

Advanced *Lung-on-Chips* for preclinical for inhalation assays: Bridging *in vitro* and *in silico* approaches

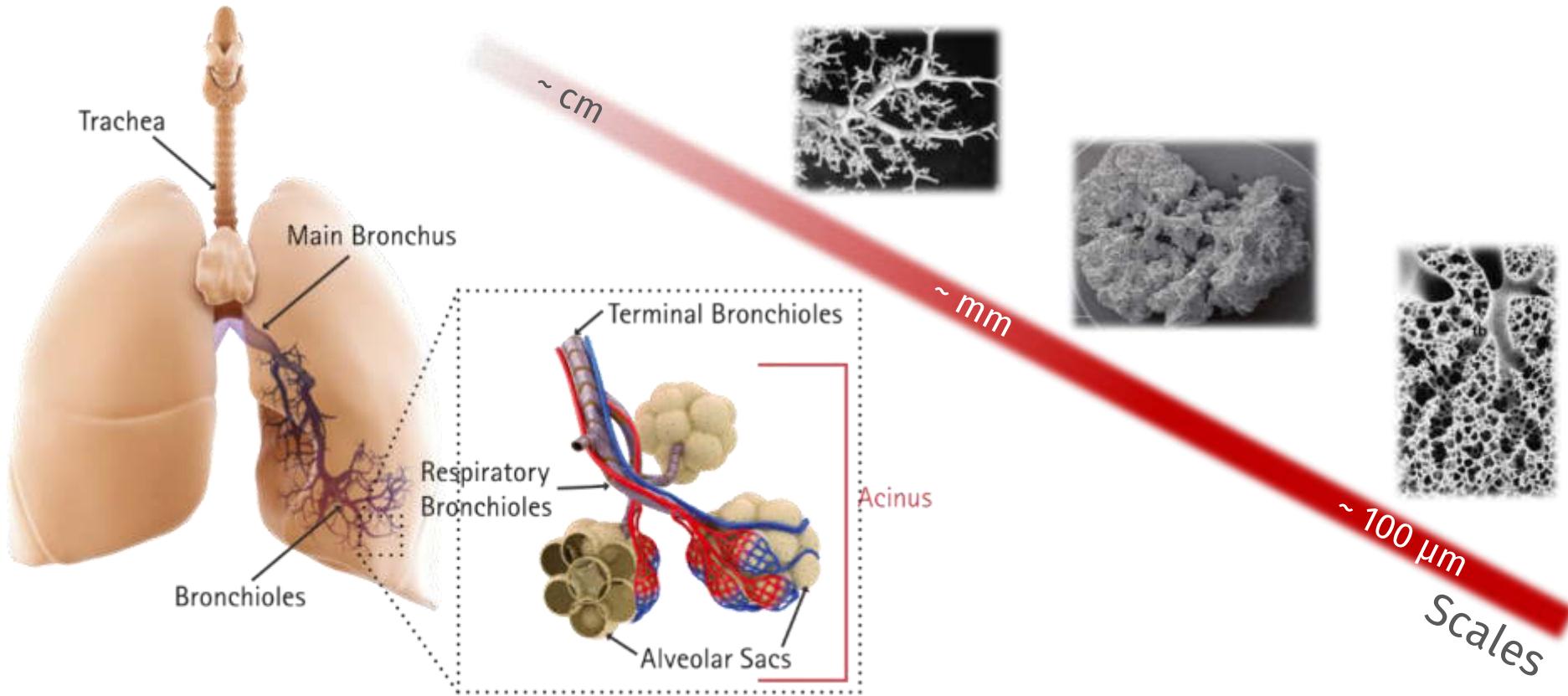
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<http://biofluids.technion.ac.il/>



The Multiscale Challenge: The Lungs

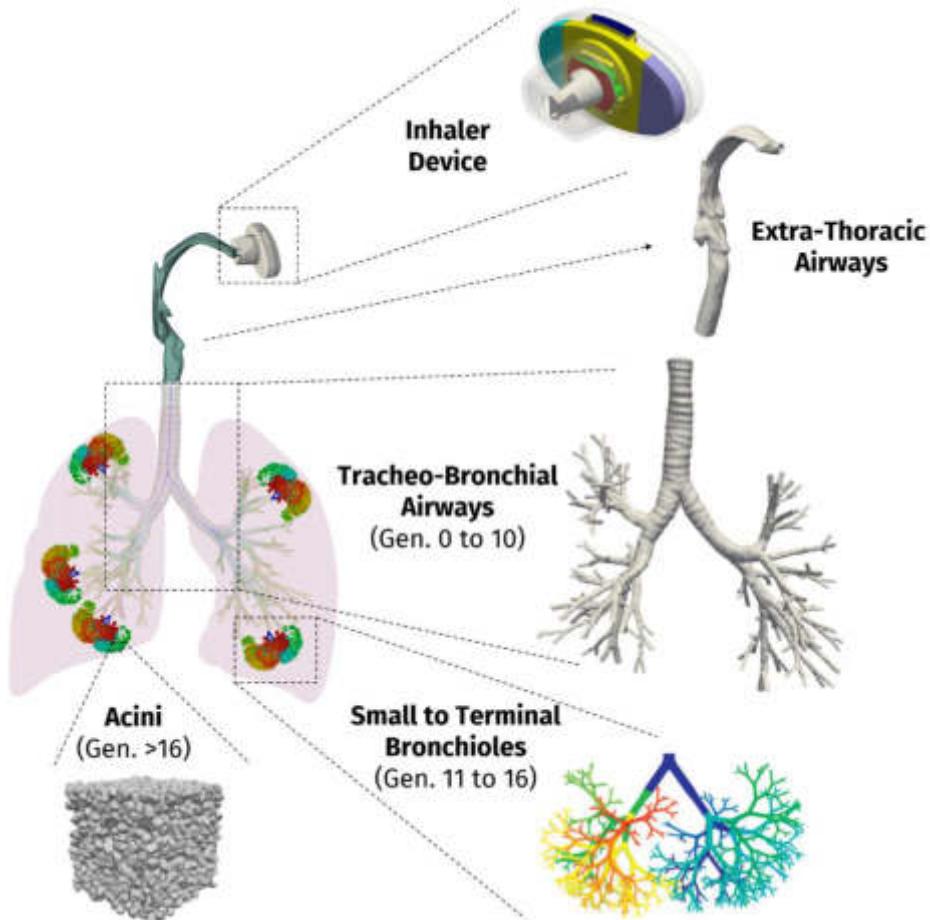
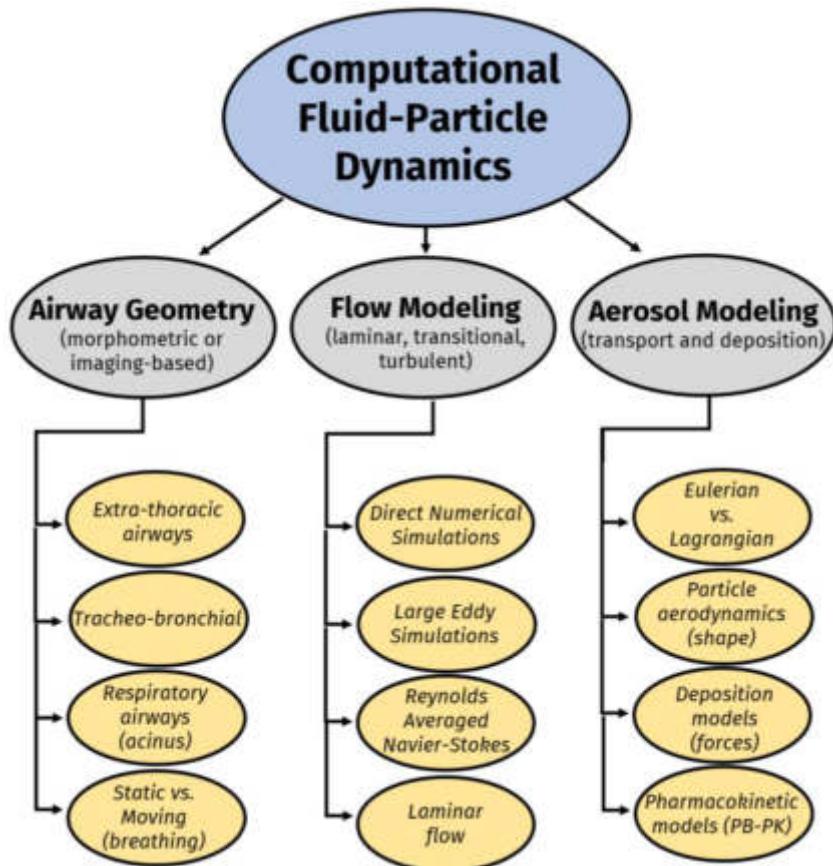


