SOT 56th Annual Meeting and ToxExpo™

In Vitro Lecture and Luncheon

Sponsored by the Colgate Palmolive Company

2017 *In Vitro* Toxicology Lecture and Luncheon

Anthony Bahinski

Speaker

Human Organs-on-Chips Testing—Strengths and Challenges

Human Organs-on-Chips

Anthony Bahinski, PhD, MBA, FAHA
Global Head, Safety Pharmacology
GlaxoSmithKline
King of Prussia, PA USA

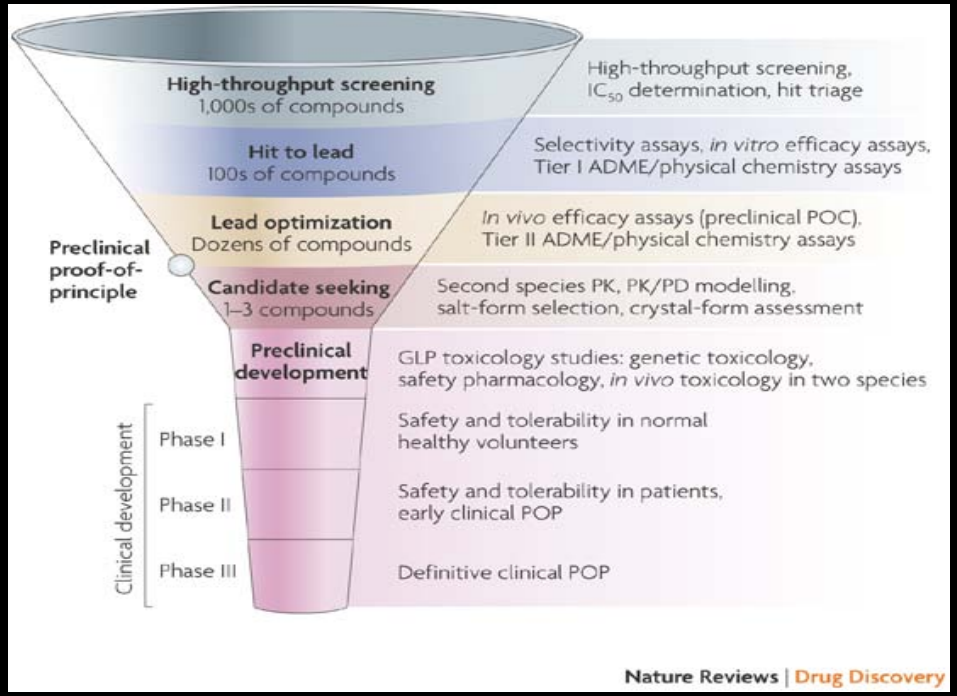
Society of Toxicology *In Vitro* Lecture
Baltimore, MD
March 13, 2017

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

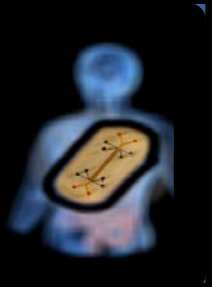


<u>Pharmaceutical Industry</u>:

- 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

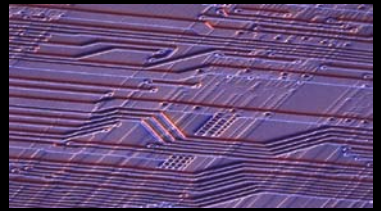
Unmet need for human relevant, predictive *in vitro* models

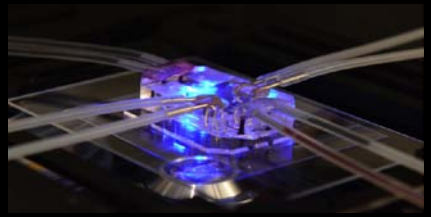
Biomimetic Microsystems

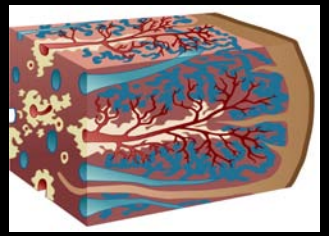


• Engineer microchips containing living human cells that reconstitute organ-level functions for drug screening, diagnostic and therapeutic applications

- *ACCELERATE drug development*
- *REFINE and REDUCE Animal Testing*
- *REPLACE animal testing: One Model at a Time*



