

Bioengineering Strategies for Targeted Therapeutic Delivery to the Lungs

Josué Sznitman, Dr. Sc.

Associate Professor

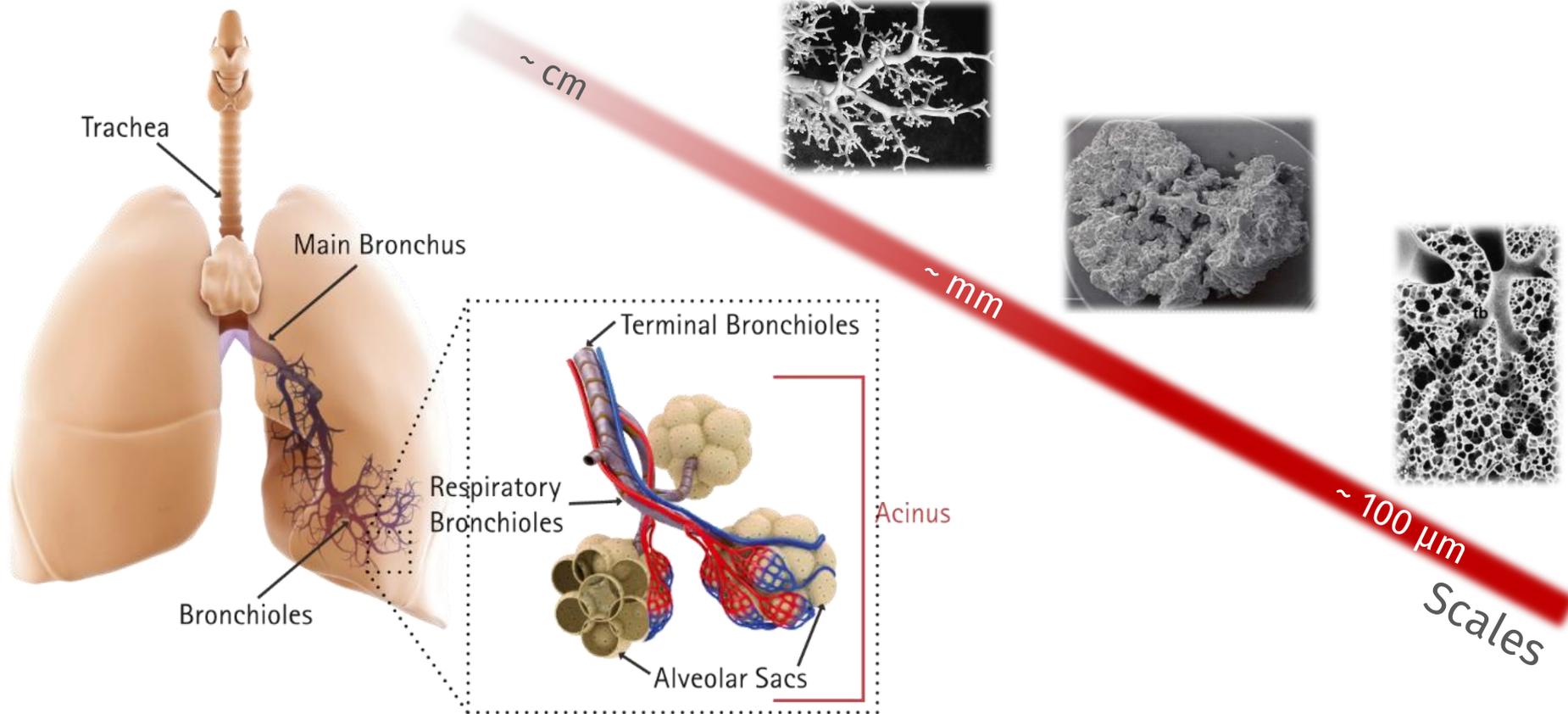
Department of Biomedical Engineering

Technion, Israel Institute of Technology

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



An Engineer's View: a Multiscale Challenge



Haefeli-Bleuer & Weibel, *Anatomical Record* 220 (1988)

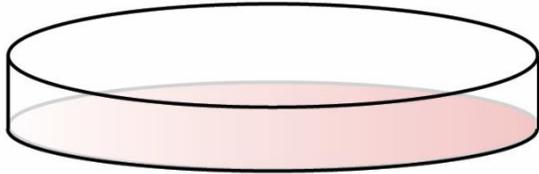
Weibel et al., *Respir. Physiology & Neurobiology* 148 (2005)

© J. Sznitman 2018

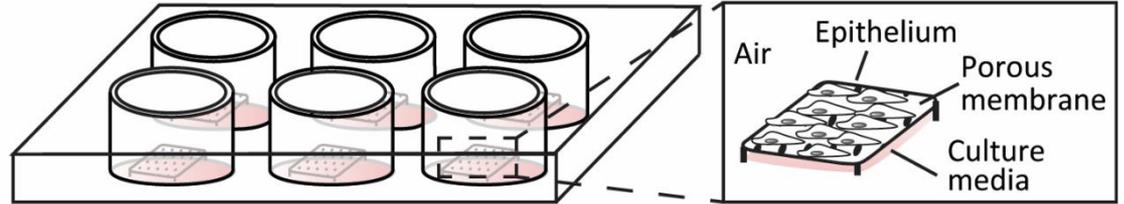
Lung-on-Chips for
In Vitro Drug Delivery Assays

Current Paradigms: *in vitro* Gold Standards

Petri dish



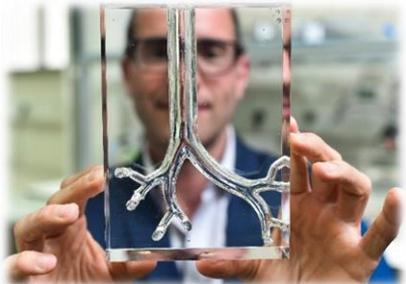
Transwell (plate inserts)



Limitations...

- Scale (size)
- Anatomy
- (Air)flow physiology
- Aerosol exposure conditions
- etc.

Our Biomimetic *in vitro* Approaches



Upper Airways



Mid Bronchi

Focus

A person wearing blue gloves is holding a clear airway model with a pink branching structure, likely representing bronchioles.

Bronchioles



Acinar Airways



centimer

3D Printing

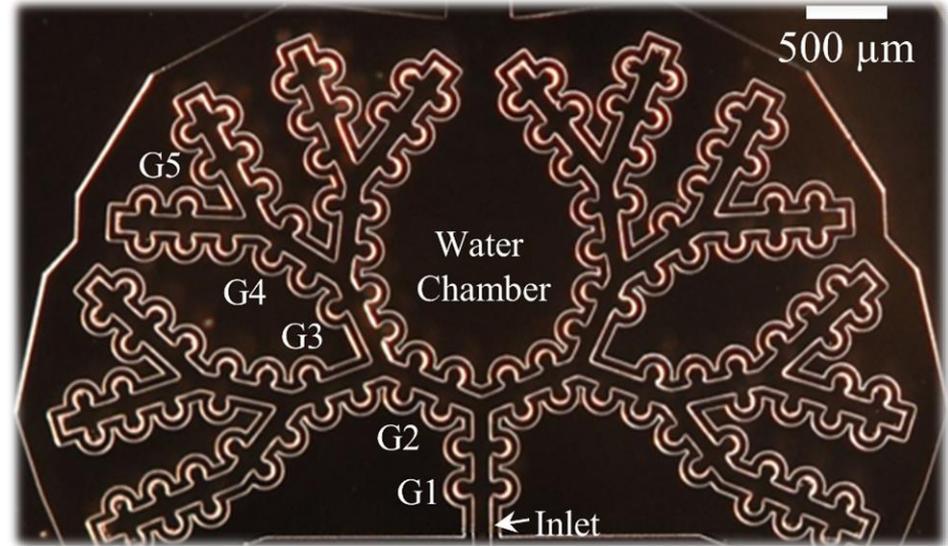
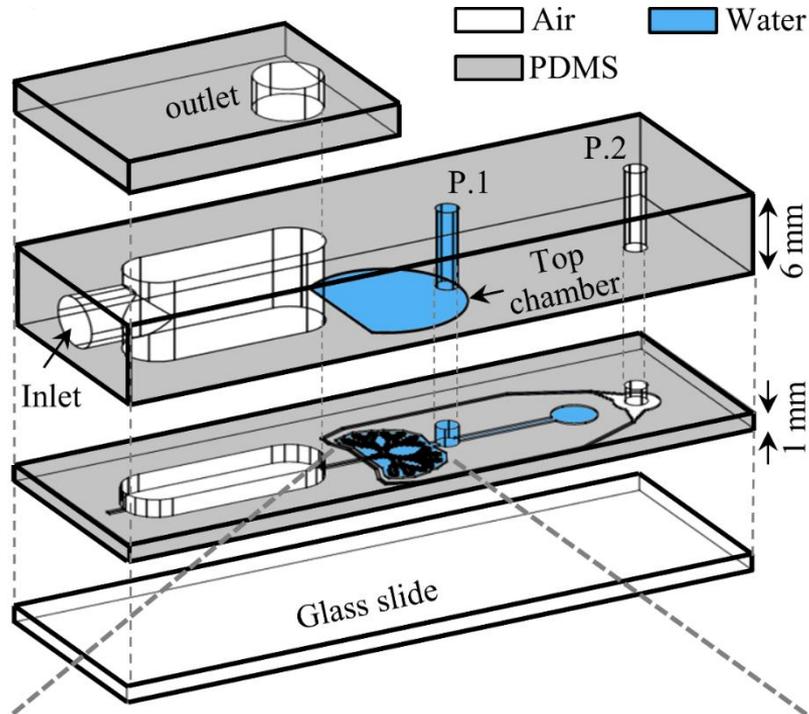
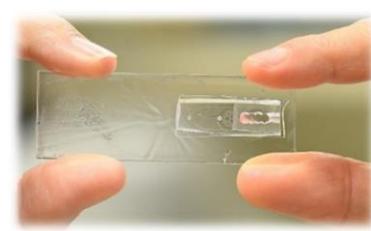