Tenenbaum-Katan et al., *Biomicrofluidics* 12 (2018)

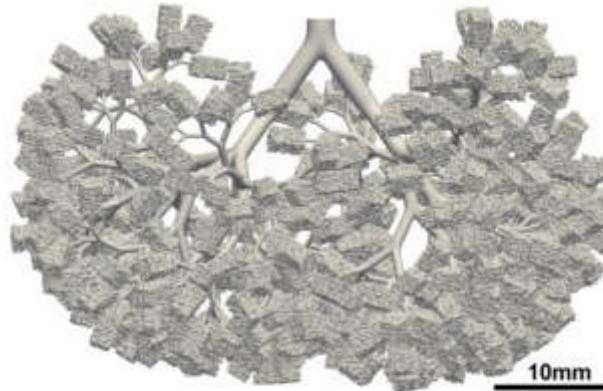
Weibel, Sapoval & Filoche, *Respir. Physiology & Neurobiology* 148 (2005)

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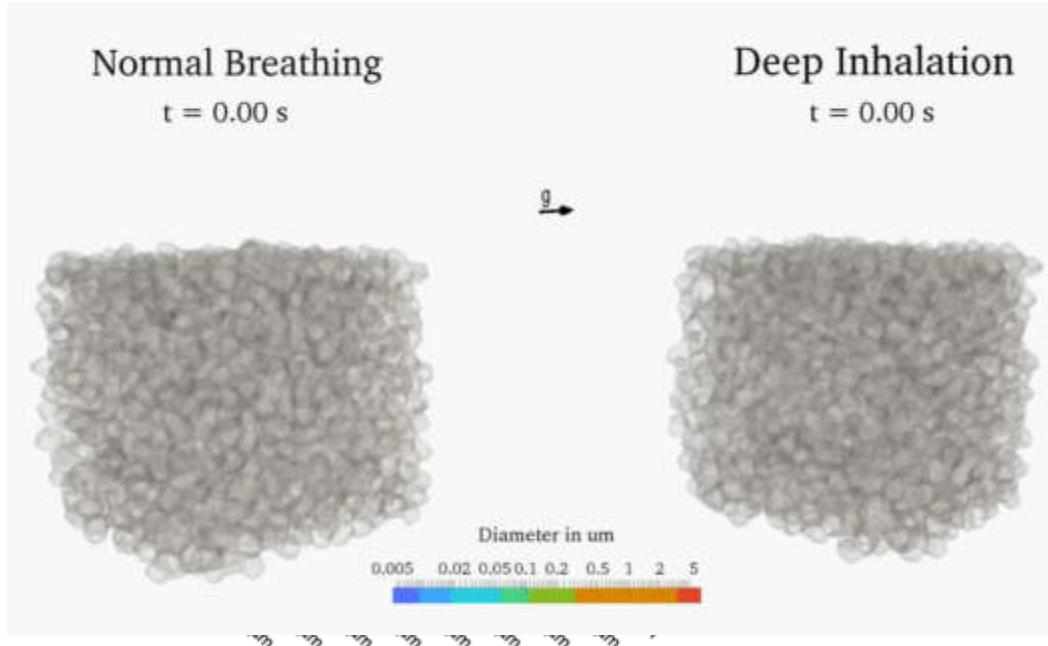
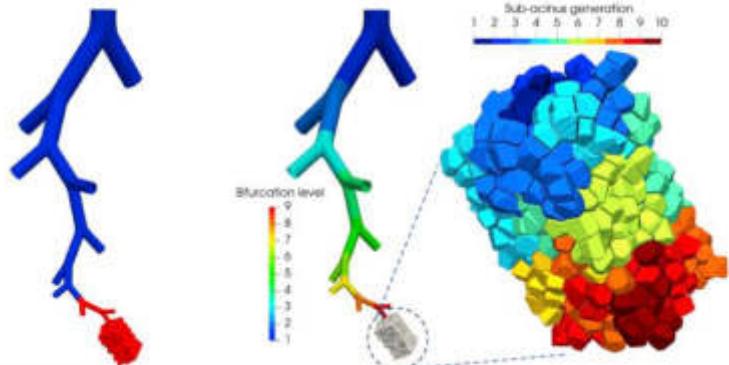
The Multiscale Challenge: *In silico* Approaches



Deep Lung *in silico* Models



(a)



Koullapis et al., J. Aerosol Sci. 144 (2020)

Hofemeier et al., Eur. J. Pharm. Sci. 113 (2018)

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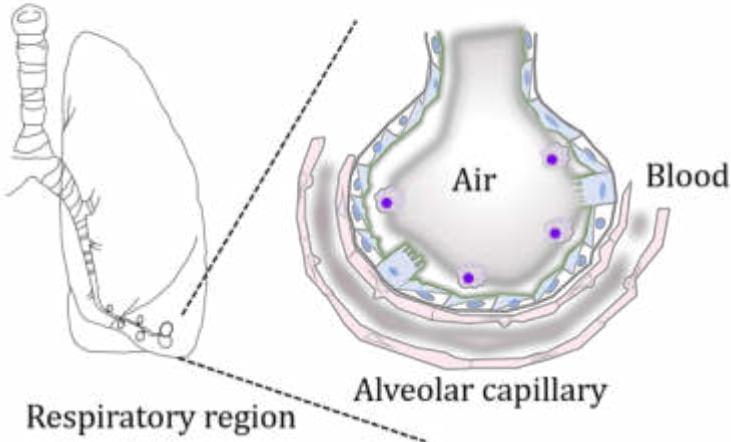
In vitro (and *in silico*) Models....

“All models are wrong but some are useful.”

- George E.P. Box

Preclinical *in vitro* Gold Standards

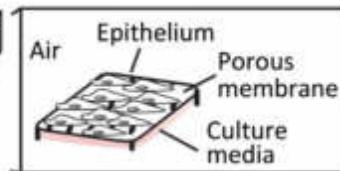
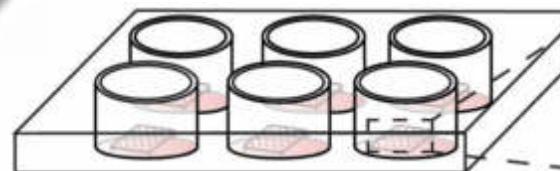
In vivo



Liquid-Liquid Interface (LLI)



Air-Liquid Interface (ALI)