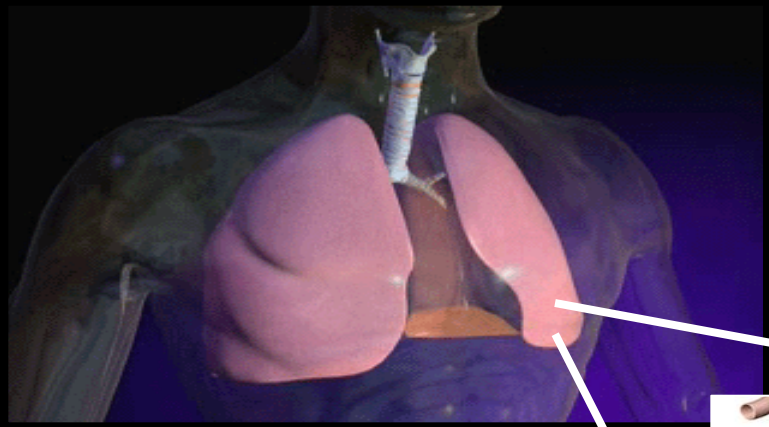


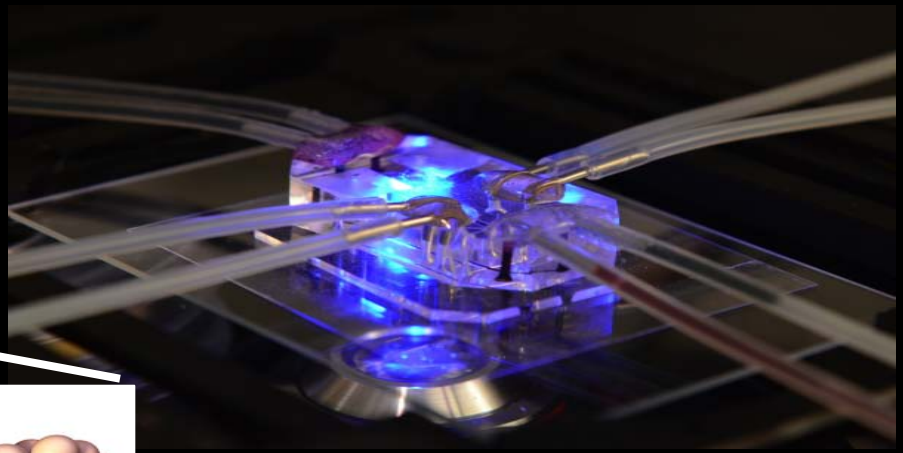


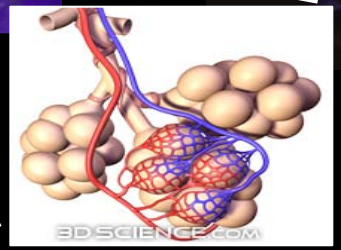
Biomimetic Spleen

A Human Breathing Lung-on-a-Chip

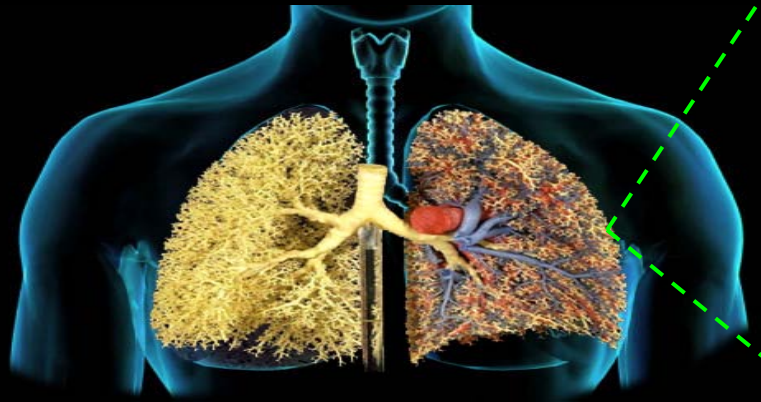
(Dan Huh, Wyss Institute; Huh et al., *Science* 2010)