millimeter

microfluidics

<1mm to 5 μ m

Tackling the Deep(er) Lungs: *Acinus-on-Chip*



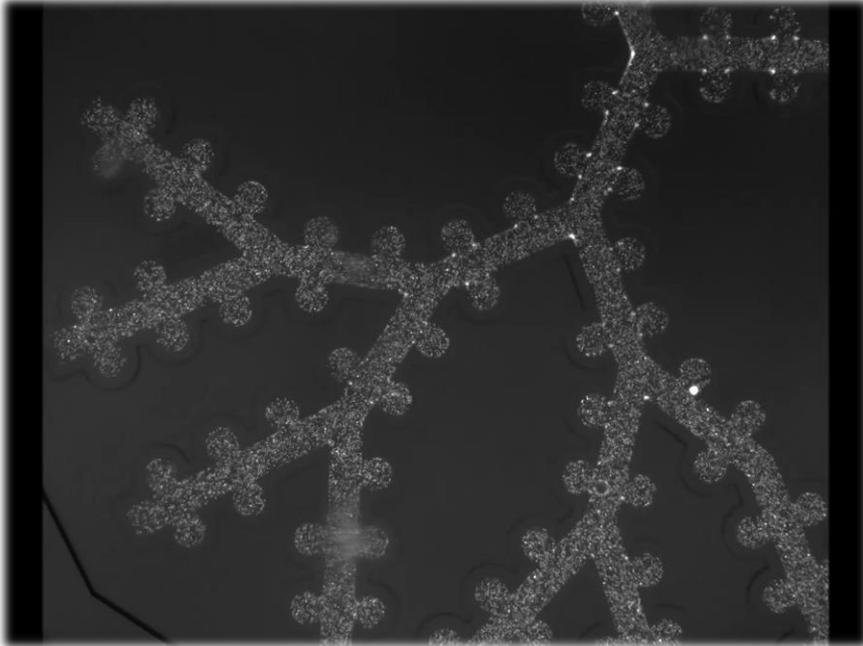
Fishler *et al.*, *Scientific Reports* 12071 (2015)

Fishler and Sznitman, US Patent 9659508B2 (2017)

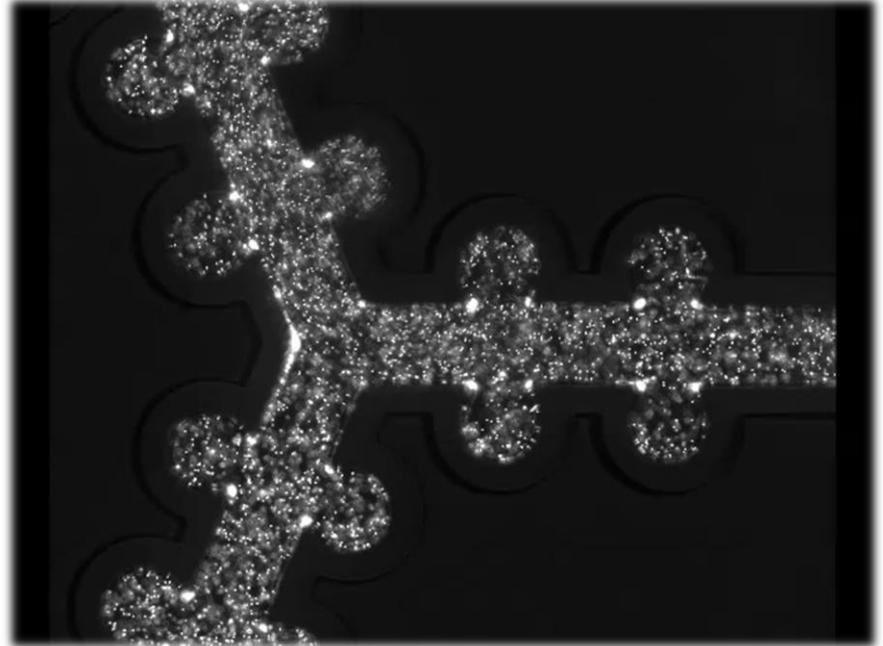
Fishler *et al.*, *Journal of Biomechanics* 50 (2017)

Acinus-on-Chip: Flow Visualization

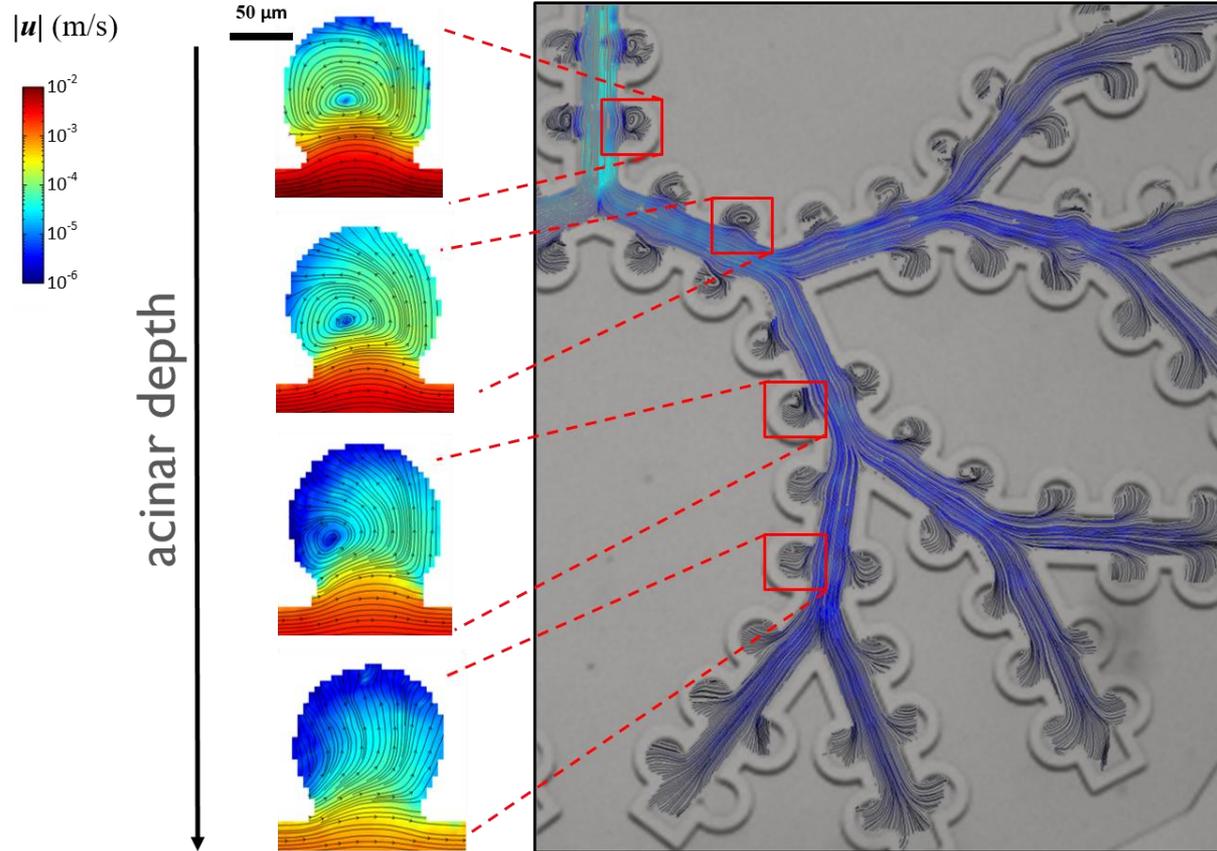
Half-tree (macro view)



Generations 1-2 (close up)



