Present and Future Approaches to siRNA Delivery

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Since initially being described by Dr. Fire and Dr. Mello in 1998, siRNA and the RNAi pathway has experienced a sharp rise in popularity with regards to both publication volume and breakthroughs discovered. The siRNA, or small interfering RNA, pathway is one modality that cells utilize to regulate and control gene expression. Unlike other methods of control that function at the genomic level, such as transcription factors and promoters, siRNA modulates gene activity by suppressing the translation of mRNA into proteins by selectively binding to mRNA in the cytoplasm. siRNA is composed of a double stranded RNA molecule that is either produced from the cell's genomic DNA or is transfected into the cell by a virus or some other synthetic pathway. One strand of the siRNA acts as the "guide" strand that binds to a complimentary single strand mRNA and signals for certain cellular machinery to degrade the mRNA, thus halting any chance of translation. Because of its unique specificity in gene targeting, siRNA shows much therapeutic potential. siRNA can be synthesized to target virtually any phenotype so long as the mRNA sequence is elucidated[1]. However, there are many challenges in introducing siRNA into the cells such as cell penetration, immune evasion, and non-specific interactions that have stymied many efforts in translating siRNA-based therapeutics into the clinic.

Fortunately, many research groups have shown that the field of nanotechnology can be utilized to overcome many of the hurdles that block siRNA therapeutic research. Advances in nanomedicine that allows for cell-specific targeting and increased circulation time have enabled researchers to construct nano-carriers that can protect and deliver siRNA to specific cells to knowkdown a gene of interest. For example, the Anderson Lab at the Massachusetts Institute of Technology have developed and screened a library of lipidoid nanoparticles (LNP) for their gene silencing ability. These LNPs consist of various amino-alkyl-acrylates that form a lipid-like bilayer in solution that essentially encapsulate the siRNA[2]. Furthermore, the lab has also developed fluorescently labeled probes that are able to track the cellular trafficking of the siRNA and their nano-carriers.

The Rosette Nanotubes (RNTs) developed in the Fenniri lab provide a novel and facile way of siRNA complexation and drug delivery because of the ability to conjugate positively charged groups to the surface of the nanotube that bind to the negatively charged siRNA through electrostatic interactions. Using the tools developed by the Anderson Lab alongside novel assays, the proposed project hopes to characterize the ability of RNTs to both deliver the payload to the target cell and knockdown the gene of interest. Because of its unique structure and chemistry, the RNTs display great potential in the advancement of siRNA-based therapeutics.

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[1] Hannon, G. J. (2002). RNA interference, 418(July), 24–26.

[2] Love, K. T. *et al*. (2010). Lipid-like materials for low-dose, in vivo gene silencing. Proceedings of the National Academy of Sciences of the United States of America, 107(5), 1864–1869.