Transwell-based microphysiological platform for high-resolution imaging of airway tissues

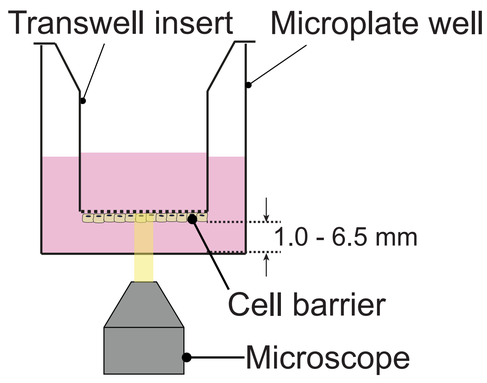
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Abstract

A microfluidic platform for long-term high-resolution imaging of transwell-based lung organoids is presented. We developed a poly(methylmethacrylate) (PMMA)-based microfluidic device to alternate between air-liquid interface (ALI) and liquid-liquid interface (LLI), which allows for cultivation of lung organoids under physiological ALI conditions, while performing high-resolution live-cell imaging under LLI conditions. The microfluidic device is conceived in a modular design, which enables flexible insertion and removal of the transwells and renders the system compatible with various up- and downstream analysis methods (e.g., TEER measurements). We used the device to monitor infections of *Pseudomonas aeruginosa* in human stem-cell-derived bronchial epithelial tissue.



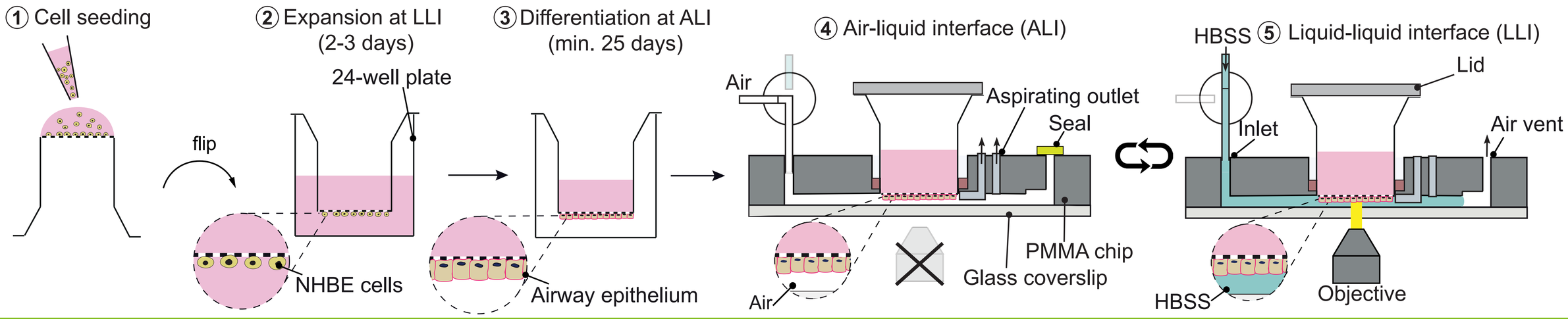


Transwell Insert, 24-well plate format

+ Various types of membranes & pore sizes
+ Easy to setup and control
+ Enables co-culture of two tissue models
+ Compatible with barrier function analysis tools (e.g., TEER measurements)
+ Cost effective

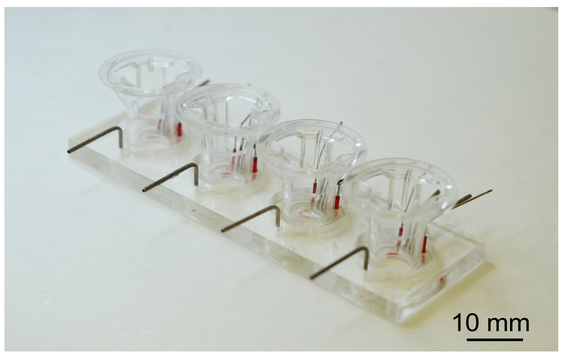
- Poor optical accessibility due to long working distance and membrane
- Static system - less biologically relevant
- Medium exchange and sampling is manual and invasive

