An Integrated Discovery Platform for Accelerating Oligonucleotide Therapeutics via Advanced Conjugate Delivery Systems

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Oligonucleotide therapeutics represent a promising modality for treating metabolic disorders, CNS diseases, muscular dystrophies, and other conditions. However, their clinical advancement is significantly hindered by the lack of efficient and specific delivery strategies. Recent progress in conjugate-based delivery systems offers potential solutions for improving the safety and targeted delivery of oligonucleotides to various tissues and organs. To accelerate the discovery of oligonucleotide drugs, we have established an integrated service platform which encompasses oligonucleotide sequence design and optimization, in vitro screening using primary human cell models, discovery and evaluation of delivery tools including conjugate and vehicle-based delivery platforms, and assessment of in vivo tissue distribution and efficacy in animal models. For Lipid-Oligonucleotide Conjugates (LOCs), we synthesized siRNAs conjugated to structurally diverse lipids (varying chain lengths, linkers, chemical groups, and conjugation sites) and labeled with a fluorophore. Utilizing high-content imaging, we demonstrated that most LOCs exhibited significantly increased cellular uptake and target knockdown efficacy in primary human adipocytes and human skeletal muscle cells compared to unconjugated siRNA controls. In vivo biodistribution studies in mice using IVIS imaging revealed that lipid conjugation significantly enhanced siRNA retention time in both hepatic and extra-hepatic tissues, correlating with improved target knockdown efficacy. For Peptide-Oligonucleotide Conjugates (POCs), we utilized cells expressing high, medium, and low levels of specific peptide receptors. High-content imaging was employed to quantitatively assess POC uptake efficiency. Different cell models proved effective for evaluating POC knockdown efficacy. Critically, peptides identified through our mRNA display platform demonstrated binding affinity and knockdown efficiency comparable to positive control peptides. These results underscore the capability of our integrated platform to support the development of both LOC and POC delivery strategies, amongst others including antibody oligonucleotide conjugates and aptamer oligo conjugates. Th