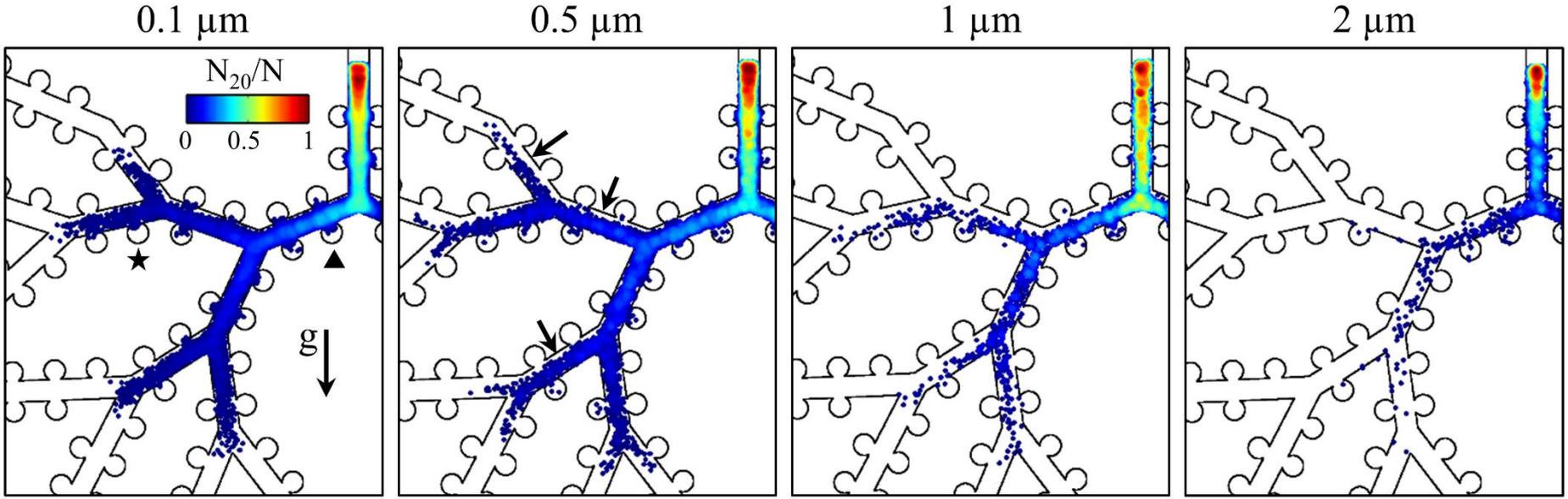
Alveolar Flow Cascade



Fishler et al., *Journal of Biomechanics* 46 (2013)

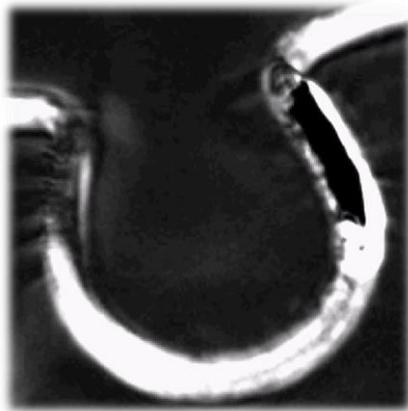
Fishler et al., *Journal of Biomechanics* 50 (2017)

In vitro Deposition Assays

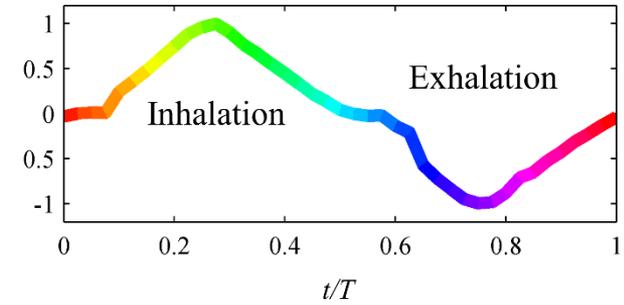
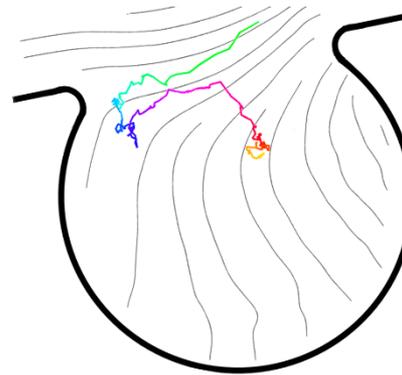
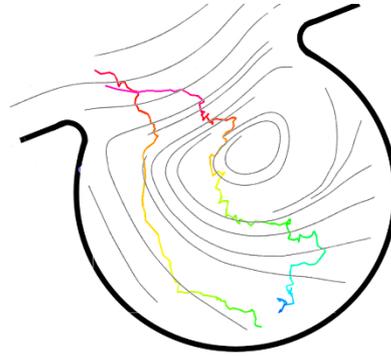


Polystyrene particles (1-3h exposure)

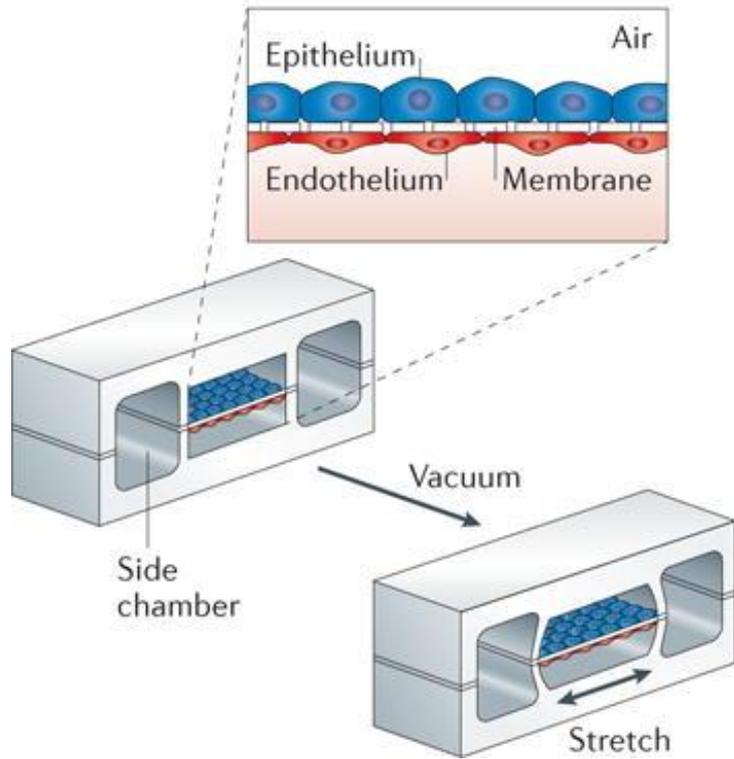
Time-Resolved Airborne Particle Tracking



Airborne smoke
(~0.1-1 μm)

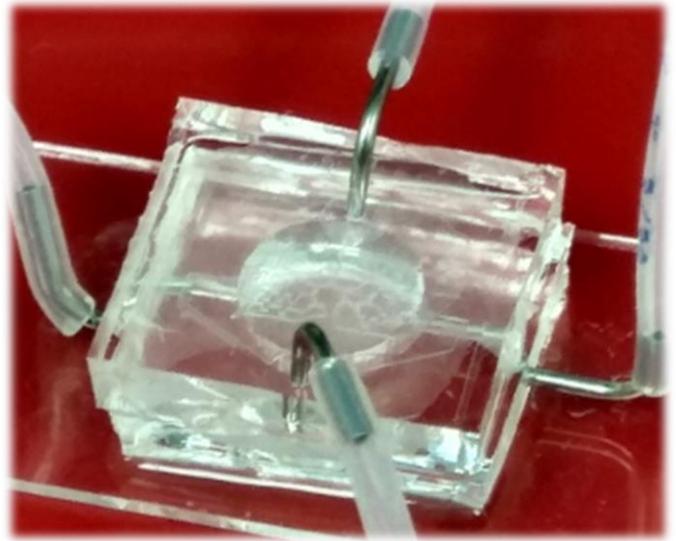
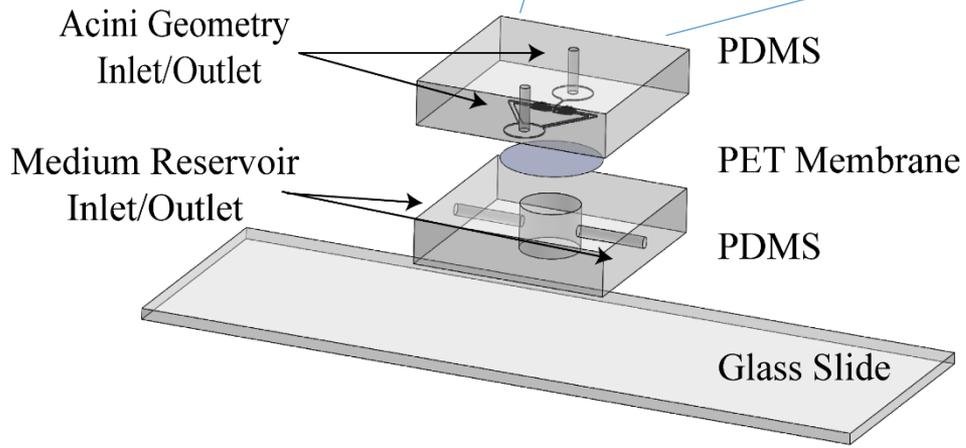
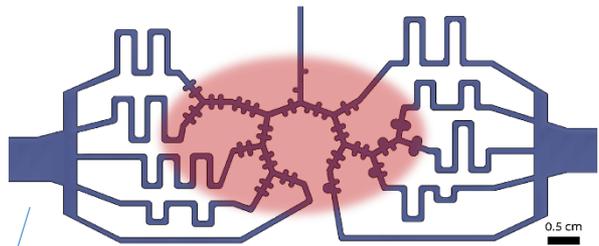