Microfluidic device for alternating ALI-LLI conditions

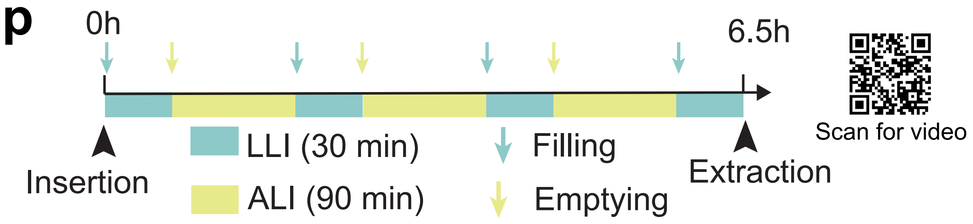


Upper airway culture on chip

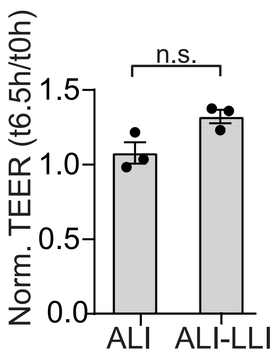
PMMA-based microfluidic chip



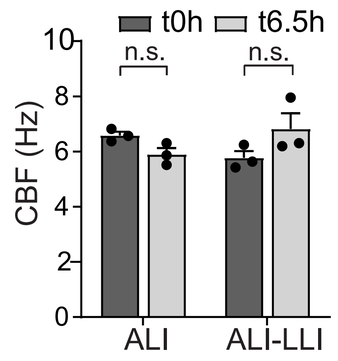
- Glass slide size (25 x 75 mm)
- 4 parallel culture units
- Compatible with commercial inserts



