Drew Weissman and Katalin Karikó,^[4] the success of mRNA vaccines also depends on the development of efficient mRNA delivery systems. Because mRNA is a single-chain biomacromolecule, it is relatively fragile and inclined to be degradable. Vectors for mRNA delivery are generally divided into viral and nonviral types. Both viral and nonviral vectors have their own unique advantages and disadvantages. Viral vectors display high transfection efficiency (95%) and higher specificity for cell targeting including unnatural cells.^[5,6] However, some of their drawbacks including immunogenicity, cytotoxicity, difficulty of assembly, inflammatory responses to repeated administration, and the potential risk of insertional mutagenesis restrict them to achieve more success.^[7] On the other hand, many nonviral nanocarriers have been developed for mRNA delivery, including lipid nanoparticles (LNPs),^[8–11] polymers,^[12–14] inorganic nanoparticles,^[15] exosomes,^[16] and so on. Among them, LNP is an excellent delivery carrier, which usually consists of four components including ionizable lipids, phospholipids, cholesterol, and a PEG-conjugated lipid. It has been widely used for RNA delivery including siRNA (small interfering RNA) and mRNA. Meanwhile, it is one of the most successful mRNA delivery vectors in clinical applications as well as commercial applications up to now. For example, both Pfizer-BioNTech and Moderna utilize LNPs as the vectors for their mRNA vaccines (BNT162b2 and mRNA-1273, respectively) to help mitigate the impact of the COVID-19 pandemic. Nevertheless, LNPs still have some limitations, including their relatively low stability which requires strict low-temperature storage conditions, the possible segregation of the neutral ionizable lipid from the four components as well as the difficulty of non-liver mRNA delivery.^[17,18]

Polymers, especially cationic polymers such as polyethyleneimine (PEI), have also received much attention to act as the potential carrier of mRNA, owing to their higher molar mass, better stability, and mechanical properties compared to lipids. Recently, Waymouth and coworkers reported charge-altering releasable transporters (CARTs) for mRNA delivery based on oligo(carbonate-*b*- α -amino ester)s with self-immolative degradation capacity, which realized highly-efficient delivery and release of mRNA in cultured cells as well as robust protein expression *in vivo*.^[19,20]

Dendrimers, as a special type of polymers with exact molecular structure and molar mass, have been reported to deliver RNA-type drugs such as siRNA, microRNA (miRNA), and mRNA as well.^[21–23] Among them, amphiphilic Janus dendrimers composed of hydrophilic and hydrophobic dendrons are an emerging type of mRNA

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