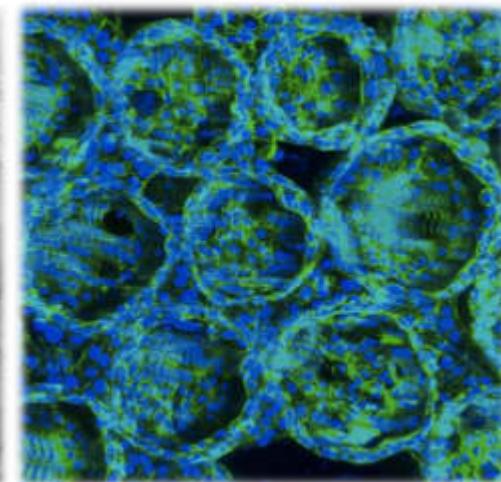
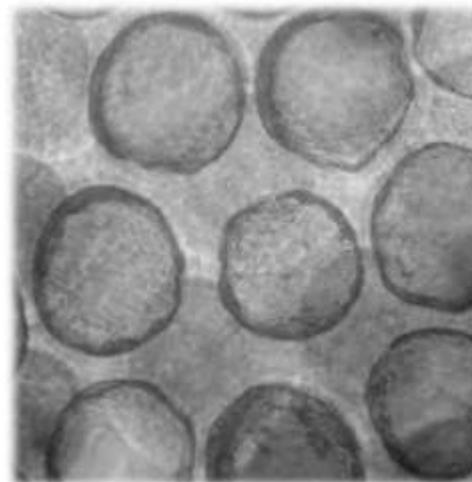
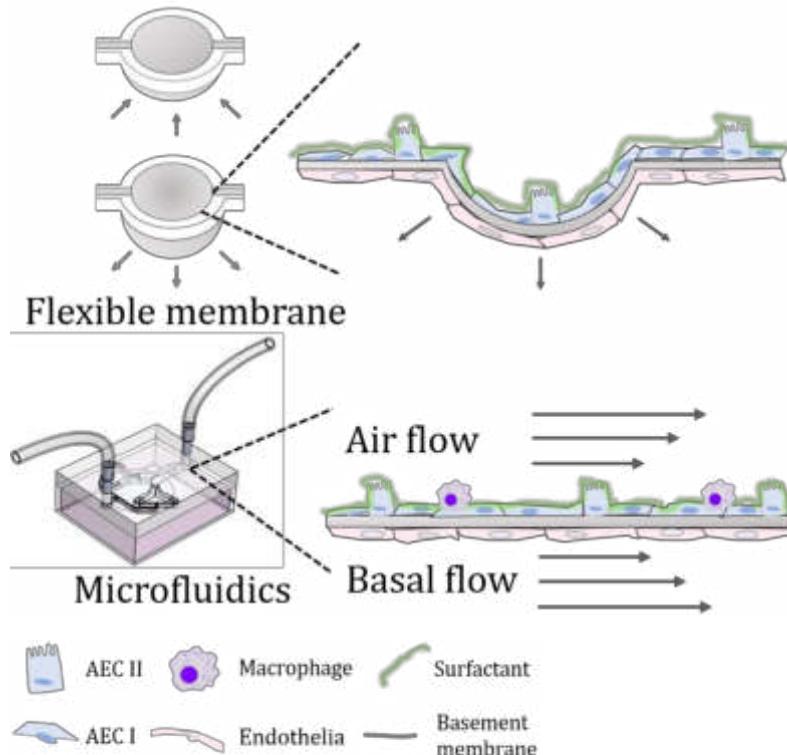


Transwell (inserts)

Limitations...

- Scale (size)
- Anatomy
- Flow physiology
- Aerosol exposure

Advanced *in vitro* Pulmonary Platforms



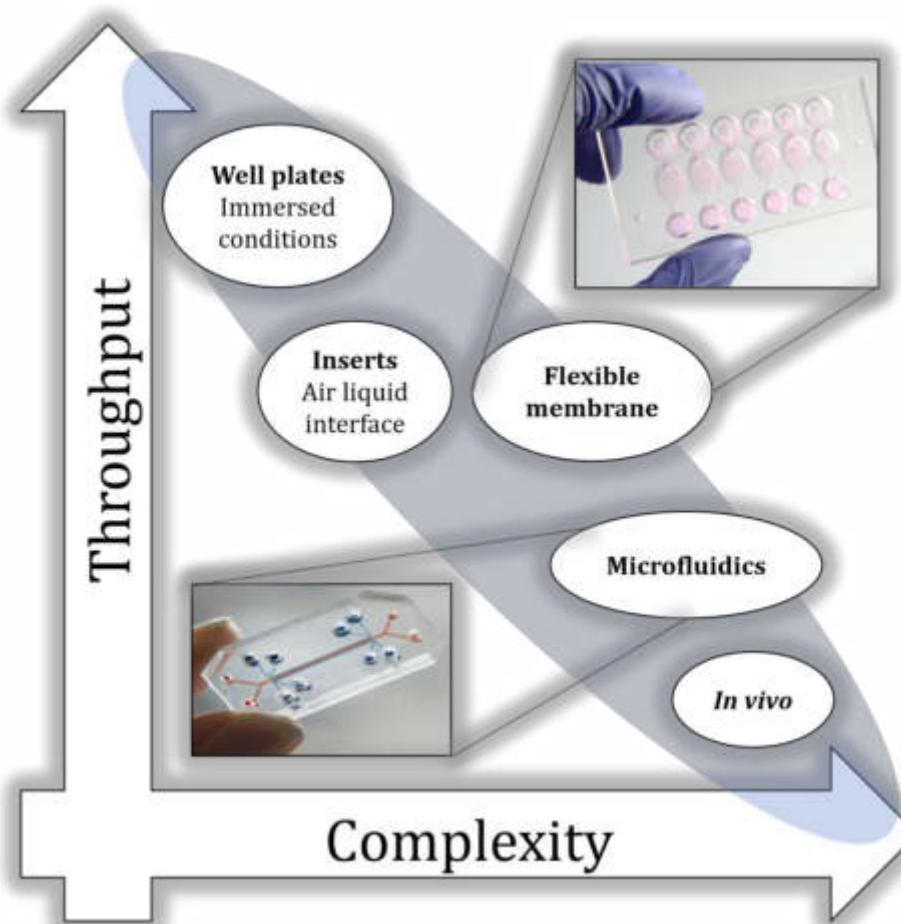
Alveolar epithelium in hydrogel structure (Huan et al. PNAS 2021)

Artzy-Schnirman et al., under review

Stucki et al., *Lab on Chip* (2015)

Guenat & Bethiaume, *Biomicrofluidics* (2018)