Stretching & Straining: a Multiscale Challenge

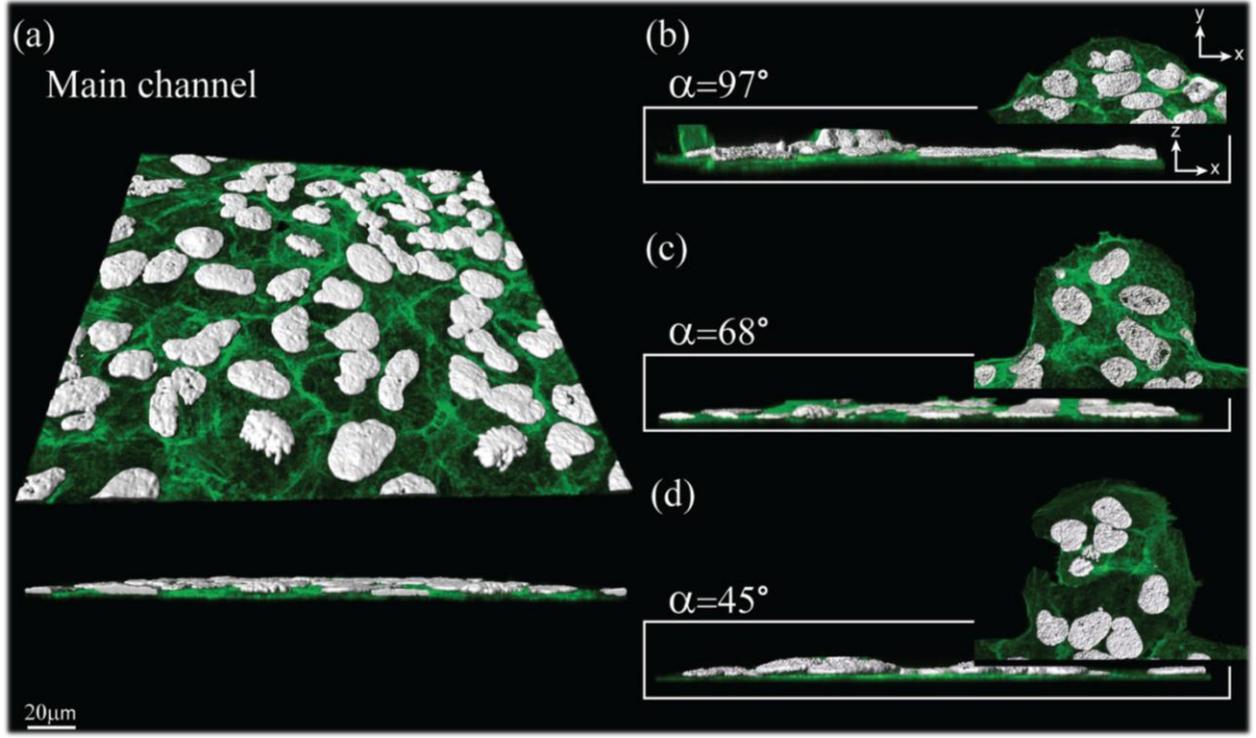
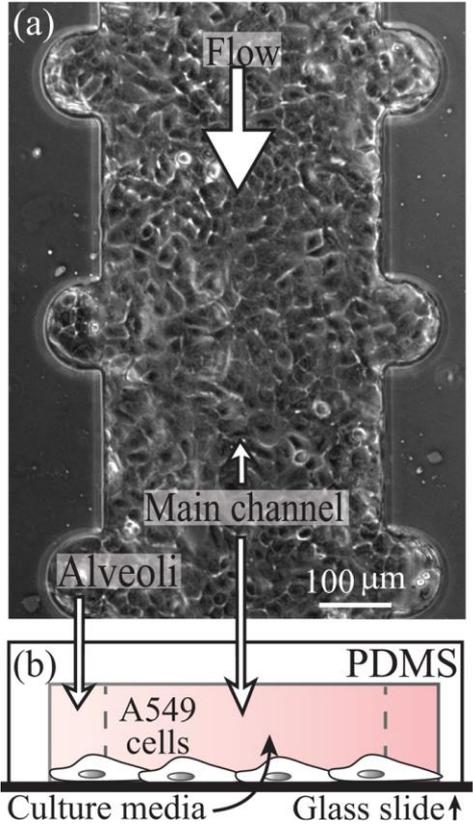


**a channel
vs. a Tree**

Reconstructing an Alveolar Epithelial Barrier



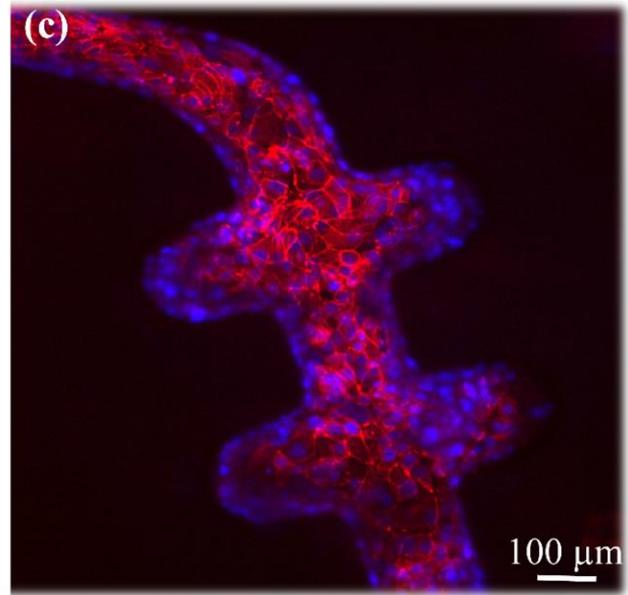
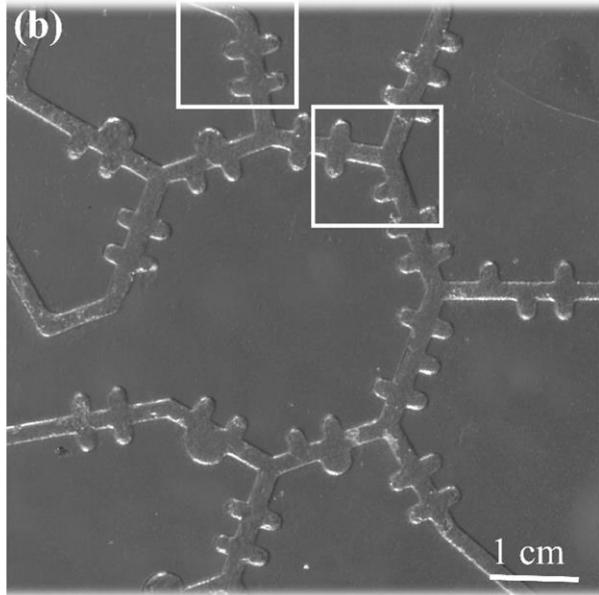
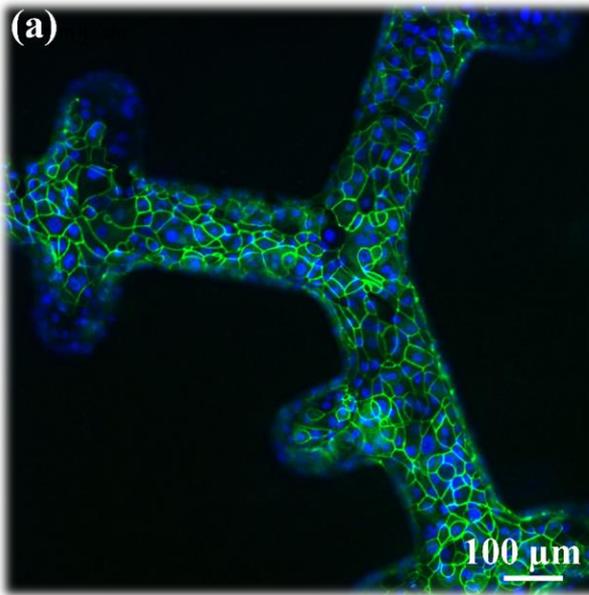
Monolayers of Alveolar Epithelial Cells (A549)



