DEPARTMENT
OF PHARMACEUTICAL SCIENCES

Seminars on Drug Sciences (SDS)

Lecture of

Prof. Dr. Olivia Merkel

Department of Pharmacy, Ludwig-Maximilians-Universität München, Germany

Therapeutic CRISPR/Cas9 delivery for KRAS-mutated lung cancer

Pulmonary RNA delivery offers a transformative strategy for treating respiratory diseases by enabling local modulation of gene expression and immune responses directly at the airway surface. Building on mechanistic insights from early pulmonary siRNA and RNAi delivery studies, research in the Merkal Lab at LMU Munich has advanced both polymer- and lipid-based delivery systems that enhance RNA stability, tissue targeting, and functional transfection in lung tissues.

The therapeutic potential of CRISPR/Cas9 for lung cancer is compelling, yet efficient and safe delivery of genome-editing machinery to the pulmonary epithelium remains a major translational bottleneck. This seminar will focus on recent work on the rational engineering of lipid nanoparticles (LNPs) for localized pulmonary delivery of Cas9 mRNA and sgRNA targeting the therapy-resistant KRAS G12S mutation in non-small cell lung cancer.

Starting from clinically validated lipid components, we implemented an orthogonal mixture design strategy combined with mRNA surrogate screening to systematically optimize lipid molar ratios for lung cell transfection. This approach identified two lead formulations with physicochemical properties tailored for pulmonary administration, including sub-120 nm particle size, low polydispersity, high encapsulation efficiency, and near-neutral surface charge. Beyond lipid composition, we demonstrate that fine-tuning the Cas9 mRNA:sgRNA weight ratio is a critical yet underexplored determinant of editing performance.

The optimized LNPs achieved up to 90% on-target gene editing in vitro, induced pronounced apoptotic signaling in KRAS-mutant lung cancer cells, and efficiently traversed mucus-producing air–liquid interface cultures. Importantly, repeated intratracheal administration in vivo was well tolerated, without systemic toxicity or cytokine induction. In an orthotopic lung tumor model, pulmonary CRISPR delivery resulted in localized gene disruption and tumor cell apoptosis, providing proof-of-concept for inhaled RNA-based genome editing in lung cancer.

Collectively, this work highlights how rational formulation engineering can redirect clinically established LNP platforms from hepatic to pulmonary delivery, advancing localized, mutation-specific gene editing as a non-invasive therapeutic strategy for lung malignancies.

Wednesday, April 22, 2026
17:15 - 18:15
Lecture Hall 1, Pharmacenter, Klingelbergstrasse, 50, Basel

Host: PhD Association & PhD Programm for Pharmaceutical Sciences

University of Basel