Evolution of preclinical *in vitro* Platforms



Our Biomimetic *in vitro* Approaches & Scales

<10 mm



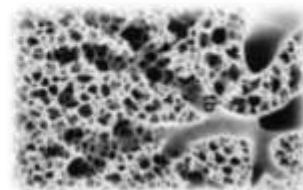
Upper Airways

<2 mm



Mid Bronchi

<500 to 5 μm



Bronchioles

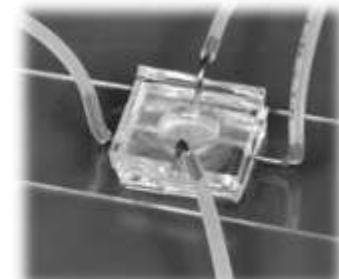
Acinar Airways



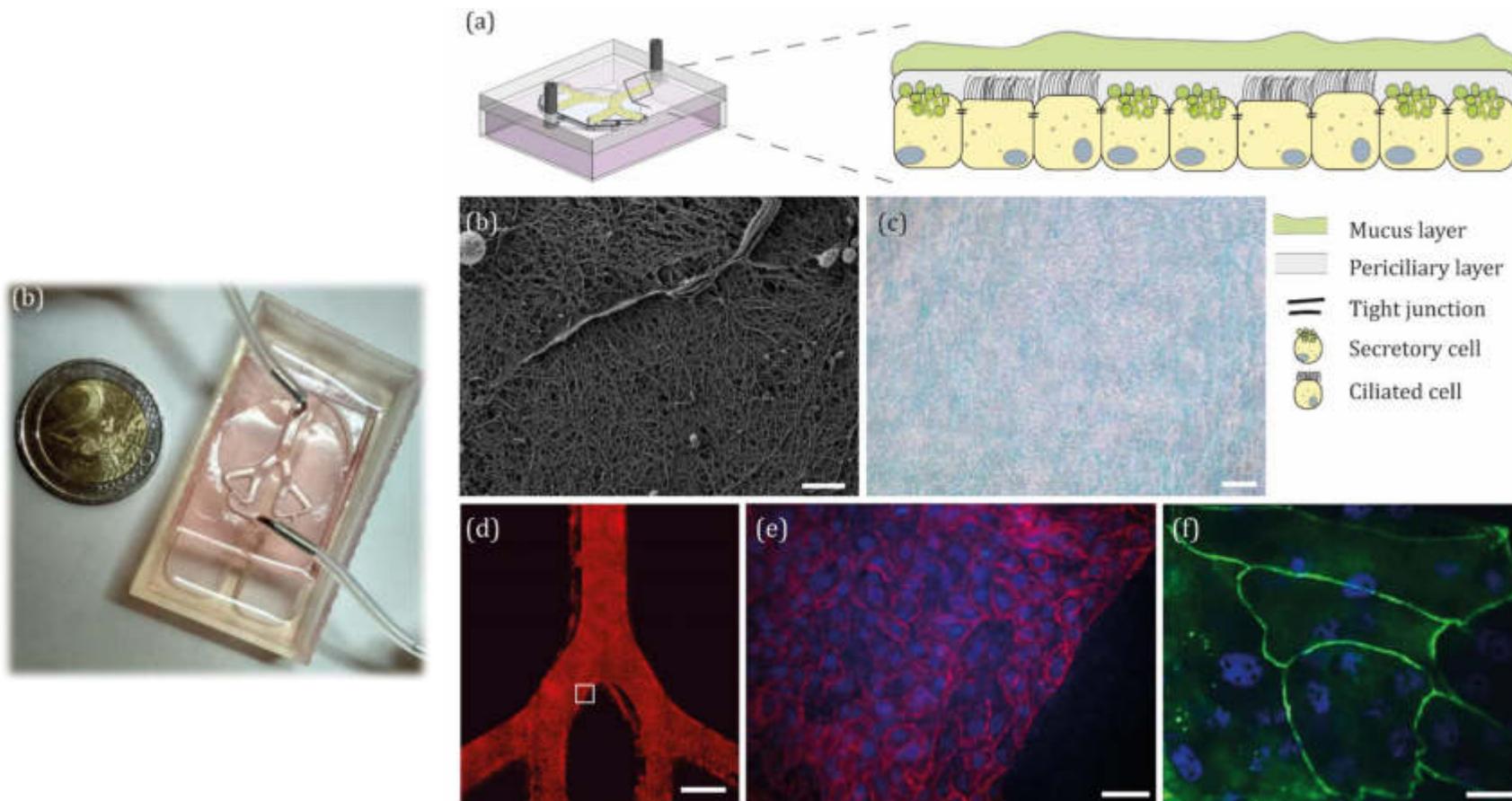
3D Printing



microfluidics



Bronchial Epithelium at Air-Liquid Interface (ALI)

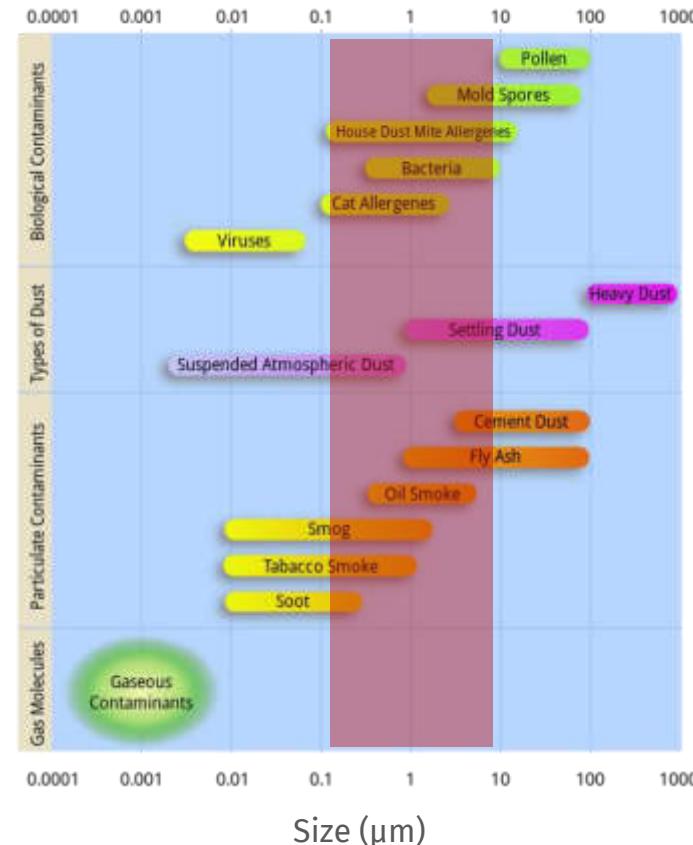


Particulate Matter (PM) Exposure in the Lungs

Adverse impacts on health...

- Aggravated asthma
- Decreased lung function
- Cardiovascular morbidity
- Chronic Obstructive Pulmonary Disease (COPD)
- **Infectious diseases (e.g. virus-laden aerosols)**

Range of interest: 0.1-10 μm

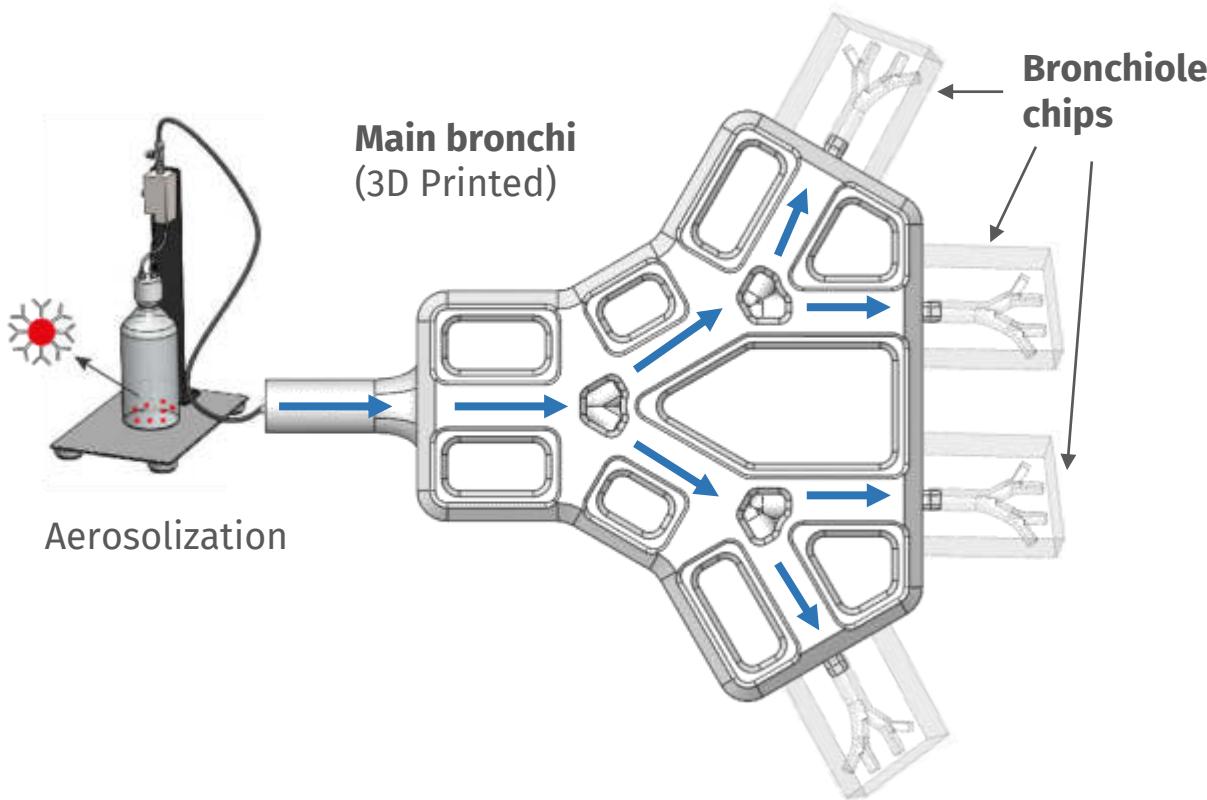


Gehr, Muehfeld, Rothen-Rutishauser & Blank. *Particle-Lung Interactions*, CRC Press (2009)

Mahto, Charwat, Ertl, Rothen-Rutishauser, Rhee & Sznitman , *Nanotoxicology* 9 (2015)

<https://upload.wikimedia.org/wikipedia/en/d/df/Airborne-particulate-size-chart.svg>