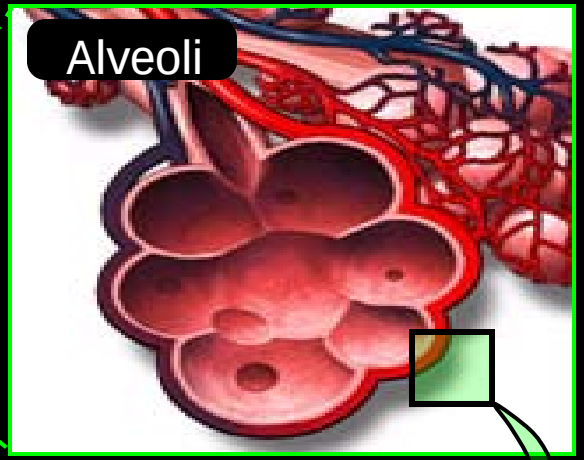


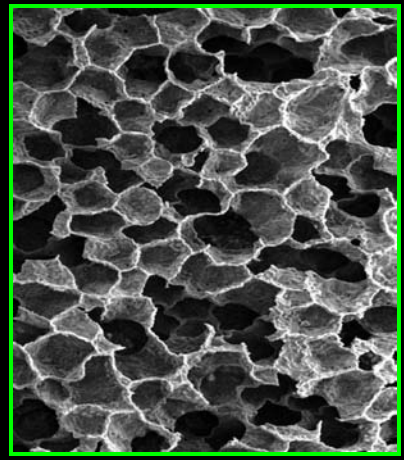


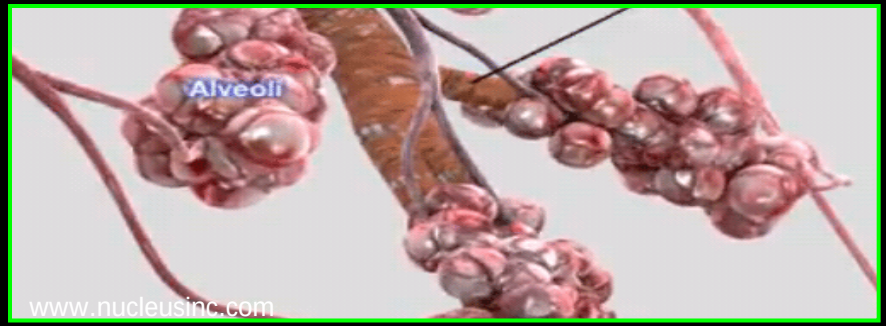


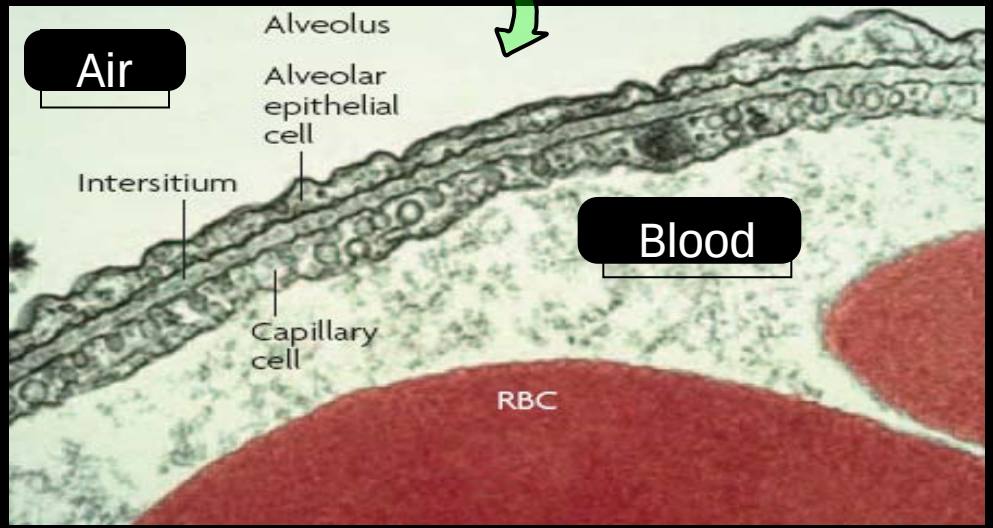
Alveoli (air sacs)







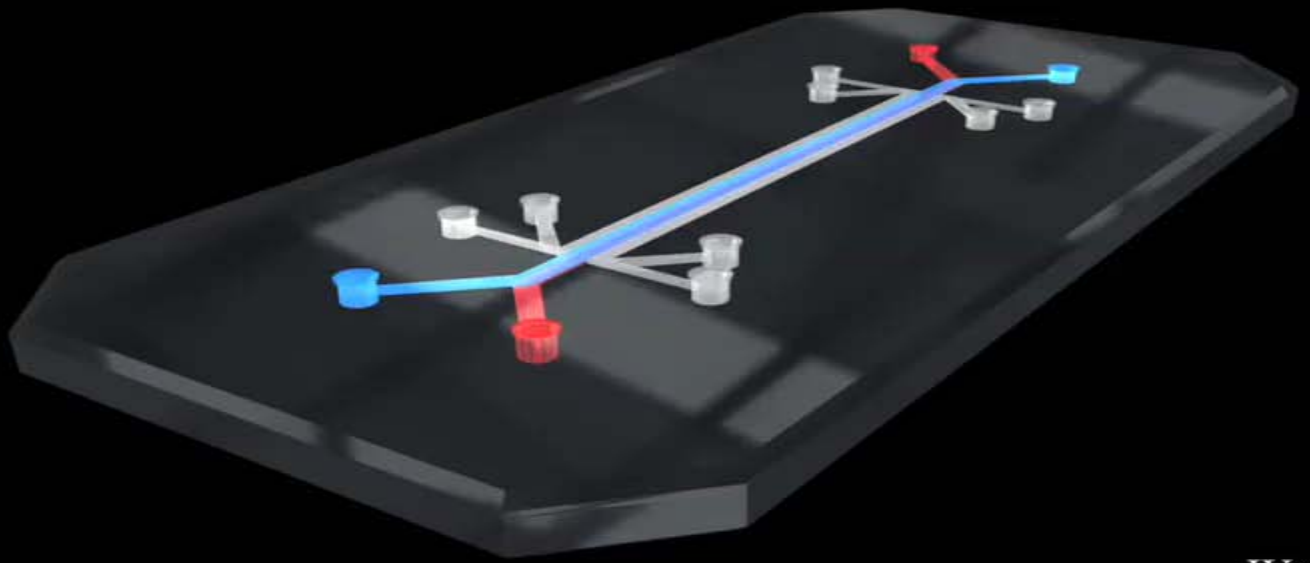




BIODESIGN PRINCIPLES:

