Materials Science and Engineering Department

Fall Seminar Series

Development of SORT and iPhos LNPs for tissue specific mRNA delivery and CRISPR/Cas gene editing

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CRISPR/Cas gene editing and messenger RNA (mRNA)-based protein replacement therapy hold tremendous potential to effectively treat disease-causing mutations with diverse cellular origin. However, it is challenging to rationally design nanoparticles that selectively target specific tissues. In this presentation, I will describe a strategy termed Selective ORgan Targeting (SORT) wherein lipid nanoparticles (LNPs) are systematically engineered to exclusively edit extrahepatic tissues via addition of a supplemental SORT molecule. Lung-, spleen-, and liver-targeted SORT LNPs selectively edited therapeutically relevant cell types including epithelial cells, endothelial cells, B cells, T cells, and hepatocytes. SORT is compatible with multiple gene editing techniques, including mRNA, Cas9 mRNA / sgRNA, and Cas9 ribonucleoprotein (RNP) complexes. I will also describe the combinatorial synthesis of multi-tailed ionizable phospholipids (iPhos) capable of delivering nucleic acids for gene editing. Optimized iPhos lipids are composed of one pH-switchable zwitterion and three hydrophobic tails, which adopt a cone shape in endosomal acidic environment to facilitate membrane hexagonal transformation and subsequent cargo release from endosomes. It is envisioned that SORT may aid development of protein replacement and gene correction therapeutics in targeted tissues.

Dr. Daniel J. Siegwart is an Associate Professor in the Department of Biochemistry and the Simmons Comprehensive Cancer Center (SCCC) at UT Southwestern Medical Center (Dallas, Texas, U.S.A.). He is also the co-director for the Chemistry and Cancer Program within the National Cancer Institute-designated SCCC. He received a B.S. in Biochemistry from Lehigh University (2003), and a Ph.D. in Chemistry from Carnegie Mellon University (2008) with University Professor Krzysztof Matyjaszewski. He also studied as a Research Fellow at the University of Tokyo with Professor Kazunori Kataoka (2006). He then completed a Postdoctoral Fellowship at MIT with Institute Professor Robert Langer and Professor Daniel G. Anderson (2008-2012).

The Siegwart Lab at UT Southwestern aims to discover and define the critical physical and chemical properties of synthetic carriers required for therapeutic delivery of short to long RNAs for gene silencing, delivery, and editing. They have focused on hepatic and extrahepatic delivery for organ and cell specific protein delivery, gene delivery, and gene editing. Their research is grounded in chemical design and takes advantage of the unique opportunities for collaborative research at UT Southwestern.

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