Optimizing Synthesis of mRNA Therapeutics

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When Katalin Kariko and Drew Weissman developed mRNA therapeutics, they packaged mRNA in 4-component lipid nanoparticles (LNPs) to prevent bloodstream degradation by RNases. Research has since shown that dendritic nanoparticles (DNPs) can similarly encapsulate mRNA therapeutics with greater stability. Unfortunately, more research is required to perfect the synthesis of Ionizable Amphiphilic Janus Dendrimers (IAJDs), molecules that self-assemble in buffer to create DNPs. This project optimizes synthesis of the IAJD hydrophobic region through new tosylated precursors allowing for different reaction conditions. 4-toluenesulfonyl chloride reacts with alcohols in large quantities at room temperature to form paraffins with optimal leaving groups for nucleophilic substitution. This makes formation of the dendrimer's branching paraffins more efficient with cleaner purification. This is partially from lower reaction temperature, preventing decomposition of dimethylformamide, the reaction solvent, and decomposition of alkylated reagents. Reactions for orthogonal synthesis were characterized by nuclear magnetic resonance (NMR) and thin layer chromatography (TLC) which guided optimization of reaction and purification. Importantly, this first alkylation step dictates the efficiency of the entire orthogonal synthesis especially as IAJDs move into scaled production. After simplifying the synthesis schematic for the hydrophilic region from the hydrophobic building block in a prior project, this project's optimization remains the primary challenge in an efficiently optimized reaction scheme oriented towards accessibility. With this modification, production of DNPs can be simpler and cheaper for use as a universal component in all mRNA therapeutics.

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