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

Paton & Byron, *Nat. Rev. Drug Discov.* 2007



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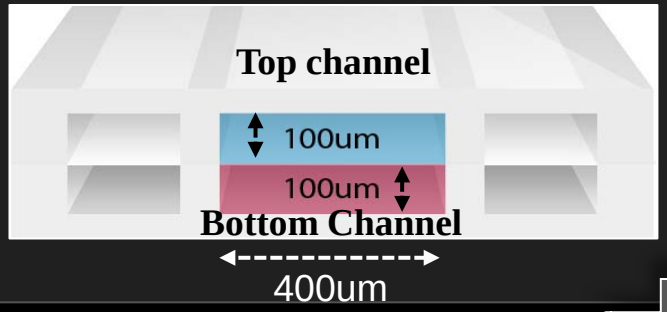
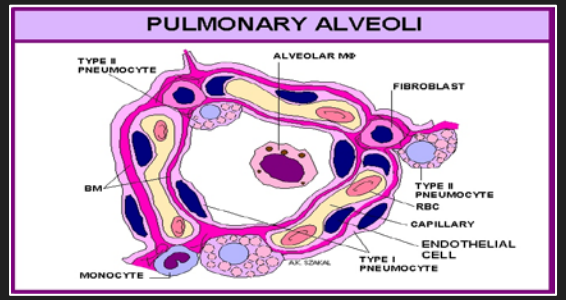
Small Airway-On-A-Chip

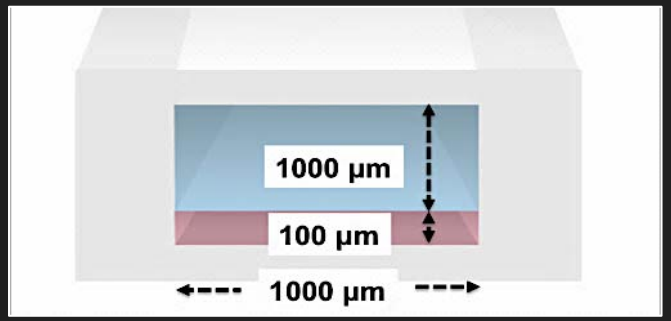
(work of Kambez Benam & Remi Villenave; Nat Meth, 2016)

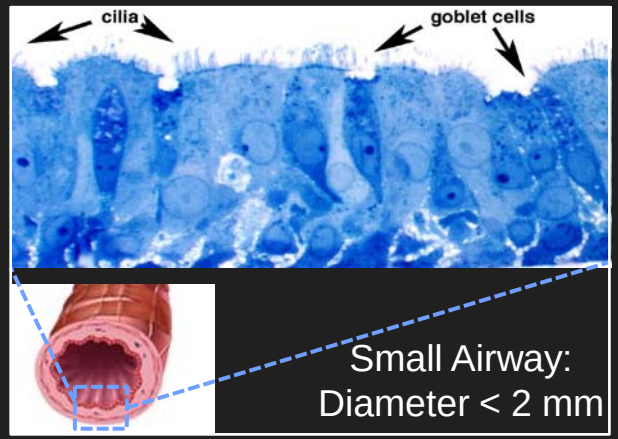
“Classic” Lung (Alveolus)-On-a-Chip





Small Airway-On-a-Chip



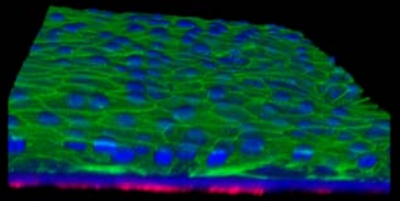


Human Lung Airway Chip Validation *In Vitro*

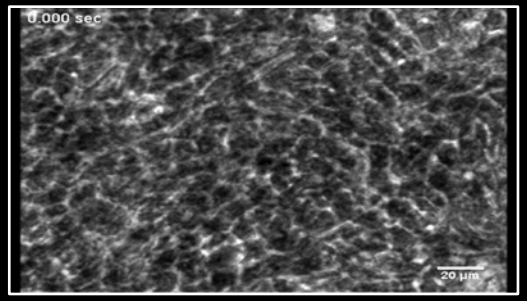
Airway Chip Recapitulates *In Vivo* Physiology

(Benam et al. **Nat Meth, 2016**)

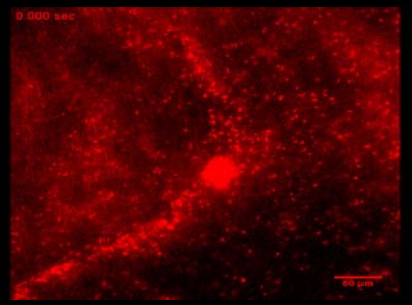
Stratified Epithelium



Active Ciliary Beating

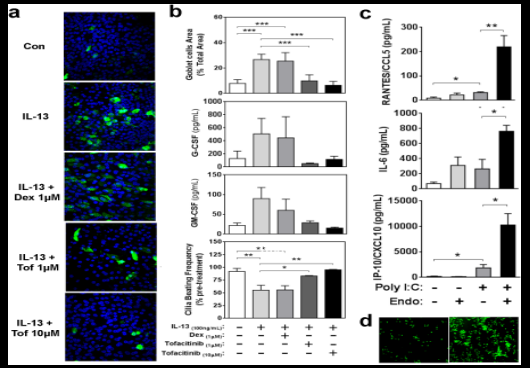


Mucociliary Clearance



Parameters	Human	On-Chip
Cilia beating frequency	10-15 Hz (1-2)	10-13Hz
Cilia length	~ 6 µm (1-2)	5-6 µm
Axoneme structure	9 + 2 microtubule (1-2)	9 + 2 microtubule
Mucociliary velocity	80-100 µm/sec (2)	50-100 µm/sec
% of ciliated cells	30-60 % (4)	30-70 %
% of goblet cells	10-20 % (3-4)	~ 30 %
Synchronization of cilia	Yes	Yes

