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BSRB, ABC Seminar rooms (Hybrid)

An Academic Approach to Oligonucleotide Therapeutics

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Abstract

Nucleic acids (NA) are becoming the third major pillar of therapeutic modalities on par with small molecules and biologics. The diversity of NA molecular mechanisms, ranging from vaccines, antisense, short interfering RNA (siRNAs), and guide RNA for CRISPR gene editing systems, enable impact on most aspects of cellular biology and thus human medicine. The foundation behind the recent oligonucleotides' clinical success is fundamental chemical innovations in RNA stability, delivery, and synthesis.

Oligonucleotides are informational drugs; thus, if chemical architectures supporting safe and efficient delivery to the tissue of interest are achieved, they can be easily reprogrammed to modulate any gene expression on demand, creating an opportunity for academic institutions to drive therapeutic innovation. However, the process is limited by access to oligonucleotide chemistry and synthetic expertise.

In the first half of the talk, I will share the experience of building and running Nucleic Acid Chemistry Center in a context of a large academic institution. The NACC provides access to therapeutic quality screening leads and large manufacturing of preclinical compounds for the academic community. The impact of the NACC and chemical innovation will be discussed in the context of two significant projects. First, I will discuss the systematic structure-activity relationship study of chemical modifications to modulate RISC loading and cleavage. Screening 1200 siRNA variants allow for defining the chemical and thermodynamic rules for RISC assembly.

A recent discovery from our lab has identified di-valent siRNA as a scaffold enabling potent and sustained modulation of gene expression in CNS of rodents and NHP with multiple compounds advancing clinic. Recently, somatic repeat expansion has been identified as the driver behind many repeat-associated disorders. Indeed, modulation of MSH3, an essential gene involved in long repeat expansion, blocked somatic repeat expansion in the Q111 model of Huntington's Disease. I would present how access to NACC allowed the development and validation of the clinical lead and define a novel therapeutic approach for the treatment of HD.