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Ph.D. DISSERTATION DEFENSE

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Degree:	Doctor of Philosophy
School/Department:	Charles V. Schaefer, Jr. School of Engineering and Science / Interdisciplinary Engineering Doctoral Program
Date:	Monday, July 1st, 2024
Time/Location:	1:00 p.m. / McLean 510
Title:	Exploring mRNA- and Cell-Based Therapies for Cystic Fibrosis
Chairperson:	Dr. Jinho Kim, Department of Biomedical Engineering, School of Engineering & Sciences
Committee Members:	Dr. Kwahun Lee, Department of Chemistry and Chemical Biology, School of Engineering & Sciences Dr. Hongjun Wang, Department of Biomedical Engineering, School of Engineering & Sciences Dr. Ansu Perekatt, Department of Chemistry and Chemical Biology, School of Engineering & Sciences Dr. Chang-Hwan Choi, Department of Mechanical Engineering, School of Engineering & Sciences

ABSTRACT

Cystic fibrosis (CF) is a life-limiting genetic disease caused by mutations in the CF transmembrane conductance regulator (CFTR) gene. The primary cause of mortality in CF patients is lung destruction and respiratory failure. Recent advancements in CFTR modulators, small molecular drugs targeting CFTR protein defects, have significantly improved symptoms, lung function, and life expectancy for many CF patients. However, these modulators are effective only for certain CFTR mutations where the CFTR protein is produced, excluding some patients from treatment. Furthermore, they cannot reverse severe lung damage, providing limited benefits for those with advanced lung damage. Therefore, further research into alternative CF treatments is crucial to benefit all patients and potentially reverse lung damage. In this context, mutation-independent therapies have emerged for CF, including gene-based therapy, mRNA therapy and cell replacement therapy. Considering the potential mutagenesis risk of gene-based therapy, my dissertation research focuses on mRNA and cell replacement therapies. For mRNA therapies, normal CFTR mRNA can be delivered via ionizable lipid nanoparticles (LNPs) into the cytoplasm of airway epithelial cells to generate functional CFTR protein. Ionizable LNPs are favored for mRNA delivery due to their ability to facilitate endosomal escape. However, most mRNA remains trapped in endosomes after entering cells and is ultimately degraded, resulting in low therapeutic efficiency. Therefore, in the first project, I explored a novel strategy to enhance endosomal escape efficiency and demonstrated that external mechanical oscillation can effectively prompt endosomal escape. Despite mRNA therapy's potential to treat all CF patients, it requires repeated injections, raising safety concerns and fails to reverse airway epithelial damage. To achieve permanent CF cure and lung regeneration, I explored cell replacement therapy focusing on cell transplantation. Collagen hydrogel was selected as a carrier for cell delivery to improve engraftment efficiency and ensure uniform distribution of implanted cells in the airways. To assess airway epithelium recovery post-cell delivery, I developed an opto-electromechanical method for detecting airway epithelial functions, which can be used to monitor airway epithelial injuries or regeneration. Collectively, this dissertation explores novel strategies for enhancing mRNA and cell replacement therapies for CF, potentially advancing better mutation-independent therapeutic methods.