Asthma & COPD Drug Responses

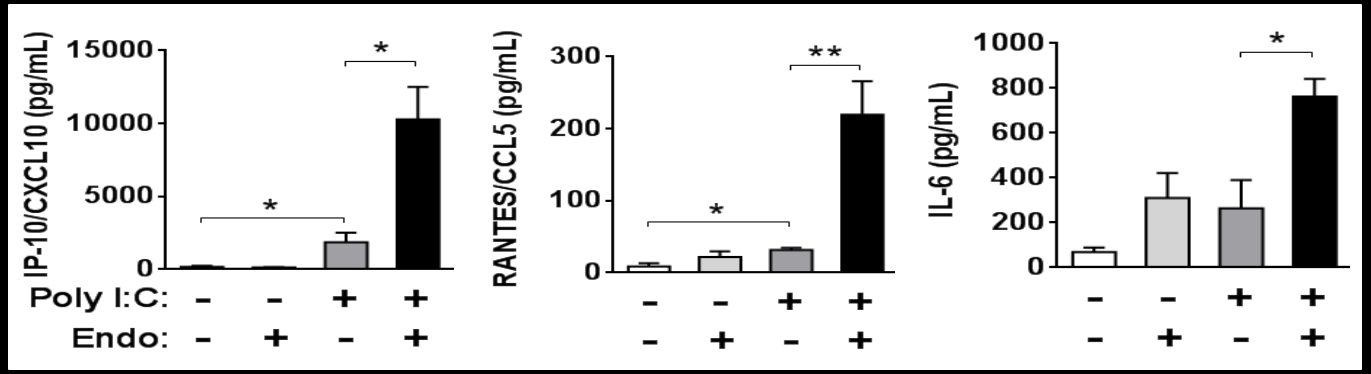


Ref: (1) Livraghi *et al*, 2007 (2) Wanner *et al*, 1996 (3) Boers *et al*, 1999 (4) Mercer *et al*, 1994.

“Flu-like” Inflammatory Response Induced On-Chip

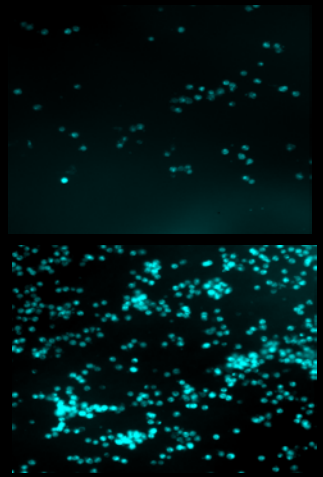
(Induced using Viral Mimic poly I:C)

Chemokine Production



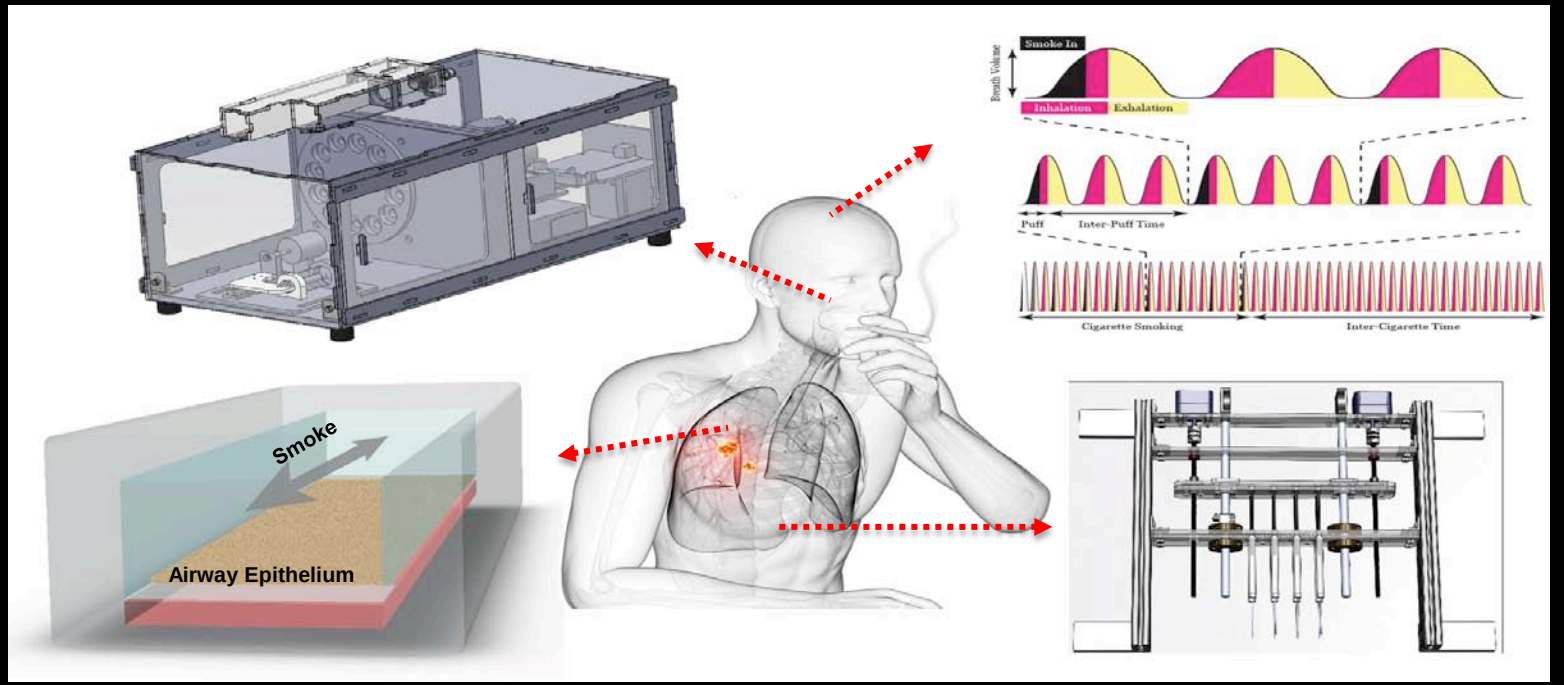
Endothelium Influences Cytokine Response to Viral Mimic

