

Pulmonary Immune Engineering: Multiscale Tools for Inhaled Drug Delivery

Cathy Fromen

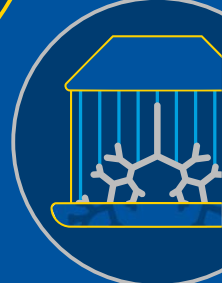
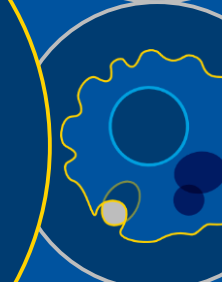
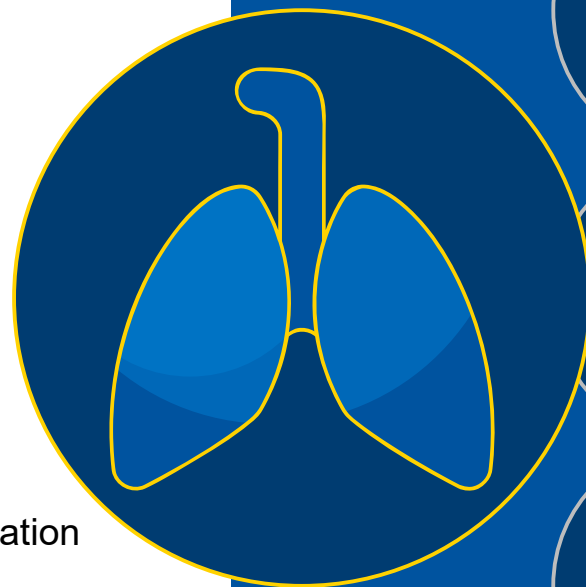


@cathy-fromen
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Centennial Term Professor for Excellence in Research and Education
Associate Professor, Chemical and Biomolecular & Biomedical
Engineering, University of Delaware

DDL 2025

December 11, 2025





Current Group

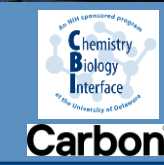
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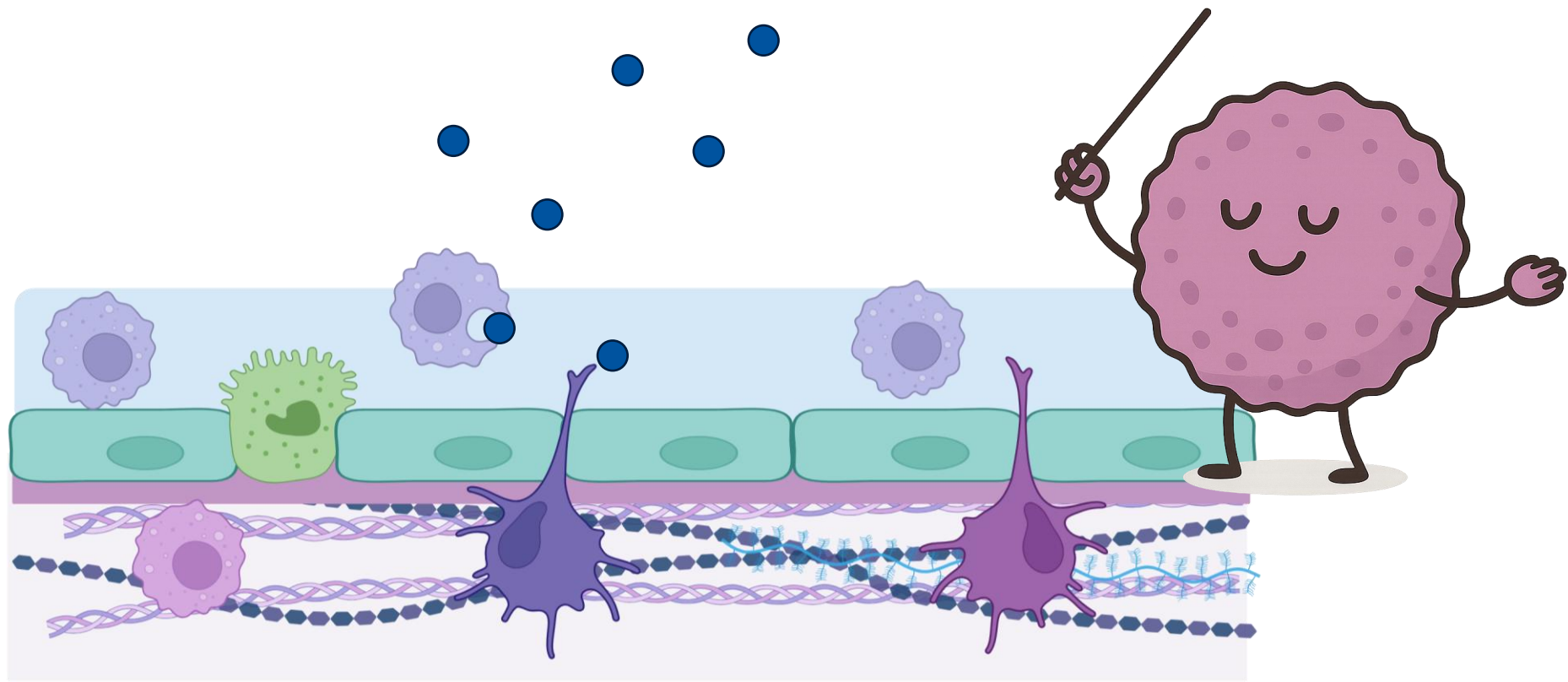
Collaborators