Kumar Mahto et al., *Am. J. Physiol. – Lung Cell Mol. Physiol.* 306 (2014)

Tenenbaum Katan et al., *Biomicrofluidics* 9 (2015)

Alveolar Epithelial Barrier (hAELVi cells)

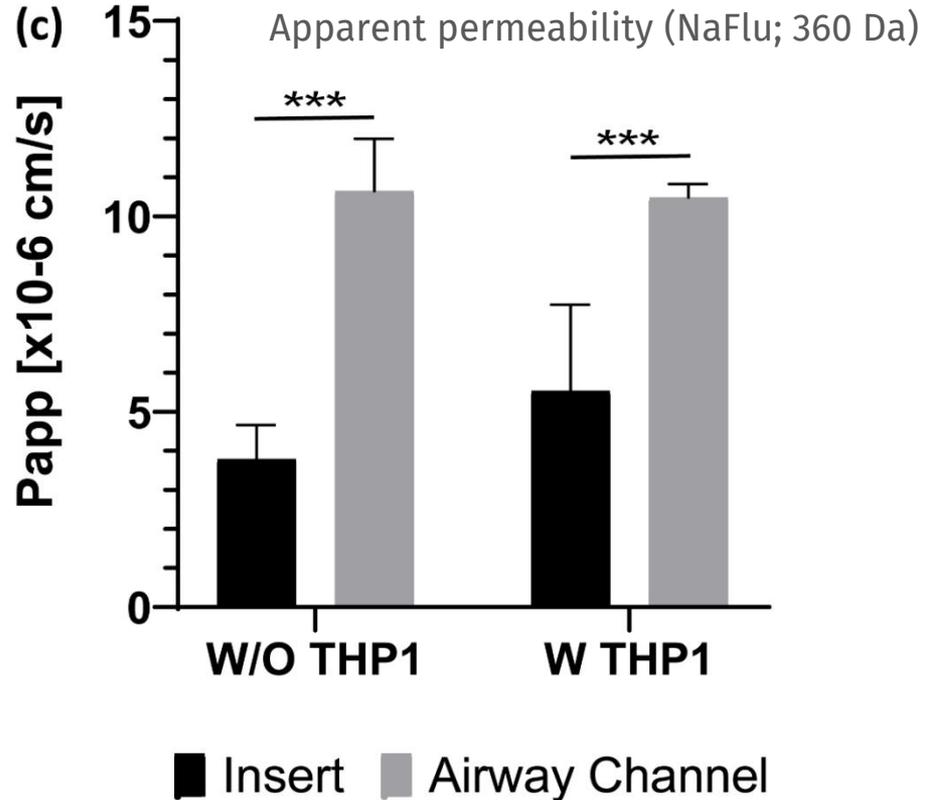
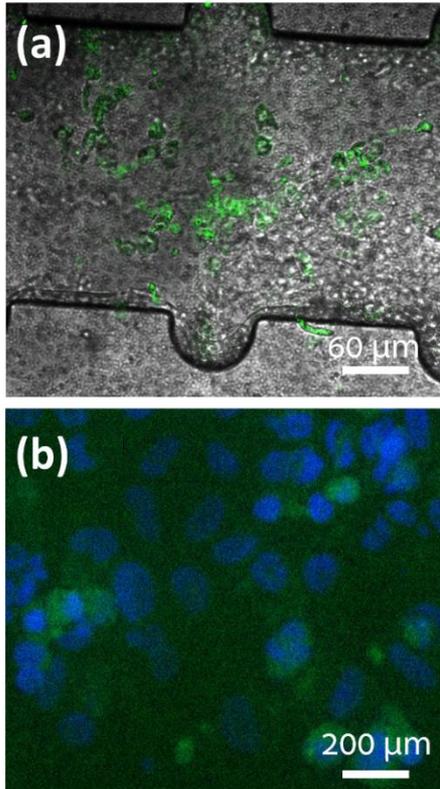


- Cell nucleus (DAPI)
- Tight junctions (ZO1)

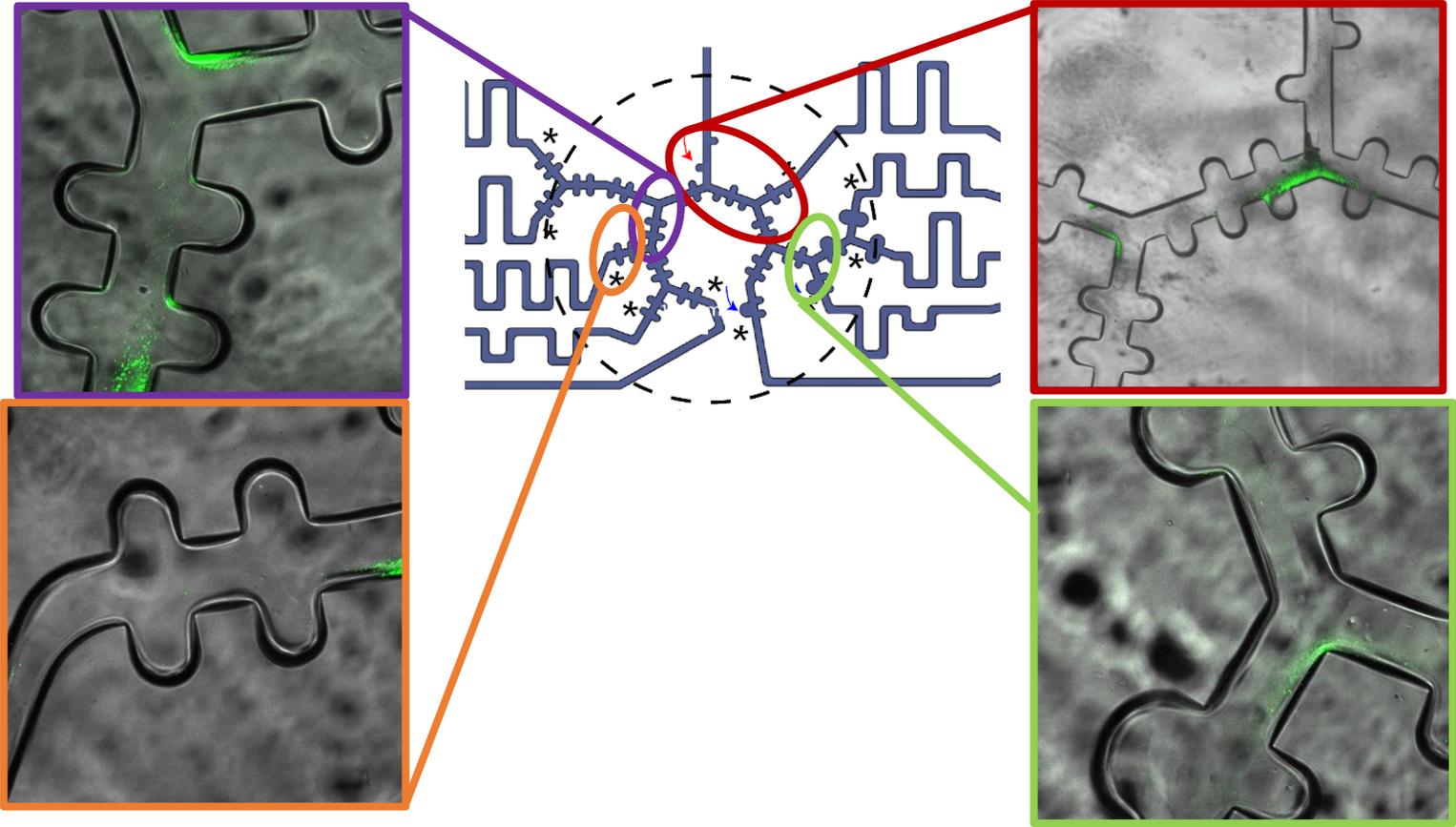
- Cell nucleus (DAPI)
- F-actin

Kuehn *et al.*, *ALTEX* 33 (2016)
Artzy-Schnirman *et al.*, *Advanced Biosystems*, under review.