Monocyte Recruitment



Smoking Lung-on-a-Chip

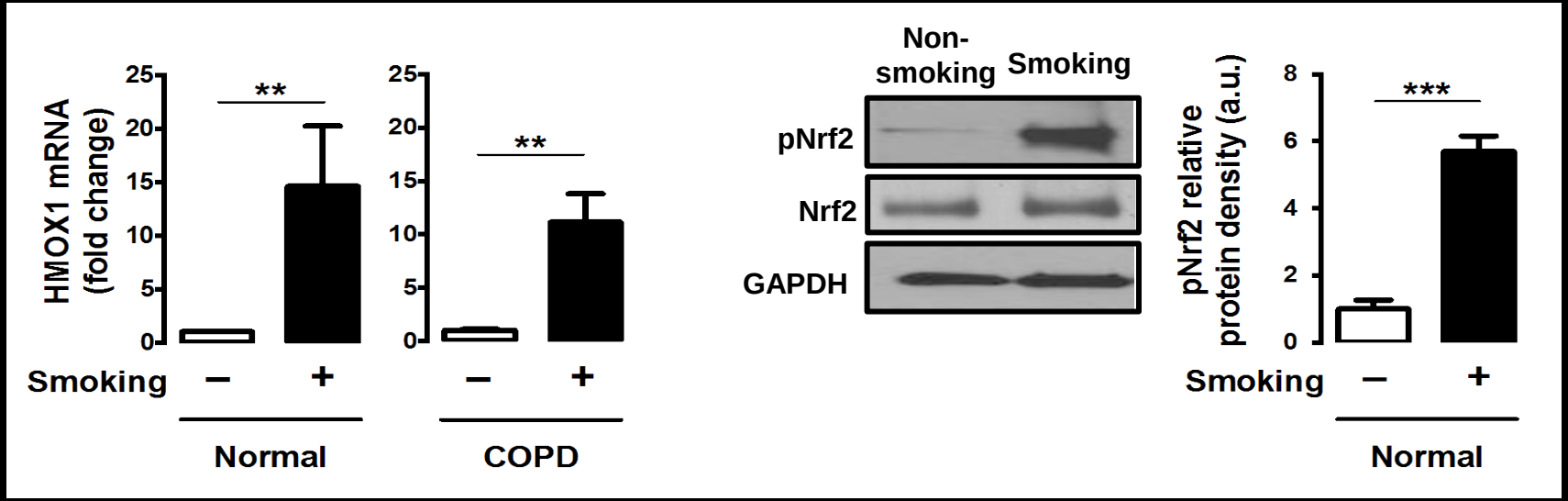
(work of Kambez Benam; Cell Syst.**, 2016)**