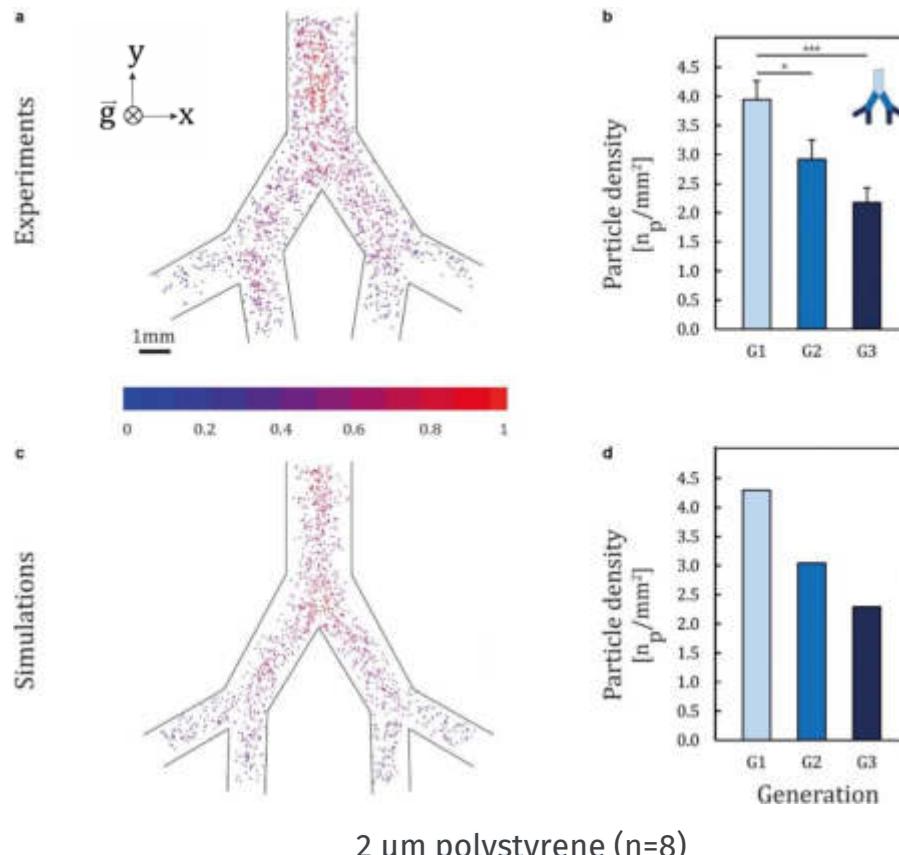
Aerosol Exposure Assays: Physiological Flows



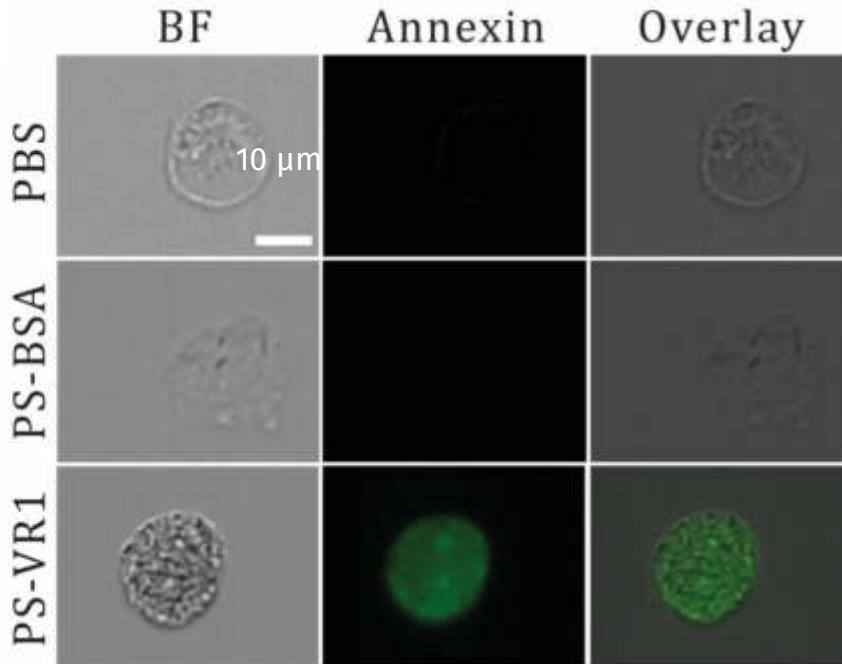
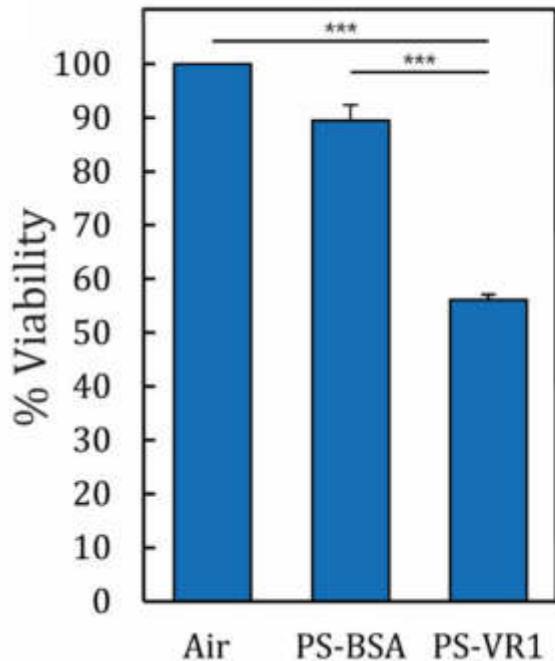
Physiological airflow matching

Airway Tree	Flow Rates (L/min)	Reynolds Number (Re)
Main Bronchi	0.2	~10-70
Chips	0.05	~1-10

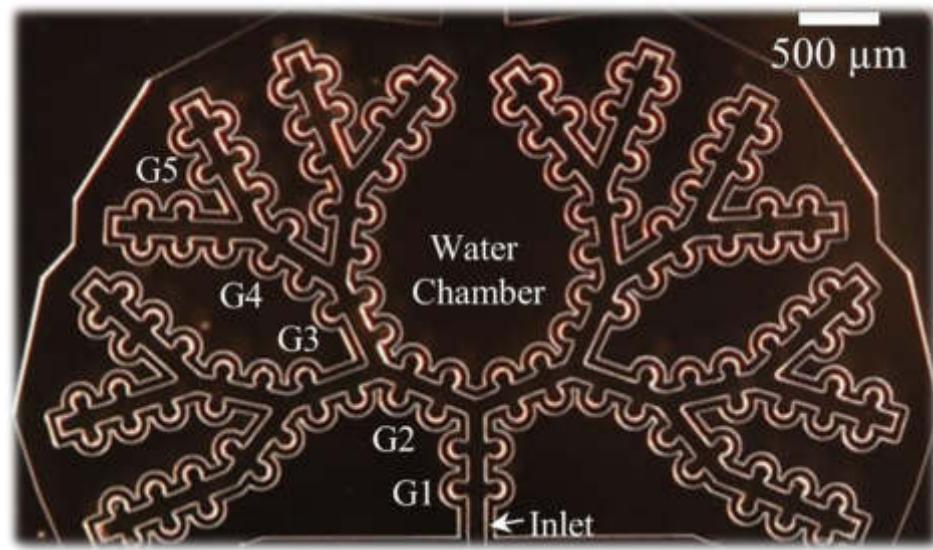
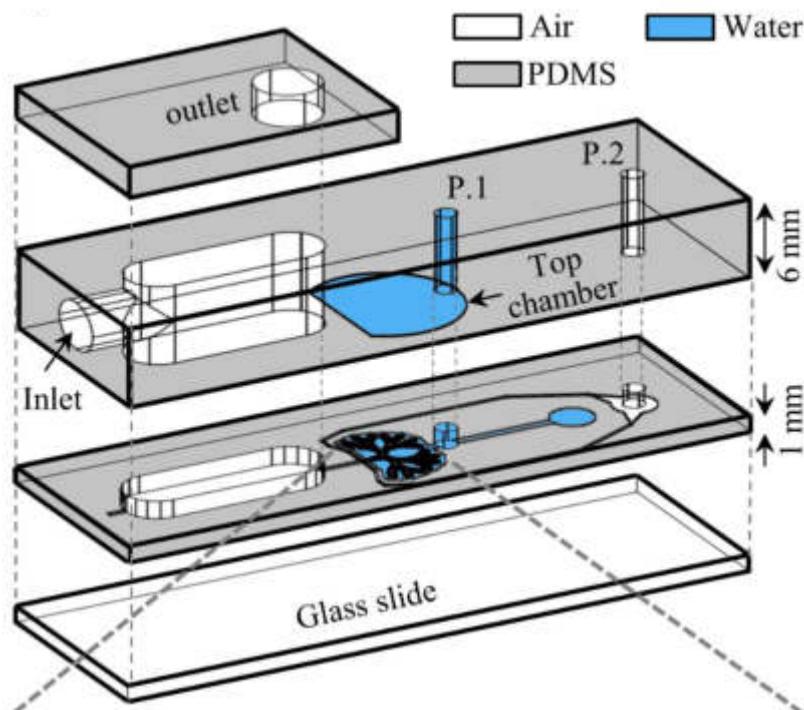
Aerosol Ensemble Deposition Patterns



