Controlled Nucleic Acid Delivery Using Photo-Responsive Polymeric Formulations

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Nucleic acid delivery has garnered significant interest as a biomedical research tool and therapeutic approach for the treatment of devastating diseases, as evidenced by the thousands of clinical trials that have been conducted over the past few decades. Small interfering ribonucleic acids (siRNA)s are particularly promising due to their ability to mediate transient post-transcriptional sequence-specific gene knockdown of aberrantly expressed proteins. Although cationic polymers have proven to be effective siRNA delivery vehicles, several problems related to a lack of spatiotemporal control over nucleic acid binding *vs.* release have hindered their clinical impact. To address these challenges, a nanocarrier system comprised of a photo-responsive block copolymer was developed that encapsulated and protected siRNA, stimulated cellular uptake, and induced light-triggered gene silencing. The work in this dissertation builds on this system to facilitate the translation of the approach into animal models and provide insights into siRNA release. Specifically, the dissertation is broken down into four primary objectives: 1) to develop a mechanistic understanding of nanocarrier disassembly and design methods for regulating the amount, location, and timing of siRNA activity; 2) to improve nanocarrier efficiencies through the formulation of mixed polymer complexes and predict dose responses using simple kinetic modeling; 3) to elucidate the effects of incorporating anionic excipients into nanocarriers and impart diagnostic characteristics into the formulations; and 4) to enable on/off control over gene silencing in human primary cells and mitigate maladaptive cellular responses that lead to high rates of cardiovascular graft failures. Overall, the work presented in this dissertation improved the efficiency and capabilities of photo-responsive siRNA delivery vehicles, provided a new combination of methods for probing the structure-function relationships of siRNA-polymer assemblies, established a simple kinetic model that accurately predicted siRNA dose responses, demonstrated the potential of lipid-polymer hybrid nanocomplexes in primary cells, and contributed new insights into the fundamental mechanisms that govern nucleic acid binding *vs.* release. These advances, along with the suggestions for future work, may help facilitate the translation of nucleic acid therapies into the clinic.