Department of Medicinal Chemistry

**Seminar Title: Development of Inhalable Lipid Nanoparticles for the Treatment of Lung Cystic Fibrosis: Overcoming Barriers to CFTR Gene Delivery**

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**Abstract:**

Cystic fibrosis (CF) is a prevalent and life-threatening autosomal recessive genetic disorder resulting from mutations in the *Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)* gene. These mutations cause the CFTR protein to become dysfunctional, which disrupts the composition, volume, and pH of airway surface liquid, alters the anatomy and function of submucosal glands, and impairs the mucociliary clearance mechanism. Advances in the development of small molecule potentiators and correctors, have helped manage symptoms and greatly improved quality of life for a large portion of CF patients. However, still ~6-10% of CF patients have no treatment approaches.

Emerging strategies such as gene addition and gene editing aim to achieve stable expression of CFTR, representing promising avenues for CF treatment. Efficient delivery of these tools is a bottleneck to achieving correction of anion channel activity in target cell types, such as lung epithelial and basal stem cells, within the airways due to obstacles including viscous mucus, immune responses, and tight junctions. Viral and nonviral approaches have achieved anion channel restoration and are advancing to clinical trials at a rapid pace, but none are approved as a gene therapy to date. Lipid nanoparticles (LNPs) have gained attention as nonviral delivery vehicles due to their high cargo capacity and potential for repeated administration.

Our research is focused on the development of inhalable LNPs that promote localized protein production in the lungs while minimizing pulmonary and systemic toxicity. We recently discovered several LNP formulations that demonstrate tropism for lung tissue; however, further optimization of ionizable and structural lipids is necessary to enhance transfection efficiency in the target cell populations. The overarching goal is to create an inhalable LNP treatment that can effectively restore normal CFTR expression in CF patients, thereby offering a novel therapeutic approach. By addressing the limitations of current treatments and leveraging the innovative potential of inhalable LNPs, we aim to significantly improve the prognosis and overall health outcomes for individuals living with cystic fibrosis.