Proof-of-Concept: Apoptosis in *airway-on-chip*

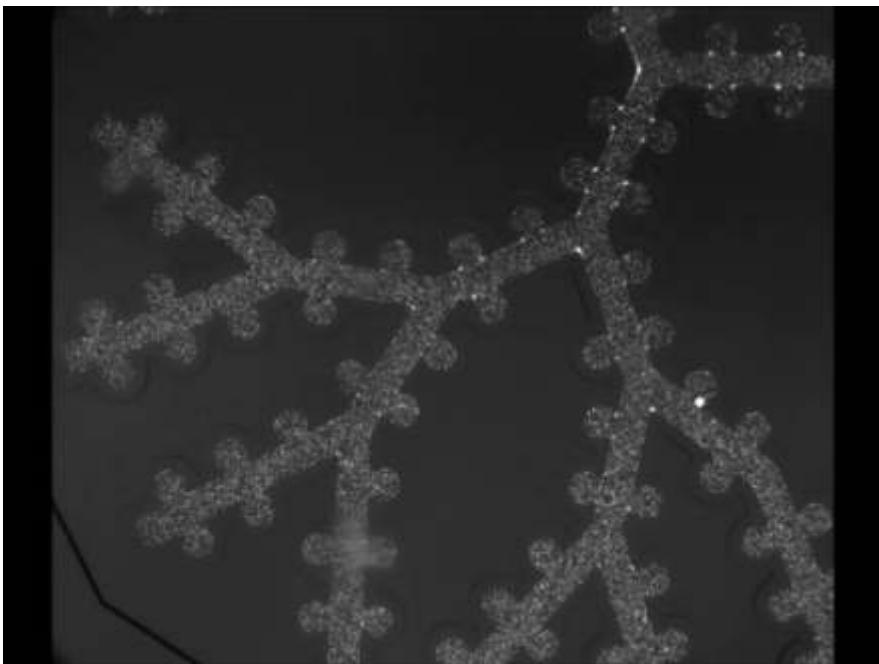


Acinus-on-Chip: a Physical Model

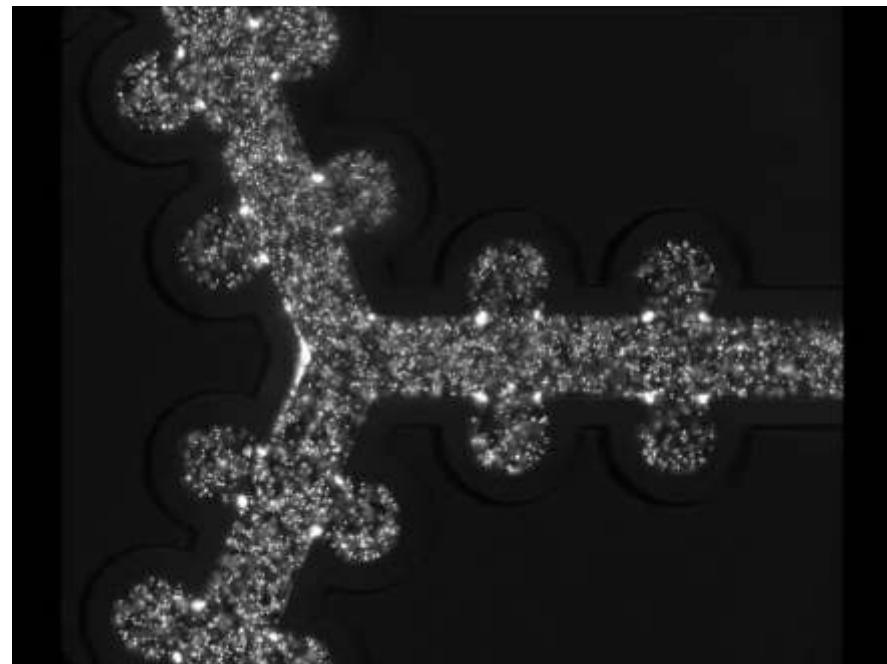


Acinus-on-Chip: Flow Visualization

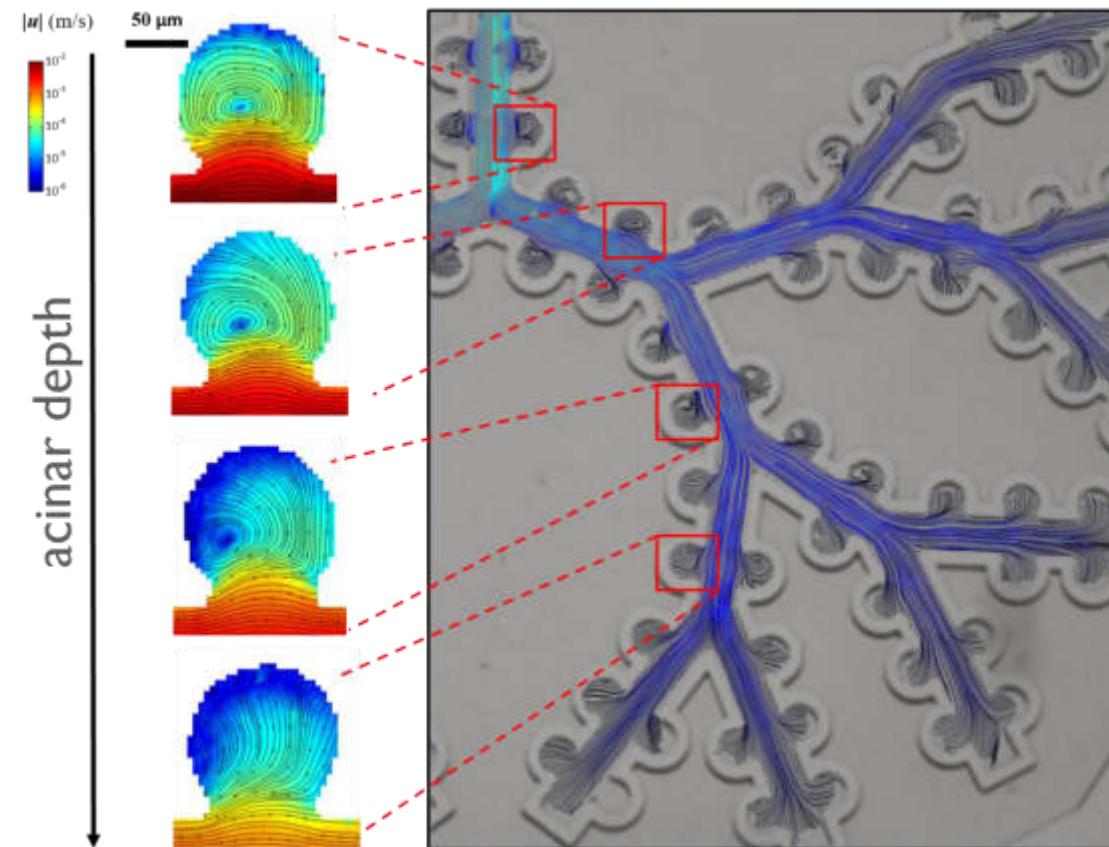
Half-tree (macro view)



Generations 1-2 (close up)



