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## Ligand-targeted, vehicle-free microRNA replacement therapy

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MicroRNAs (miRNAs) are exceptional candidates for combating many diseases such as cancer; however, their therapeutic power is dwarfed by the lack of safe, robust, specific, and efficient delivery methods. In theory, miRNAs represent the "poster child" for therapeutics. Firstly, miRNAs are small, and thus, easily penetrate the dense architecture of the tumor and microenvironment, which is a challenge for larger molecules or carrier vehicles. Secondarily, miRNAs are expressed endogenously, and due to tremendous selective pressure that has been imposed, adaptation has occurred. Thus, slight perturbations in miRNA concentration are unlikely to produce toxic effects in normal cells. Thirdly, the pleotropic and promiscuous nature of miRNAs makes a miRNA analogous to a multi-drug cocktail through targeting multiple complementary pathways. It is therefore unlikely that acquired resistance, which is an unforeseen hallmark of most targeted therapeutics, would occur. Regardless, the power of miRNA therapeutic use is stifled due to lack of delivery methods that allow the miRNAs to reach and penetrate targeted tissues with unwanted toxicity. MiRNAs have exclusively been delivered inside of various protective vehicles (dendrimer, Copolymer or liposome) to protect the miRNA from serum nucleases. Unfortunately, the benefit of protecting the miRNA cargo comes with unwanted toxicity. One way to avoid vehicle associated toxicity is to remove the vehicle entirely. This approach requires that i) the miRNA bases are heavily modified to protect it from nucleases, or ii) the unprotected miRNA is rapidly taken up by the cells such that it is not in circulation for an extended time and exposed to nucleases. Because of the reduced activity associated with nucleotide modifications, we evaluated a high-risk approach based on enhancing the delivery kinetics. Our data support rapid and specific uptake of a therapeutically-relevant miRNA that is conjugated directly to folate (FolamiR). We show that folate-mediated miRNA delivery is a first-in-class method that can be used to deliver miRNAs completely unprotected specifically to tumor cells in culture and in multiple in vivo models, including the murine Kras; p53 double mutant of non-small cell lung cancer (NSCLC). Through characterizing this model, we determined that like human NSCLC, tumors in this model overexpress the folate receptor and thus are sensitive to tumor suppressive FolamiRs. Importantly, efficacy of FolamiR-34a in all the models happens without unwanted toxicity. Additional evidence indicates that a small molecule ionophore can enhance endosomal mediated escape of the miRNA increasing cytosolic concentrations and targeting. Overall the data generated from these studies showcase a major advance in tumor specific uptake of naked miRNAs, resulting in reducing dosage, toxicity, and tissue off targeting. The intent is to fully develop and test ligand-mediated delivery to generate evidence that will be used to advance this innovative RNA delivery vehicle into clinical trials.

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