Smoking-induced oxidative stress in epithelial cells-on-chip

Anti-oxidant heme oxygenase 1 (HMOX1) gene expression

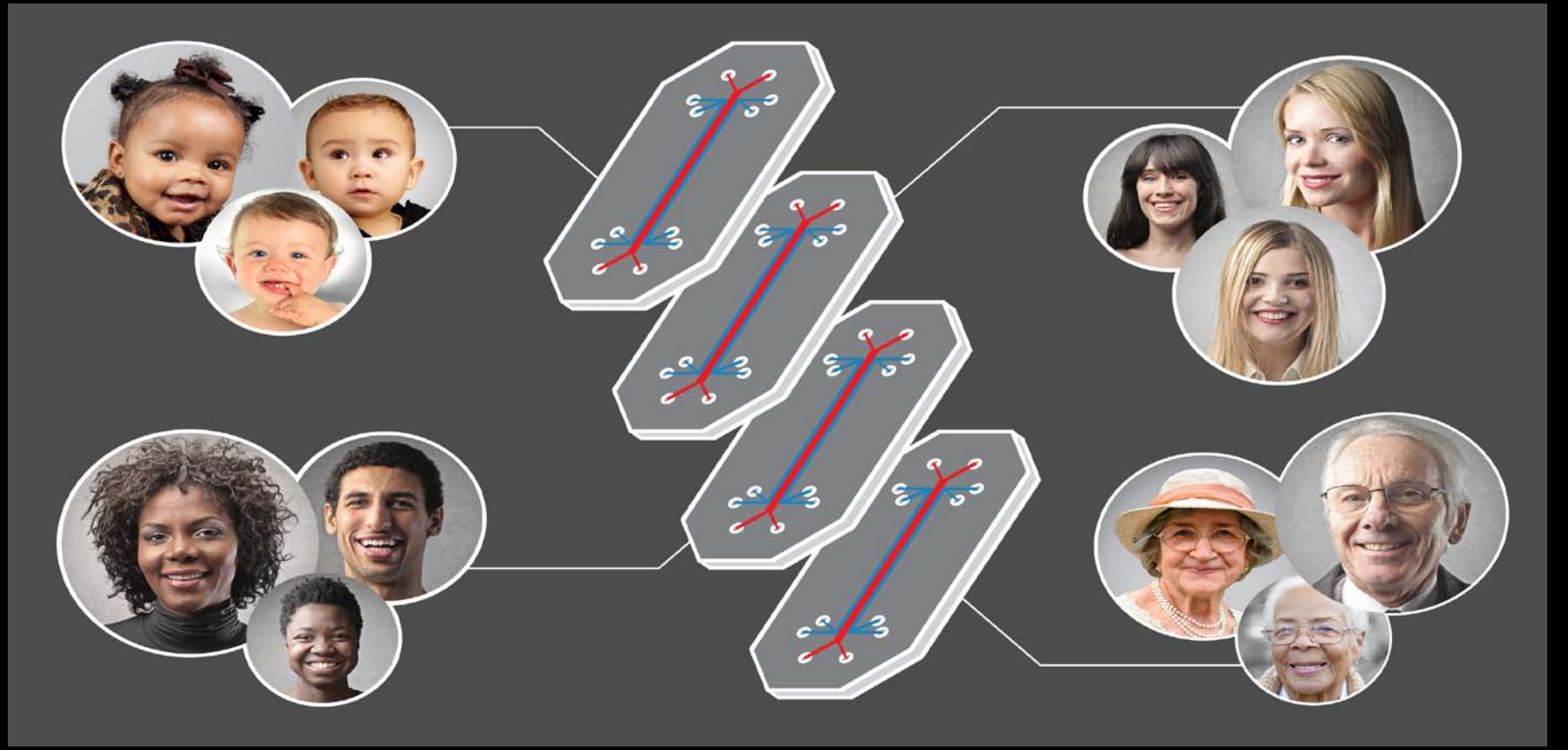
Oxidative stress-induced Nrf2 protein phosphorylation



(**Benam, et al;** Cell Syst., **2016**)

Personalized Organs-on-Chips

(from individuals to populations)

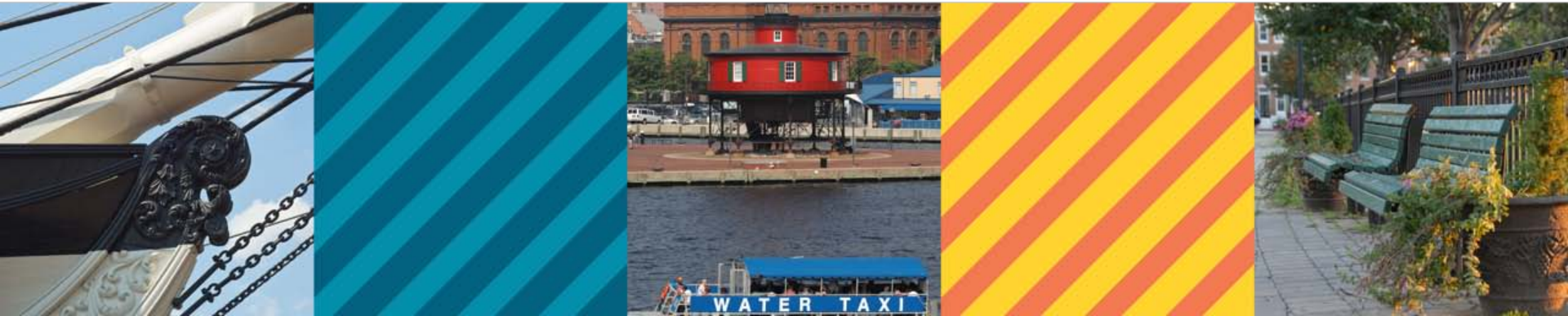


Integrated Human Body-on-Chips

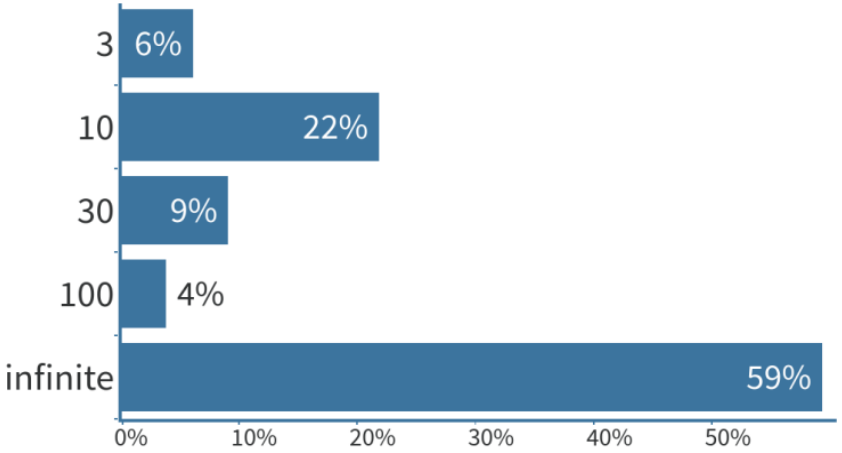

Discussion



Summary



A: How many tissue types do you think can be in a 3D organ model?



