RNA Innovation Seminars

M | RNA BIOMEDICINE

Monday, September 30th, 2019 4:00-5:00 PM
Forum Hall, Palmer Commons

"RNA Therapeutics: The Future of Human Medicine"

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Abstract

With the first drugs approved, oligonucleotides are rising to become a new, major class of therapeutic modalities on par with small molecules and biologics.

RNAi enables simple and specific modulation of gene expression when the chemical architecture supporting efficient delivery in vivo is defined. Currently, in liver, a single subcutaneous administration supports a year of clinical efficacy, changing our vision of how medicine will be practiced in the future.

The unprecedented duration of effect relies on oligonucleotide endocytosis and entrapment within endosomal/lysosomal compartments. These naturally formed, intracellular deposits provide a continuous release of compounds for RISC loading and productive silencing, supporting multi-month efficacy. Of course, this approach is dependent on extensive and complex chemical stabilization that ensures the survival of the oligonucleotides in highly aggressive biological environments.

In the context of fully stabilized compounds, we have used diverse chemical engineering to define the rules driving oligonucleotide distribution, efficacy, and toxicity. At this point, efficient modulation of gene expression in multiple extrahepatic tissues is possible (muscle, heart, fat, placenta, etc). One of our engineering efforts resulted in the identification of a di-branched chemical scaffold that enables potent and durable gene silencing in the brain and spinal cord. Using huntingtin – the causative gene in Huntington disease – as a model, we demonstrate that CNS-active RNAi induces potent protein silencing (~ 90%) in all brain regions tested in both rodents and non-human primates. Silencing persists for at least six months, with the degree of gene modulation correlating to the level of the guide strand tissue accumulation.

Demonstration of extrahepatic activity, in particular the development of a CNS-active RNAi scaffold, is opening other tissues and the brain for RNAi-based modulation of gene expression and establishing a path toward the development of new cures for genetically-defined neurodegenerative disorders.