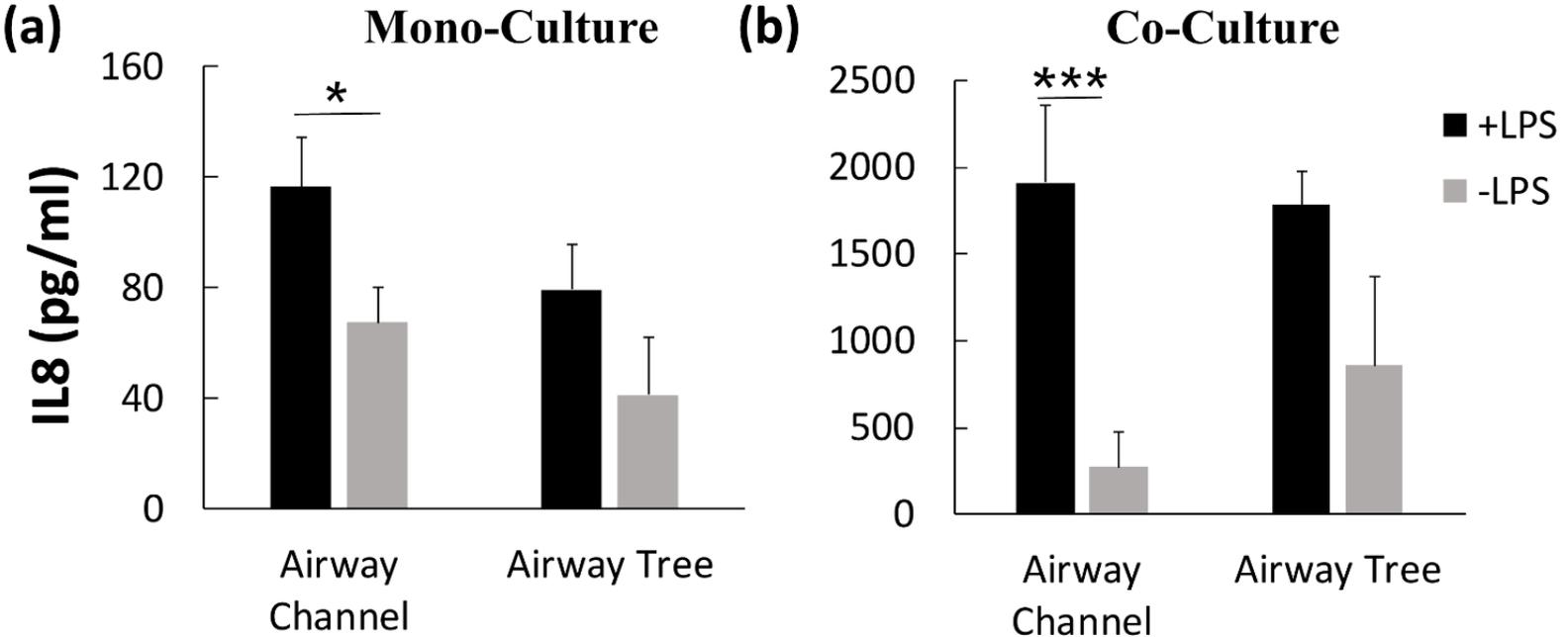
A Functional Epithelial Barrier: w/o Macrophages



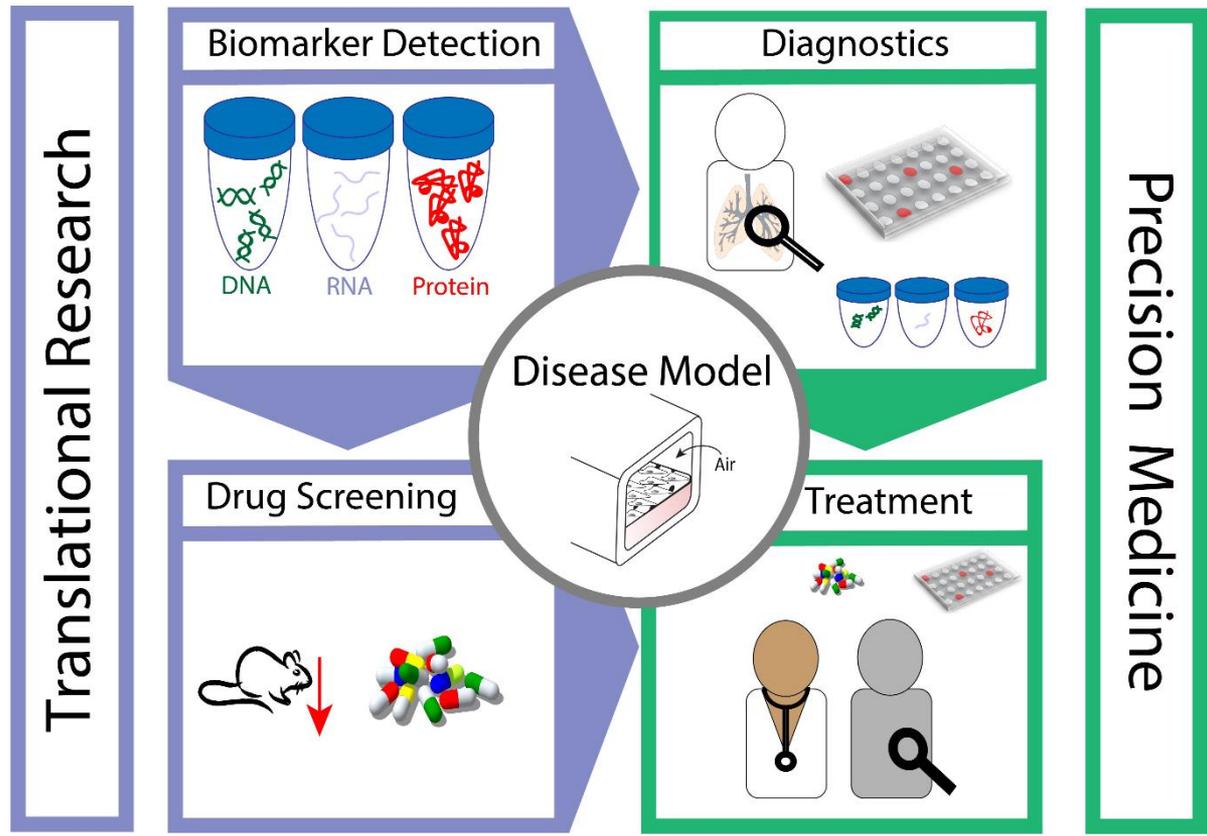
Proof-of-Concept: Aerosol Exposure Assay



Proof-of-Concept: Bacterial Inflammation Exposure



A (Cautious) Vision for *in vitro* Platforms...



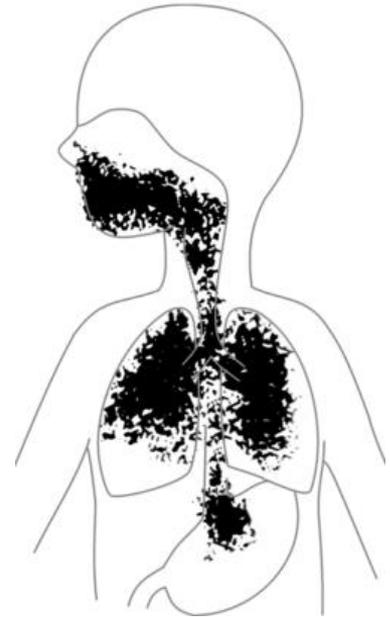
Targeting Aerosol Delivery with *In Silico* Methods

Pediatric Inhalation Therapy

- Increasing prevalence of childhood **asthma**¹
- Inhalation **guidelines** from adult studies²
- Children **dosages** adapted w/ body weight³
- **Low deposition** outcomes⁴ (~5-40%)

recommended by the manufacturers in the UK is 40 mg (500,000 IU) every 12 h for patients with bodyweights of ≤40 kg and 80 mg (1 million IU) every 12 h for patients with bodyweights of >40 kg [1]

medscape.com



Radiolabeled aerosols⁵
(nebulizer)

¹ Akinbami et al., *Pediatrics* 137 (2016)

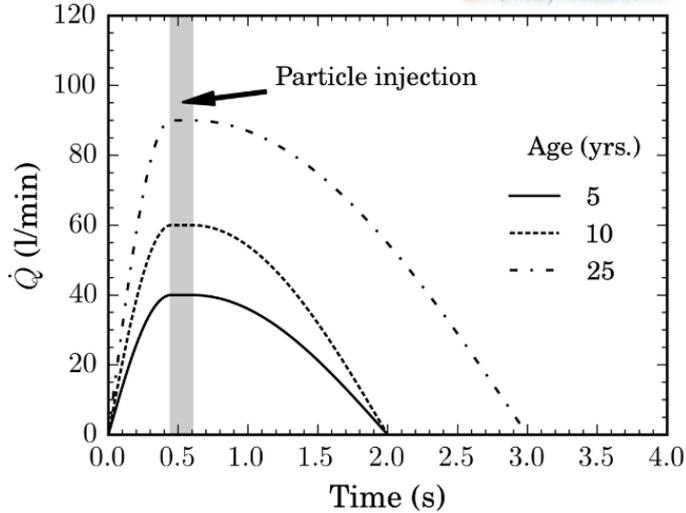
² Kwok & Chan, *Adv. Drug Deliv. Rev.* 73 (2014)

³ Batchelor & Marriott, *Br. J. Clin. Pharmacol.* 79 (2015)

