"Overcoming Multiscale Barriers to Therapeutic siRNA Delivery"

Abstract: RNA interference (RNAi)-based therapeutics are approaching clinical approval for genetically defined diseases. Small molecule conjugation has established itself as the most promising platform for safe and targeted siRNA delivery. Lipophilic conjugates represent a major class of modifications that can be engineered to improve siRNA drug-like properties and enhance cellular uptake. We have demonstrated that the increased circulation time, systemic biodistribution, and efficacy of lipid-conjugated siRNAs hinges on their interactions with native lipid trafficking complexes, such as high- and low-density lipoproteins. As a result of their enhanced pharmacokinetic properties, lipid-conjugated siRNAs have potent gene silencing activity in a broad range of tissues, particularly within the central nervous system. Recent advances in the preclinical development of lipid-conjugated siRNAs, particularly for Huntington’s disease, will be discussed.