Optimization of One-Component Ionizable Amphiphilic Janus Dendrimer Design for Enhanced Dendrimersome Nanoparticle mRNA Delivery

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Ionizable lipid nanoparticles (LNPs) are the mainstream delivery mechanisms for mRNA therapeutics. pH-sensitive protonation allows their membranes to favorably (de)stabilize based on the surrounding pH, minimizing bloodstream toxicity & facilitating post-endocytic escape. However, LNPs are limited in their mRNA transfection efficiency (TE) into target cells. Dendrimersome nanoparticle (DNP) delivery systems were recently developed using ionizable amphiphilic Janus dendrimers (IAJDs) to overcome such limitations and have emerged as a promising alternative for their structural (one-component) simplicity and improved stability. This study sought to clarify the impact of particular IAJD structural components on mRNA TE and develop novel IAJD candidates for maximum predicted TE and reduced synthetic complexity. Structural constituents and DNP formulation conditions were systematically defined & encoded for computational analysis. Luciferase-induced HEK293T luminescence was used as a quantitative metric for mRNA TE. A new TE prediction model was developed using Extreme Gradient Boosting that overcame imbalanced datasets and ultimately yielded three novel, optimized IAJD candidates surpassing previously identified IAJDs in predicted TE. The first design exhibited lower synthetic complexity than IAJD22 (existing IAJD with the highest in vitro luminescence), indicating enhanced feasibility for laboratory-scale/industrial synthesis without compromising TE. These findings highlight the potential of ML-driven IAJD optimization. Combined with high-throughput in vitro assays, this method could significantly hasten mRNA therapeutics development with an improved delivery mechanism. This study presents the first computational investigation of IAJD structural optimization for mRNA TE.

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