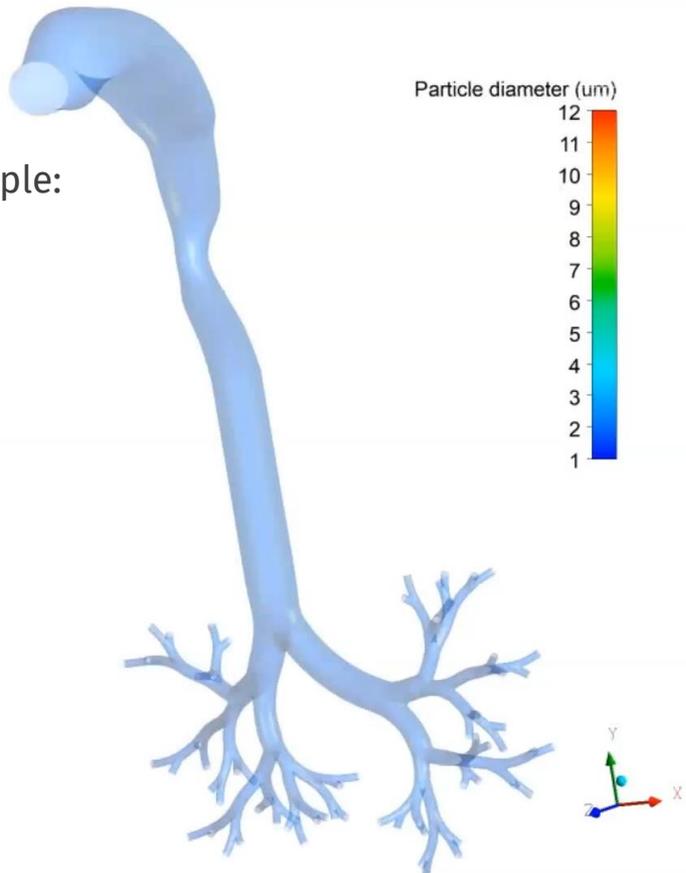
⁴ Schueepp et al., *Resp. Med.* 103 (2009); ⁵ Erzinger et al., *J. Aerosol Med.* 20 (2007)

Aerosol Inhalation: Computational Fluid Dynamics

Dry Powder Inhaler

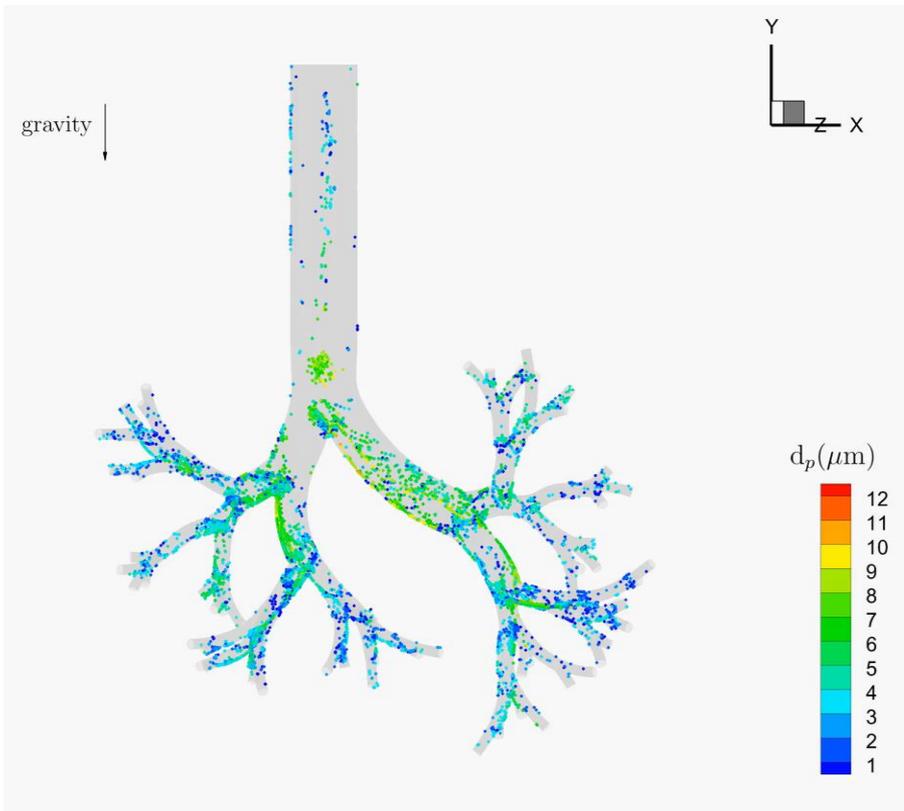
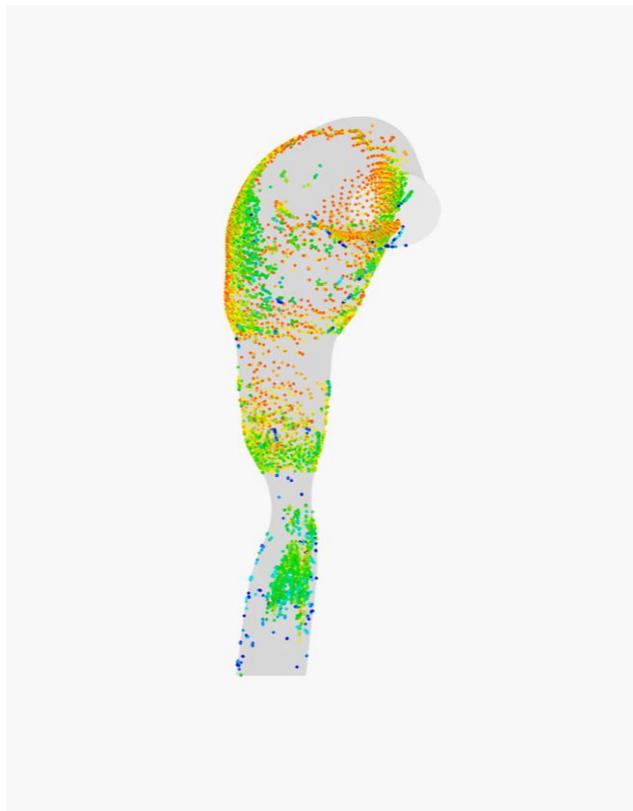


Example:
5 y.o.



Amirav et al., *Ped. Pulm.* 39 (2005)
Das et al., *PLoS One* 13 (2018)

Deposition Pattern: DPI (5 y.o.)



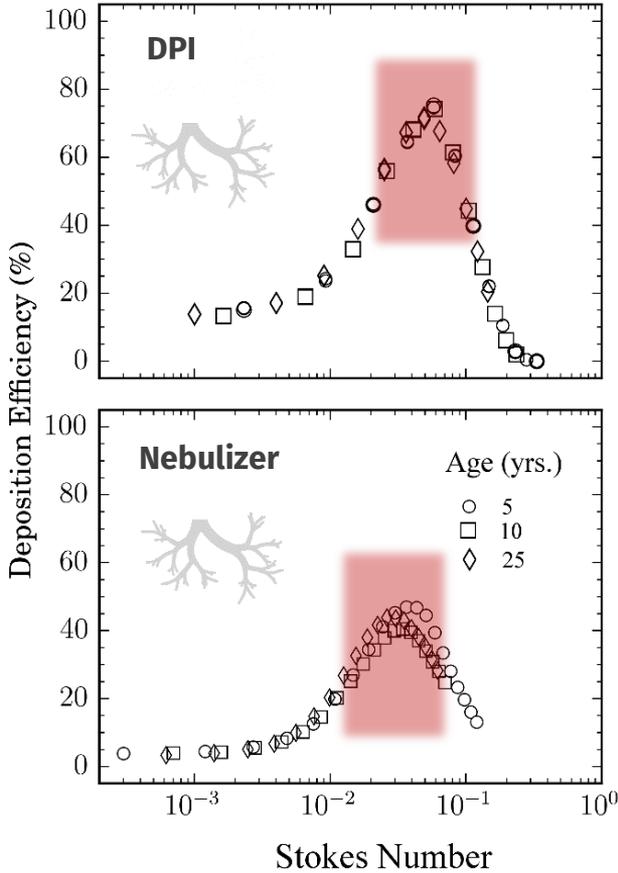
Optimizing Upper Airway Targeting

Dimensionless particle Stokes number:

