In Vitro Lecture and Luncheon

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Human Organs-on-Chips Testing—Strengths and Challenges

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Speaker
Human Organs-on-Chips

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Society of Toxicology In Vitro Lecture
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Credit & Disclaimer

The work presented was conducted at the Wyss Institute for Biologically Inspired Engineering at Harvard University.

The views and opinions expressed in the following presentation are solely those of the individual presenter and do not reflect the opinion or position of GlaxoSmithKline.
Organs-On-Chips Technologies as Predictive Tools for Drug Discovery and Development Applications

Pharmaceutical Industry:

- Weak pipelines and high attrition rates
- Poor prediction from animal models
- Fail “fast and cheap”
- Improve efficacy and safety profiles, select better drug candidates
- Reduce failure rates

Unmet need for human relevant, predictive in vitro models
Biomimetic Microsystems

• Engineer microchips containing living human cells that reconstitute organ-level functions for drug screening, diagnostic and therapeutic applications

• ACCELERATE drug development
• REFINE and REDUCE Animal Testing
• REPLACE animal testing: One Model at a Time
A Human Breathing Lung-on-a-Chip

(Dan Huh, Wyss Institute; Huh et al., Science 2010)

Alveoli (air sacs)
BIODESIGN PRINCIPLES:

- Tissue-Tissue Interface
- Dynamic Flow
- Cyclic Breathing Movements

Paton & Byron, Nat. Rev. Drug Discov. 2007
Small Airway-On-A-Chip
(work of Kambez Benam & Remi Villenave; Nat Meth, 2016)

“Classic” Lung (Alveolus)-On-a-Chip

Top channel

100um

Bottom Channel

100um

400um

Small Airway-On-A-Chip

Small Airway:
Diameter < 2 mm
Human Lung Airway Chip Validation In Vitro

Airway Chip Recapitulates In Vivo Physiology
(Benam et al. Nat Meth, 2016)

Stratified Epithelium

Active Ciliary Beating

Mucociliary Clearance

### Parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Human</th>
<th>On-Chip</th>
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<tbody>
<tr>
<td>Cilia beating frequency</td>
<td>10-15 Hz (1-2)</td>
<td>10-13Hz</td>
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<tr>
<td>Cilia length</td>
<td>~ 6 µm (1-2)</td>
<td>5-6 µm</td>
</tr>
<tr>
<td>Axoneme structure</td>
<td>9 + 2 microtubule (1-2)</td>
<td>9 + 2 microtubule</td>
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<tr>
<td>Mucociliary velocity</td>
<td>80-100 µm/sec (2)</td>
<td>50-100 µm/sec</td>
</tr>
<tr>
<td>% of ciliated cells</td>
<td>30-60 % (4)</td>
<td>30-70 %</td>
</tr>
<tr>
<td>% of goblet cells</td>
<td>10-20 % (3-4)</td>
<td>~ 30 %</td>
</tr>
<tr>
<td>Synchronization of cilia</td>
<td>Yes</td>
<td>Yes</td>
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Asthma & COPD Drug Responses
“Flu-like” Inflammatory Response Induced On-Chip

(Induced using Viral Mimic poly I:C)

Chemokine Production

Endothelium Influences Cytokine Response to Viral Mimic
Smoking Lung-on-a-Chip

(work of Kambez Benam; Cell Syst., 2016)
Smoking-induced oxidative stress in epithelial cells-on-chip

Anti-oxidant heme oxygenase 1 (HMOX1) gene expression

Oxidative stress-induced Nrf2 protein phosphorylation

(Benam, et al; Cell Syst., 2016)
Personalized Organs-on-Chips
(from individuals to populations)
Discussion
Summary
How many tissue types do you think can be in a 3D organ model?

- 3: 6%
- 10: 22%
- 30: 9%
- 100: 4%
- Infinite: 59%
A: What two things do you think are critical to establish a 3D model?
A: What disease states can be modeled with a 3D model?
In vitro systems are important models for identifying effects and mechanisms by which xenobiotics produce toxicity. With testing advances, we continue to refine, replace, and reduce experimentation with animal models.