Alveolar Flows and Inhaled Aerosol Dynamics

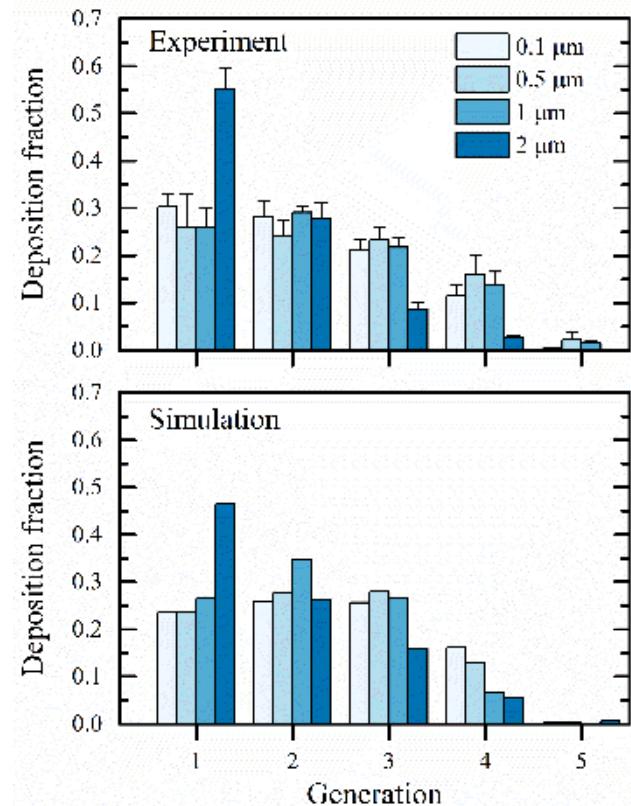
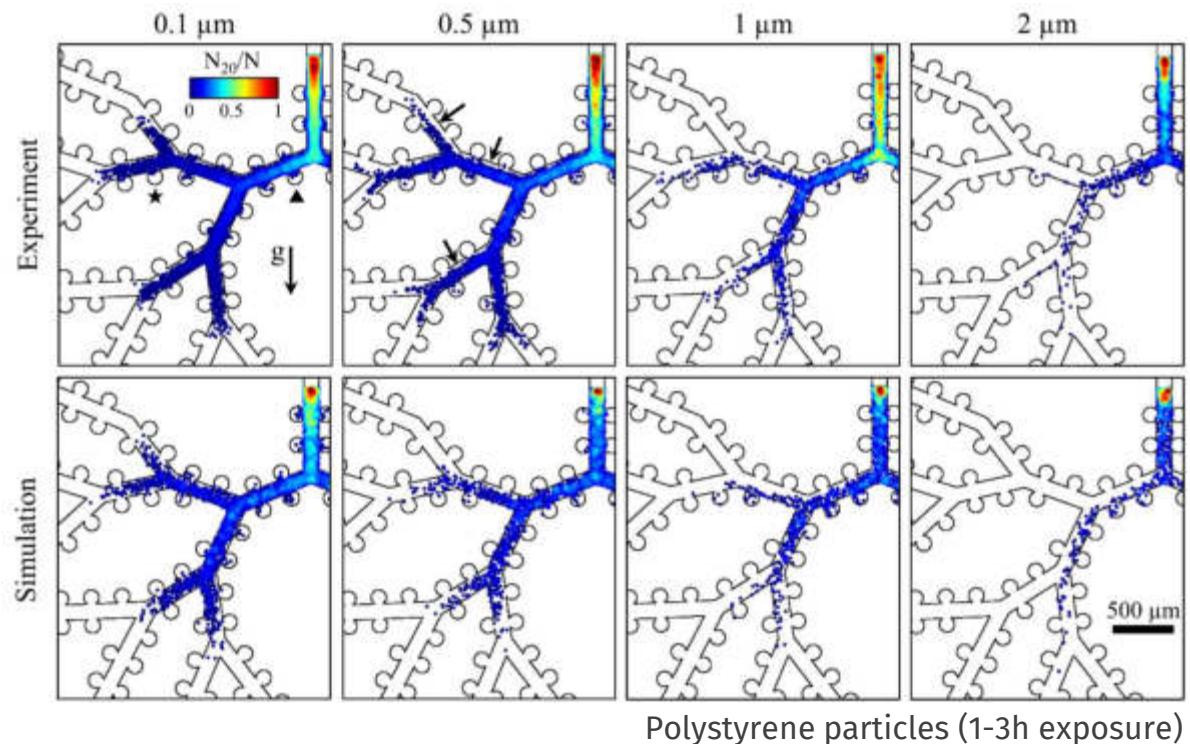


Fishler et al., *J. Biomechanics* 46 (2013)

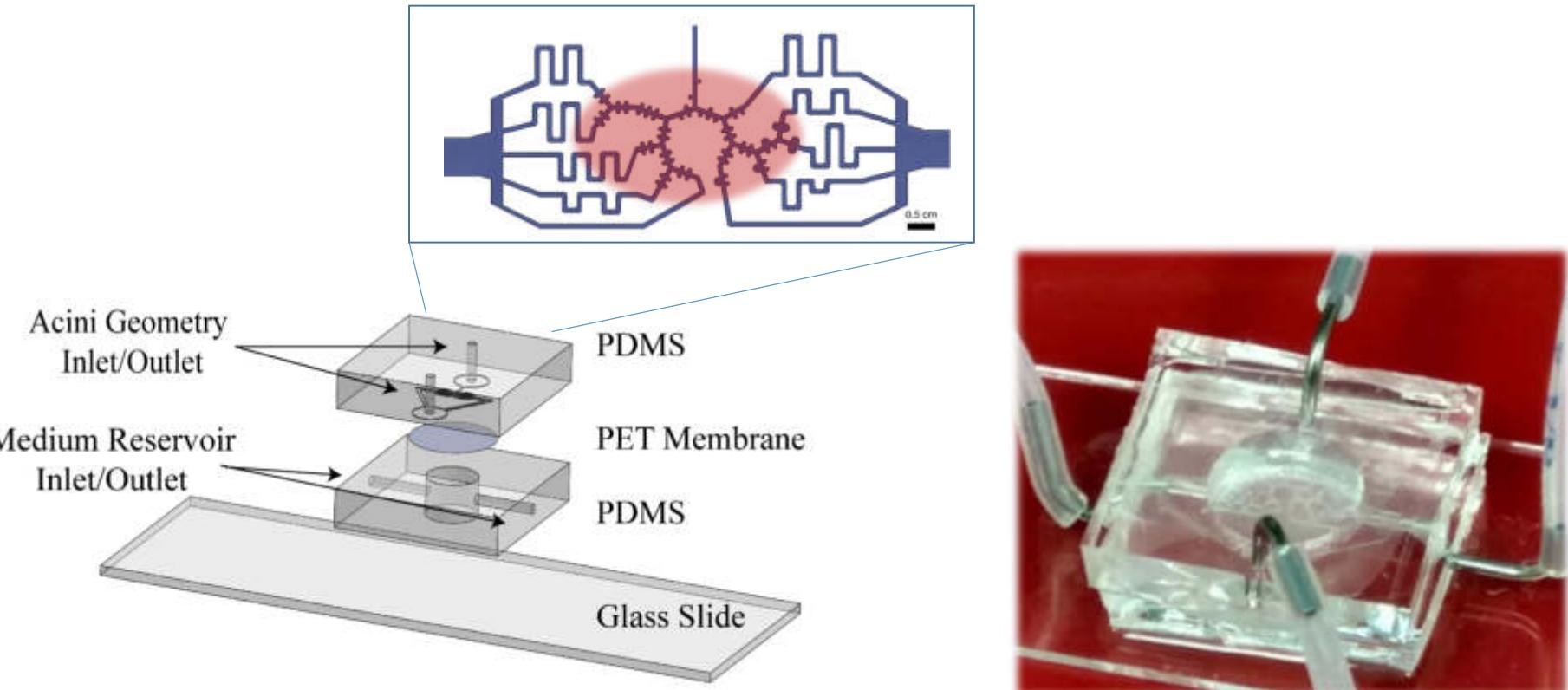
Fishler et al., *Scientific Reports* 12071 (2015)