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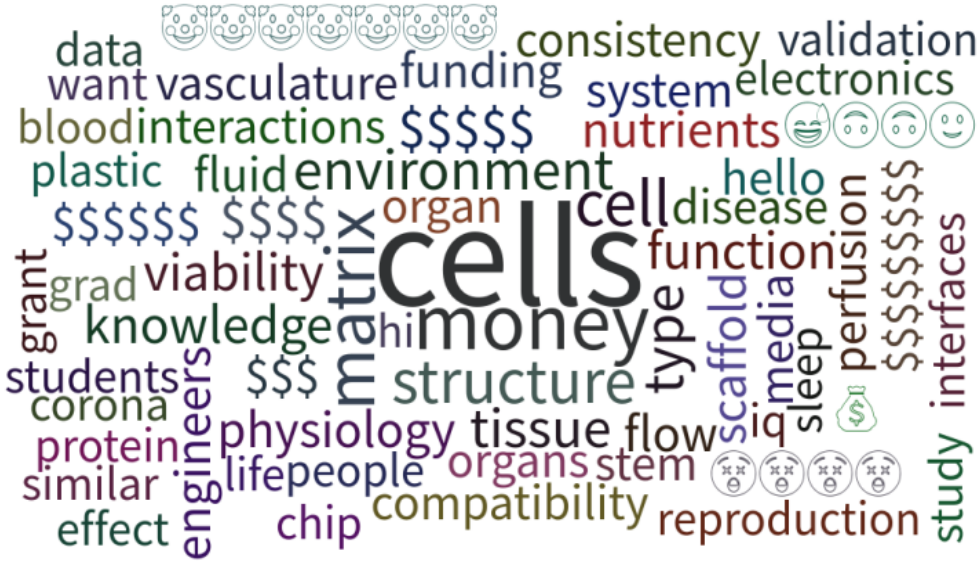
Poll Everywhere

: What two things do you think are critical to establish a 3D model



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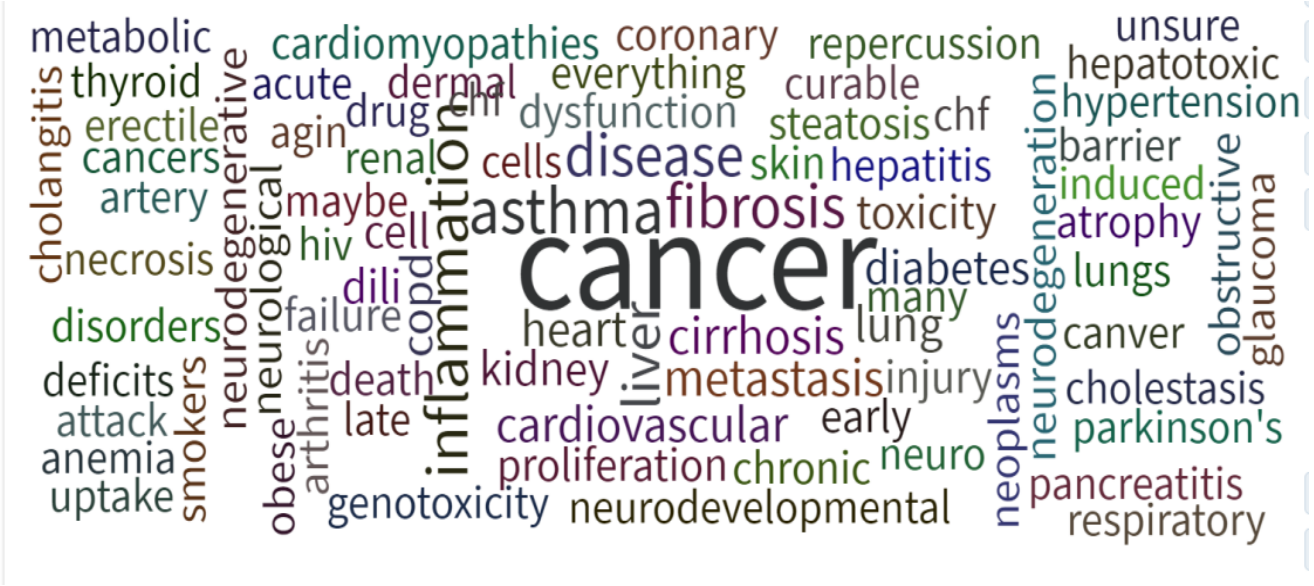
Poll Everywhere

A: What disease states can be modeled with a 3D model?



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Key Messages

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.