Ionizable Amphiphilic Janus Dendrimer Optimization: Investigating Dendrimersome Nanoparticles for Enhanced mRNA Transfection in vitro

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Ionizable lipid nanoparticles (LNPs) are the mainstream delivery mechanisms for mRNA vaccines, with their pH-sensitive protonation facilitating post-endocytic endosomal escape. However, LNPs are limited in their mRNA transfection efficiency (TE). Dendrimersome nanoparticle (DNP) delivery systems, using ionizable amphiphilic Janus dendrimers (IAJDs), have emerged as a promising alternative due to their structural simplicity and improved stability. This study sought to develop & verify in vitro novel IAJD candidates for maximum predicted TE. Luciferase-induced luminescence was used as a quantitative metric for mRNA transfection. The study systematically defined & encoded structural constituents (hydrophilic, ionizable amine, & hydrophobic regions) to develop a new TE prediction model was built using eXtreme Gradient Boosting (RMSE 243,088 AU, $R^2 = 0.9761$; 5-fold CV RMSE mean 456,561 AU). The model yielded four novel optimized IAJD candidates with projected luminescence of 7,108,495 AU. To verify these results, a new IAJD was synthesized and formulated into DNPs by co-assembling the IAJD with Luciferase mRNA. After dialysis, the DNP solution was transfected into HEK 293T cells. In vitro luminescence in the cells demonstrated that the IAJD-DNP (251,422 ± 14,630 AU) significantly outperformed the SM-102 LNP positive control (152,297 ± 15,813 AU) ($F = 766.18$, $p < 0.0001$; $t = 11.29$, p ˜ 5.8×10?5). This study presents the first computational investigation of IAJD structural optimization of this scale. While further verification of the optimal designs is required, these findings highlight the potential of ML-driven IAJD optimization. Combined with high-throughput in vitro assays, this method could significantly accelerate vaccine development with an improved delivery mechanism.

Awards Won:

Second Award of $2,400