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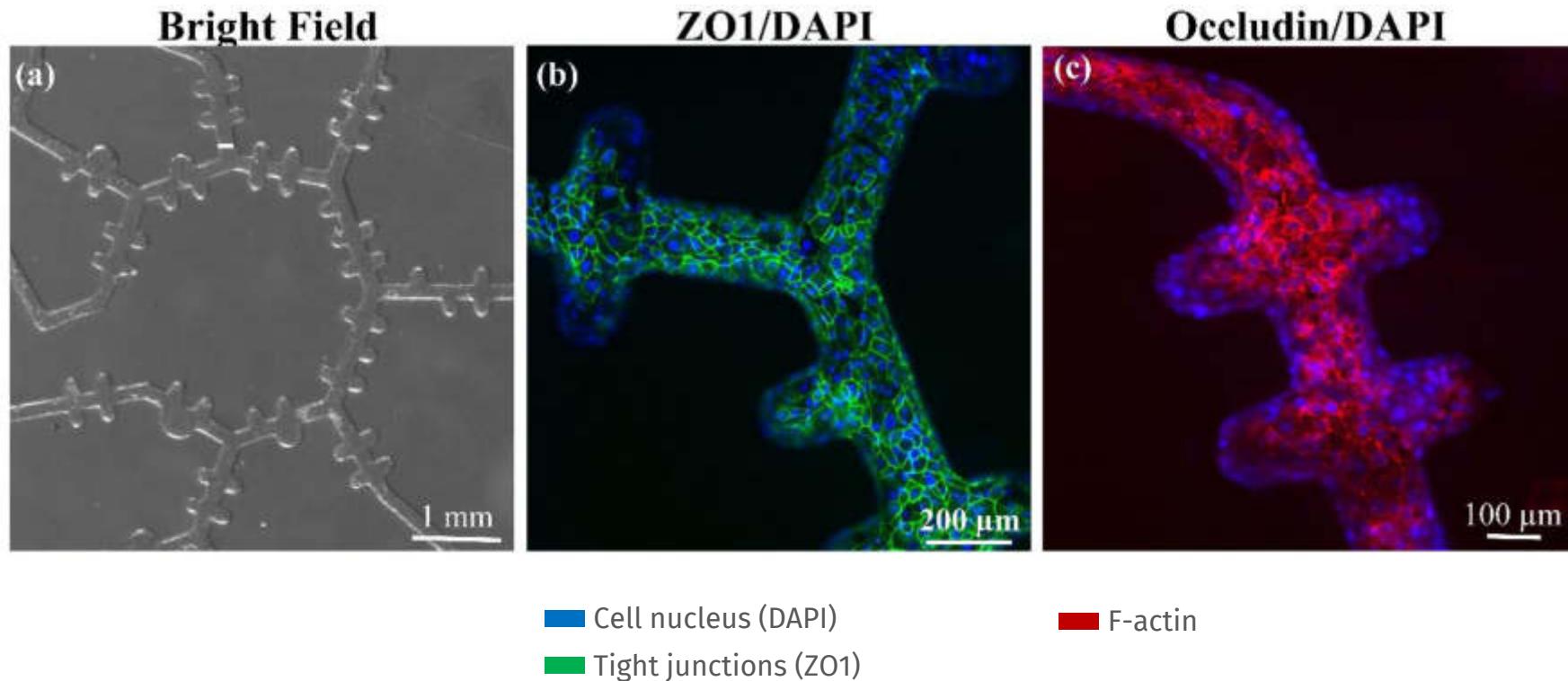
Acinus-on-Chip: In vitro Deposition Assays



Reconstructing an Alveolar Epithelial Barrier



Alveolar Epithelial Barrier (hAELVi cells)

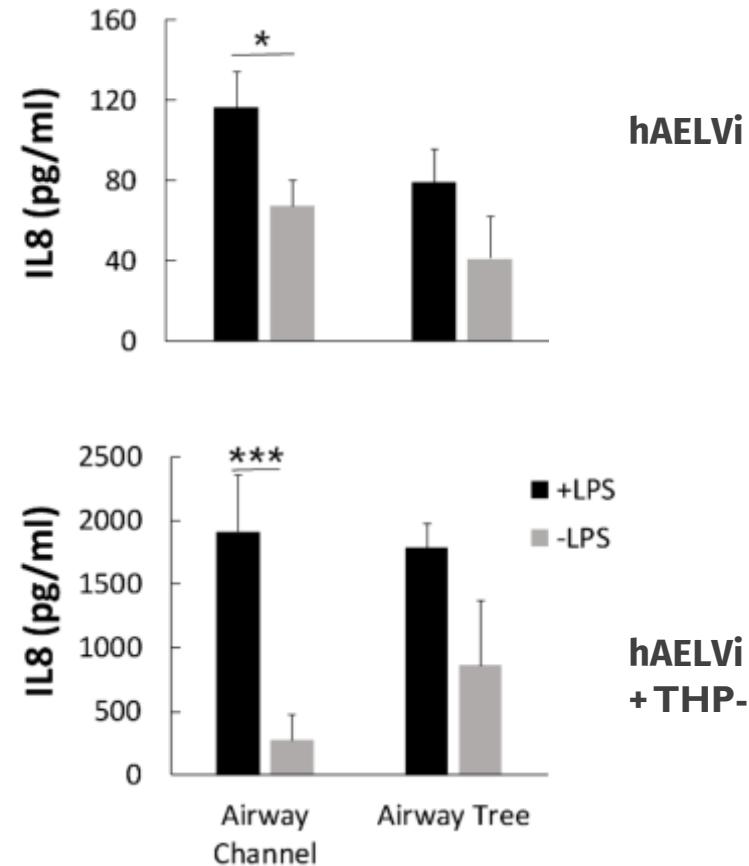
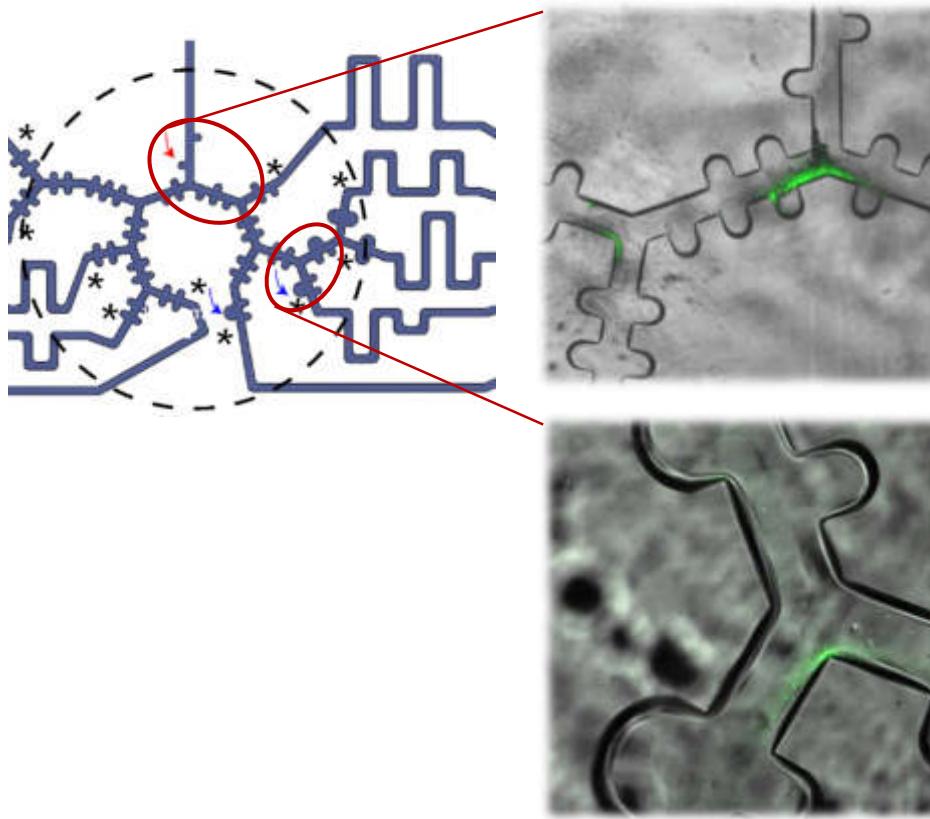


Kuehn *et al.*, ALTEX 33 (2016)

Artzy-Schnirman *et al.*, Advanced Biosystems 3 (2019)

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Aerosol Exposure Assay: onset of Bacterial Infection



Acknowledgements



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