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Giving genes the silent treatment : Lipid-like materials for siRNA delivery

By

Dr. Kathryn Whitehead
Department of Chemical Engineering
Department of Biomedical Engineering
Carnegie Mellon University

Despite the promise of RNA interference therapeutics, progress towards the clinic has been slowed by the difficulty of delivering short interfering RNA (siRNA) into cellular targets within the body. siRNA is large (~13 kDa) and negatively charged; it does not have favorable biodistribution properties in vivo nor an ability to cross the cellular membrane of target cells. In order to facilitate these transport processes, a class of lipid-like materials termed 'lipidoids' has been synthesized and studied for applications in siRNA-mediated gene silencing. Although efficacious, initial lipidoids identified for siRNA delivery applications in vivo can have limited utility in therapeutic settings due to toxicity and non-degradability issues. In response to these challenges, a library of biodegradable lipidoids was synthesized and novel high-throughput methodologies were employed to demonstrate lipidoid gene silencing potential both in vitro and in vivo. Degradable lipidoids induced near-complete gene silencing at low siRNA doses in a variety of biological systems, including hepatocytes, myeloid and lymphoma cells, and ovarian cancer tumors. Furthermore, structure-function analysis has revealed material design criteria that reliably predict in vivo delivery efficacy without the need for any biological testing. Together, these results indicate that lipidoid materials can achieve potent, specific and non-toxic siRNA delivery in a variety of biological contexts and have the potential to hasten the advent of RNA interference therapeutics in the clinic.

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