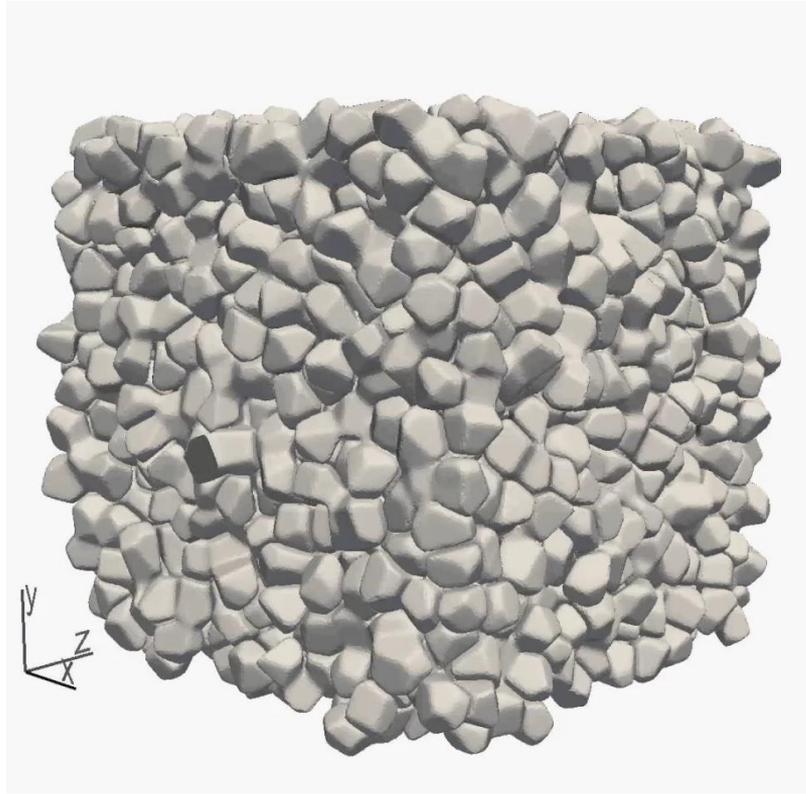
$$Stk = \frac{U_o d_p^2 \rho_p C_c}{18 \mu_f D}$$

From “*master curves*”

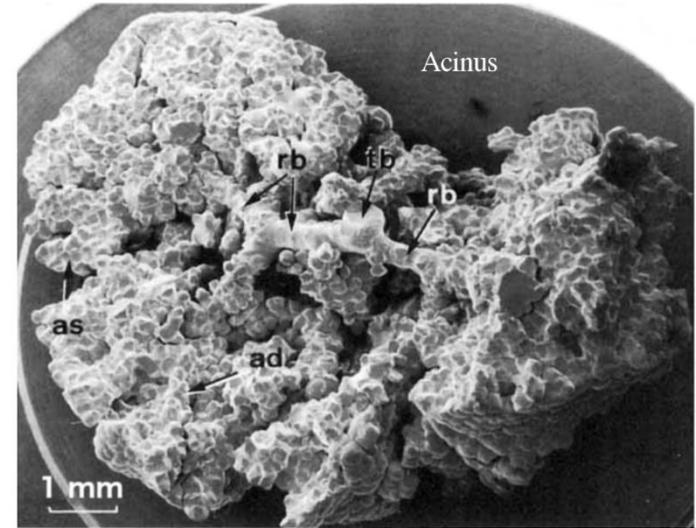
...to *optimal size range* with age.



In Silico Models of the Acinus...and Limitations



Sub-acinus



An acinus (Haefeli-Bleuer & Weibel, 1988)

Simulating Aerosol Inhalation

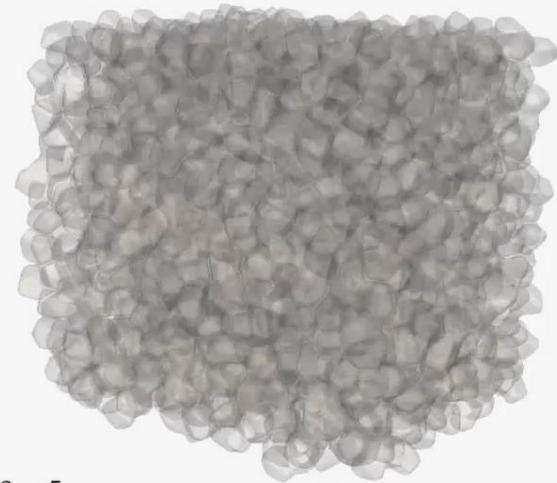
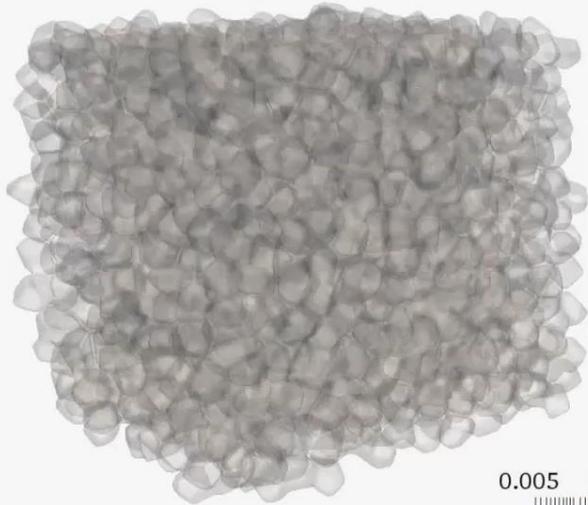
Normal Breathing

$t = 0.00$ s

Deep Inhalation

$t = 0.00$ s

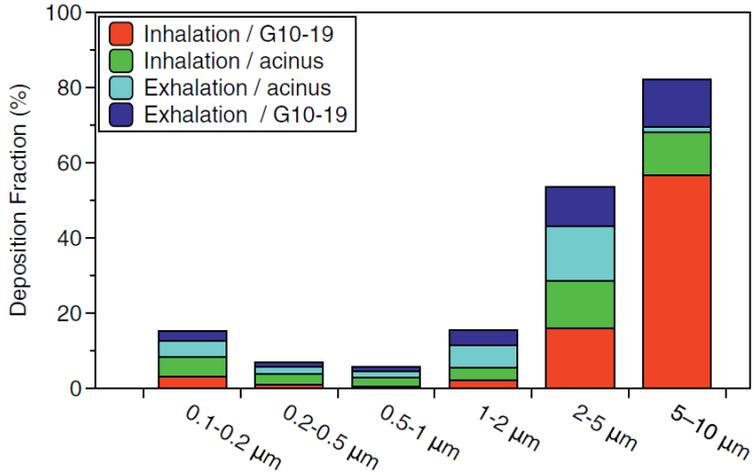
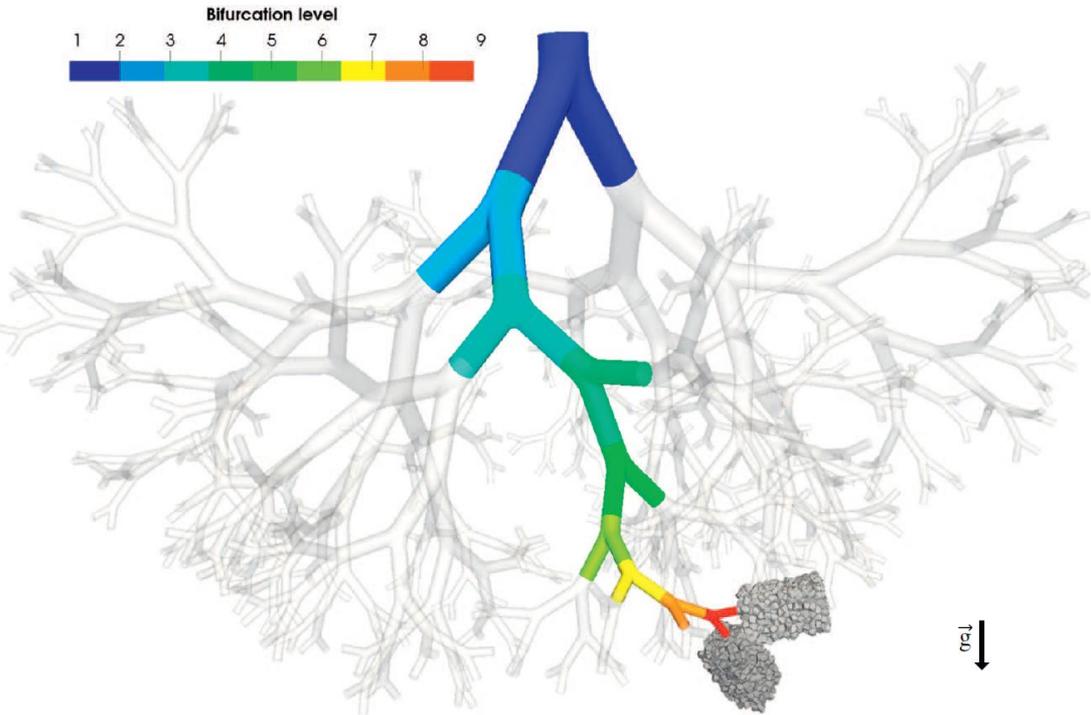
$g \rightarrow$



Diameter in μm



Returning to the Multiscale Problem...



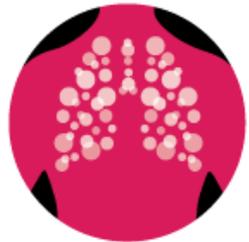
Acknowledgements



Helmholtz-Institut für Pharmazeutische Forschung Saarland



SimInhale
COST ACTION
MP1404



Russell Berrie Nanotechnology Institute
Technion - Israel Institute of Technology