Controlling and Predicting siRNA Delivery to Accelerate the Development of Clinically Relevant Nucleic Acid Therapeutics

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Zoom: https://udel.zoom.us/j/9361250352, Password: siRNA

The therapeutic use of short-interfering RNAs (siRNAs) has garnered significant interest as an approach to combat a wide range of intractable diseases, but the clinical translation of nucleic acid-based drugs remains limited because of the inability to formulate and test these treatments for therapeutic potential in an expedient manner. Elucidating structure-relationships between siRNA nanocarriers and gene silencing kinetics can advance clinical application of siRNA therapeutics by guiding the design of more effective nanocarriers and dosing regimens, ultimately reducing the heavy reliance on tedious, experimental testing of current screening methods. In this dissertation, three approaches were explored to gain fundamental insights into interactions between (1) siRNA and delivery materials and (2) delivery materials and biological barriers. In the first approach, a layer-by-layer nanocarrier was formulated by varying cationic block lengths of photo-responsive polymers to modulate siRNA binding efficiency, which enabled the encapsulation of multiple siRNA doses and precise control over the release of each individual dose. In the second approach, a simplified kinetic model was developed by identifying and including only key rate-limiting steps of the RNA interference process, resulting in a model capable of accurately predicting siRNA formulation efficacies both *in vitro* and *in vivo* using as few as experimental data from a single time point as an input. In the third approach, a modified kinetic model was developed by identifying a lipid nanoparticle (LNP) characteristic (*i.e.*, measurement of solubility) that showed good correlation to major biological barriers identified using the second approach, and this model was able to predict the effect of changing ionizable lipid structures and the molar ratios of LNP components without experimental testing. Taken together, these approaches have elucidated key structure-function relationships related to siRNA delivery using both polymers and lipid nanocarriers and are expected to guide formulation strategies that can enhance the efficacy of next-generation siRNA delivery technologies.