MICROFLUIDIC ACINI-ON-CHIP PLATFORMS AS A TOOL TO STUDY BACTERIAL LUNG EXPOSURE

Arbel Artzy-Schnirman, Department of Biomedical Engineering, Technion-Israel Institute of Technology, Haifa, Israel, arbel@bm.technion.ac.il
Patrick Carius, Helmholtz-Institute for Pharmaceutical Research Saarland (HIPS), Saarbrücken University, Germany
Shani Elias-Kirma, Department of Biomedical Engineering, Technion-Israel Institute of Technology, Haifa, Israel.
Nicole Schneider-Daum, Helmholtz-Institute for Pharmaceutical Research Saarland (HIPS), Saarbrücken University, Germany
Claus-Michael Lehr, Helmholtz-Institute for Pharmaceutical Research Saarland (HIPS), Saarbrücken University, Germany
Josué Sznitman, Department of Biomedical Engineering, Technion-Israel Institute of Technology, Haifa, Israel

Key Words: Acinus-on-chip, Epithelial barrier, Bacterial contamination, Cytokines secretion, Lipopolysaccharide

Bacterial invasion of the respiratory system leads to complex immune responses involving many cell types. In the alveolar regions, the first line of defense includes the alveolar epithelium, secreted surfactant, alveolar lining fluid and alveolar macrophages. The epithelium consists of alveolar type I and type II cells. Both cell types are known to have immuno-modulatory functions characterized by the secretion of pro-inflammatory cytokines. Epithelial *in vitro* models offer attractive platforms to investigate biological functionality, but have typically relied on traditional well plate assays that come short of mimicking the complexity of the airway environment and do not capture physiological flows or relevant anatomical features. In the last decade, microfluidics have gained significant momentum in laying the foundations for constructing *in vitro* models that mimic physiologically-relevant organ functions. Here we propose to use acinus-on-chip platforms that mimic more closely native acinar microflows at true scale in a multi-generation alveolated tree. Acinar chips are cultured with human Alveolar Epithelial Lentivirus immortalized (hAELVi) cells at an air-liquid interface (ALI); such cells show alveolar type I like characteristics and maintained barrier function, leading to high trans-epithelial electrical resistance (TEER) in analogy to primary cells harvested from human tissue. To model bacterial infection, i.e. a strong stimulator of the innate arm of the immune system, lipopolysaccharides (LPS) will be used. LPS is a major outer surface membrane protein expressed on Gram-negative bacteria. The alveolar epithelium is exposed to LPS-laden aerosols and cell response is monitored mainly by secretion of pro-inflammatory cytokines. Our acinus-on-chip allows quantitative on-line measurements of alveolar barrier function, absorption kinetics and immunologically relevant responses, giving further insight to the role played by type I alveolar cells in lung immunity.

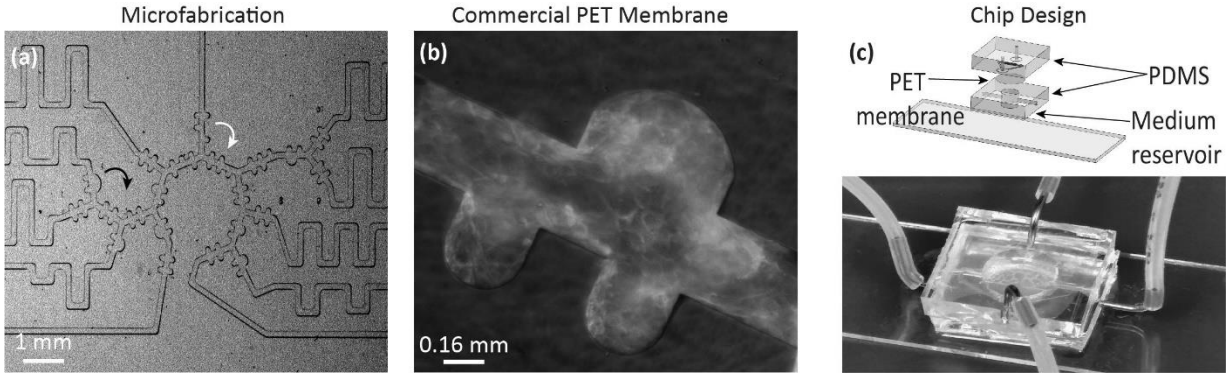

Figure 1 (a) PDMS-based model of developing acinar airways, demonstrating saccular alveolar spaces (dark arrow) and under-alveolated acinar ducts (white arrow). (b) Z-stacks of images from confocal microscopy. A commercial PET membrane (DOW Corning) (10 µm thick) with 0.4 µm pore size, seeded with hAELVi cells, phalloidin actin staining (white). (c) Upper panel, Exploded and assembled computer-aided drawing (CAD) views of a pulmonary tree-on-a-chip device. Bottom panel, view of a complete pulmonary tree-on-a-chip device.