Advanced in vitro Lung-on-Chip Platforms for Inhalation Screening Assays

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Our Bioengineering Approaches

...still expanding
An Engineer’s View: the Multiscale Challenge

Haefeli-Bleuer & Weibel, Anatomical Record 220 (1988)
Current Paradigms: *in vitro* Gold Standards

**A NEED FOR:**

Pre-clinical **Human** *in vitro* Models

Alternative to **animals**

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From Prospect to Pipeline...

**Input**
- Carrier: Size, Shape, Surface chemistry
- Therapeutic Inhalation: Delivery device, Breathing rate, Flow pattern, Concentration, Formulation

**In vitro platform**

**Output**
- Viability
- Gene expression
- Cytokine secretion
- Deposition
- Barrier properties

"All models are wrong, but some are useful."

- George E.P. Box
Our Biomimetic *in vitro* Approaches

Upper Airways

Mid Bronchi

**Focus**

Bronchioles

Acinar Airways

3D Printing

< 10 mm

< 2 mm

< 500 to 5 μm

microfluidics

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In vitro Bronchi-on-Chip Platforms

(a) Cell seeding tube
Multi-generation geometry
PET membrane
Medium reservoir

(b)
Bronchi-on-Chips: Pipeline to Assay

Fabrication

- Multi-generation geometry
- PET membrane
- Medium reservoir

Cell seeding

~1-2 days

Barrier reconstruction

~ weeks to month

NHBE (primary) cells

Elias et al., under review.
Bioengineered Models vs. Reality
Bronchial Epithelium at Air-Liquid Interface (ALI)

Elias et al., under review.
In Situ-like Aerosol Exposure Assays

Main bronchi (3D Printed)

Bronchiole chips

Aerosolization

Elias et al., under review.
Ensemble Deposition Patterns on Chip

Physiological airflow matching

<table>
<thead>
<tr>
<th>Airway Tree</th>
<th>Flow Rates (L/min)</th>
<th>Reynolds Number (Re)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main Bronchi</td>
<td>0.2</td>
<td>~10-70</td>
</tr>
<tr>
<td>Chips</td>
<td>0.05</td>
<td>~1-10</td>
</tr>
</tbody>
</table>

Physiological airflow matching

Main Bronchi

Chips

Experiments

2 μm (n=8)

Simulations

Deposition fraction

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Elias-Kirma et al., under review.
Recapitulating Apoptopic Cascade


NHBEs in 96 well plates
2 μm PS w/ VR1 antibodies
Proof-of-Concept: Apoptosis in bronchi-on-chip

Elias-Kirma et al., under review.
Acinus-on-Chip: a Physical Model

Fishler et al., J. Biomech. 46 (2013)
Fishler et al., Scientific Reports 12071 (2015)
Acinus-on-Chip: Flow Visualization

Half-tree (macro view)  
Generations 1-2 (close up)

Fishler et al., Scientific Reports 12071 (2015)
Alveolar Flow Cascade

Fishler et al., J. Biomechanics 46 (2013)
Fishler et al., J. Biomechanics 50 (2017)
Acinus-on-Chip: In vitro Deposition Assays

Polystyrene particles (1-3h exposure)

Fisher et al., Scientific Reports 12071 (2015)
Airborne smoke (~0.1-1 µm)

Fishler et al., Scientific Reports 12071 (2015)
Stretching & Straining: a Multiscale Challenge

Huh et al., Science 328 (2010)
Reconstructing an Alveolar Epithelial Barrier

Monolayers of Alveolar Epithelial Cells (A549)

Tenenbaum-Katan et al., Biomicrofluidics 9 (2015)
Functional Alveolar Epithelial Barrier (hAELVi cells)

Kuehn et al., ALTEX 33 (2016)
Aerosol Exposure Assay: onset of Bacterial Infection

Outlook: a Vision for \textit{in vitro} Platforms...?
Acknowledgements