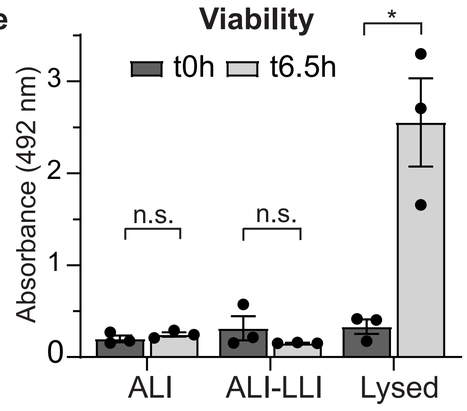
Barrier function



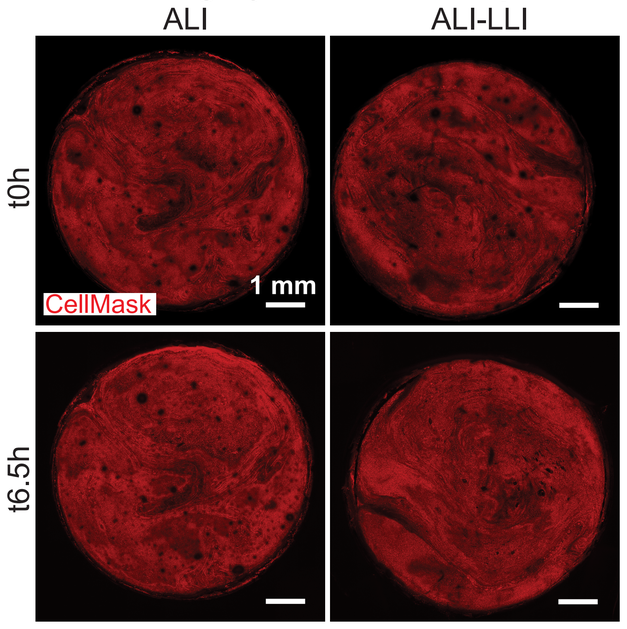
Mucocilliary clearance



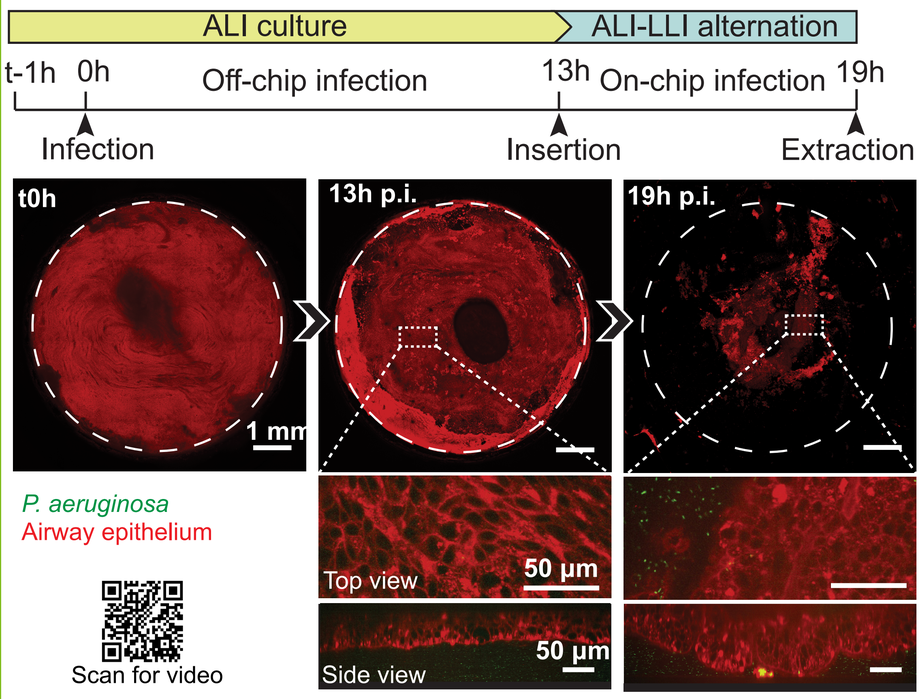
Viability



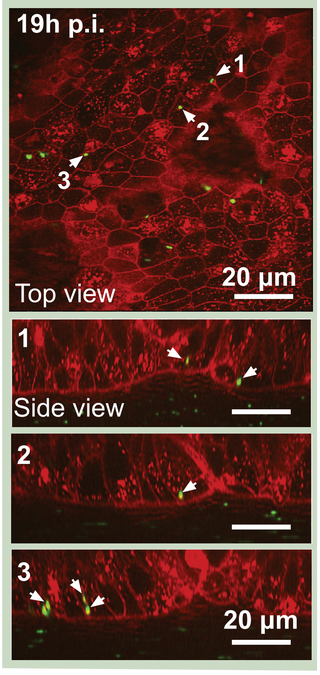
Tissue integrity after an on-chip culture



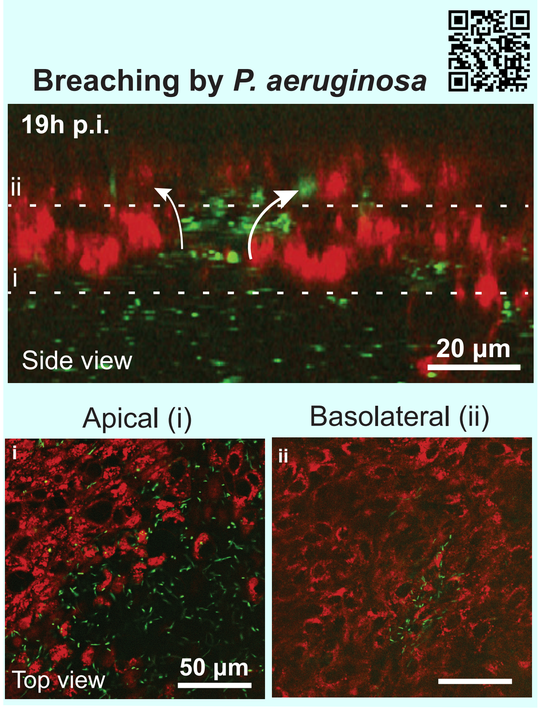
Pseudomonas aeruginosa (PAO1) infection of upper airway tissue



PAO1 internalization



Breaching by *P. aeruginosa*



Main features of the proposed system

Modular design
- Tissue formation off-chip
- Bacterial infection studies on chip

Chip fabrication in hard plastics
- No absorption of small molecules
- Reusability of the chips
- Biocompatible, chemically inert

Pump-driven flow
- Dynamic microenvironment
- Non-invasive sampling of perfusate

High-resolution imaging
- 40X or 60X magnification

Future outlook

PK-PD studies
- Generate patient-like compound exposures for infected tissue models
- Determine compound penetration through epithelial barrier

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