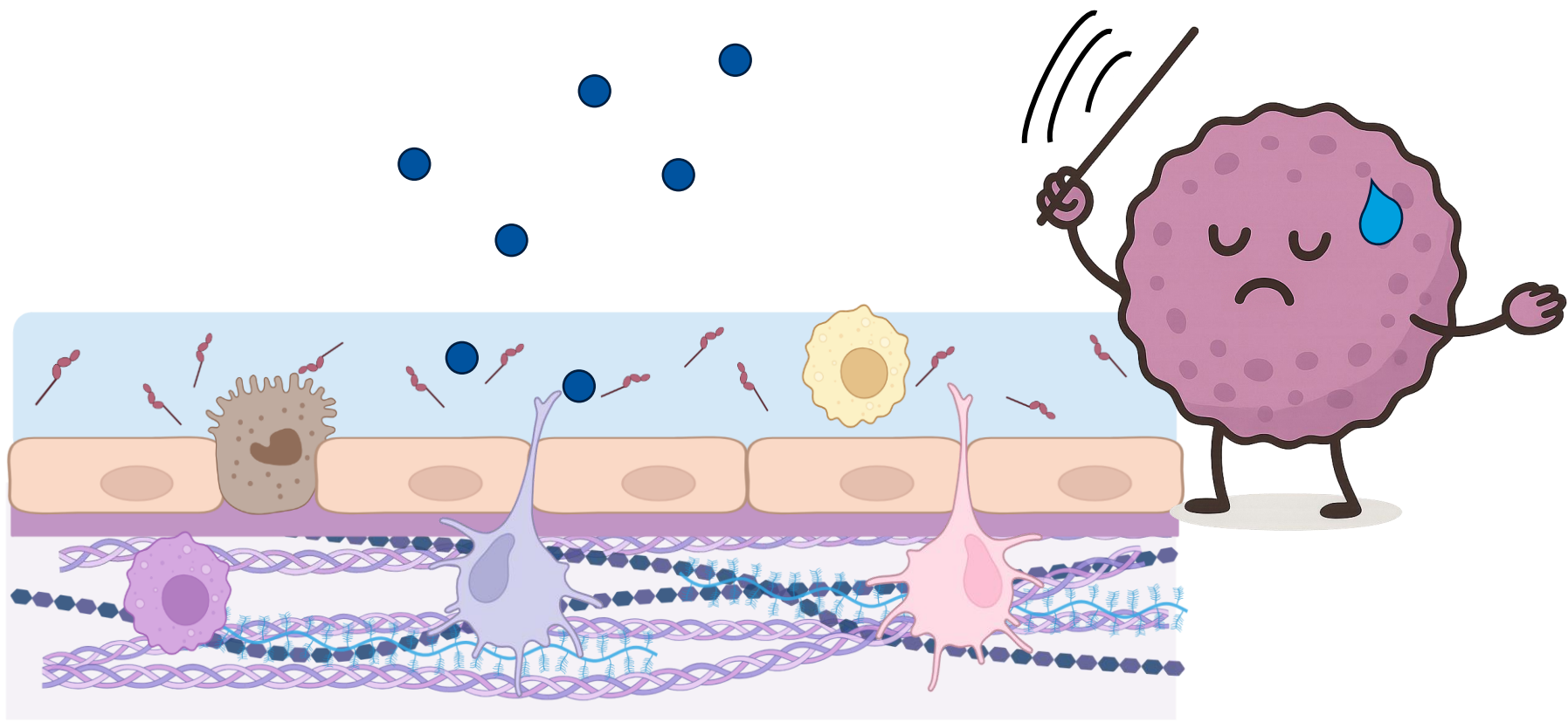
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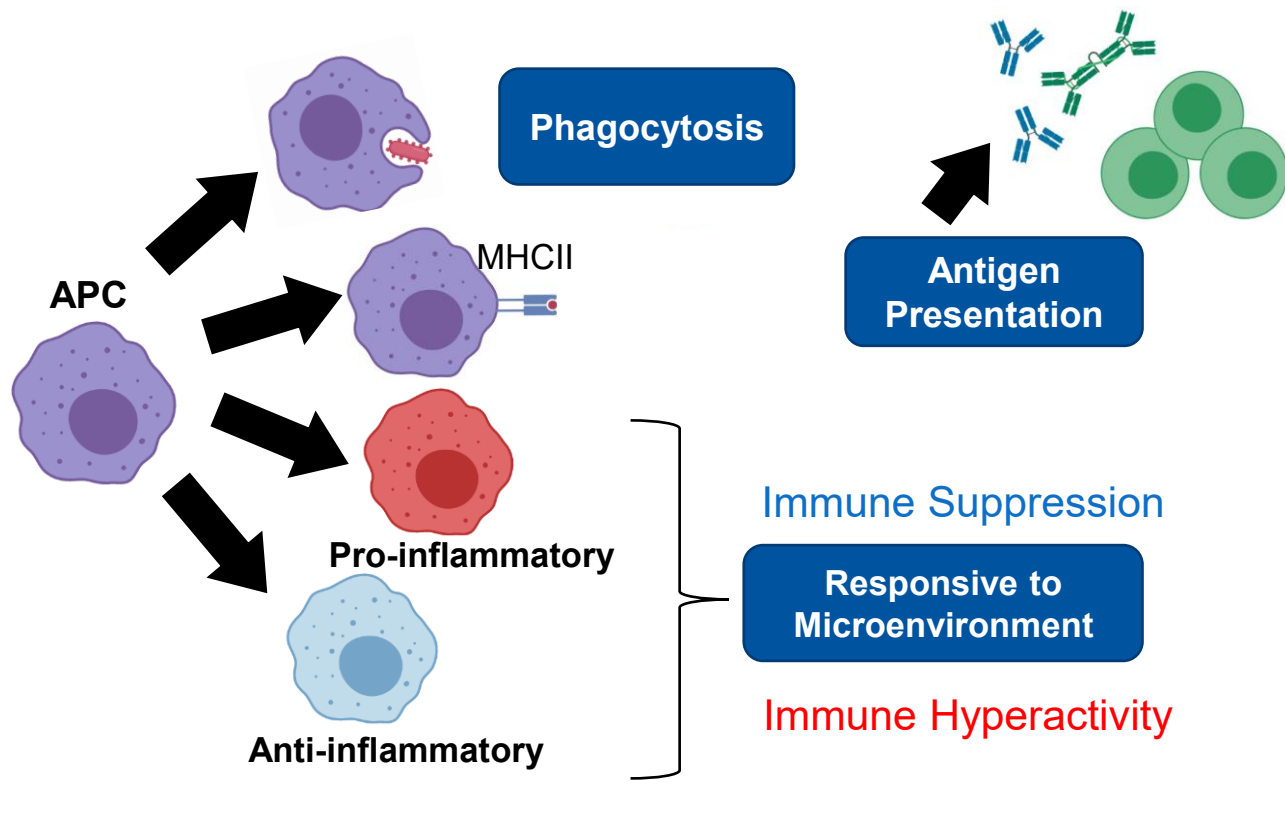
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Local innate immune cells regulate the lung microenvironment



Innate immune APCs are the gateway to “immune engineering”

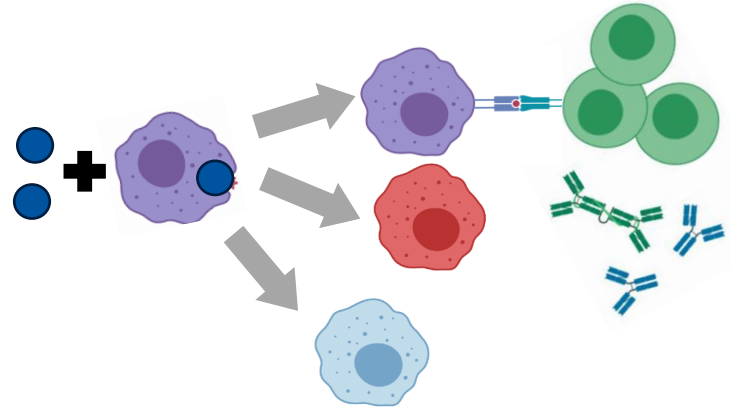
Respond to
molecular cues

Execute a complex
“Playbook”



Particles:
Extracellular
Intracellular

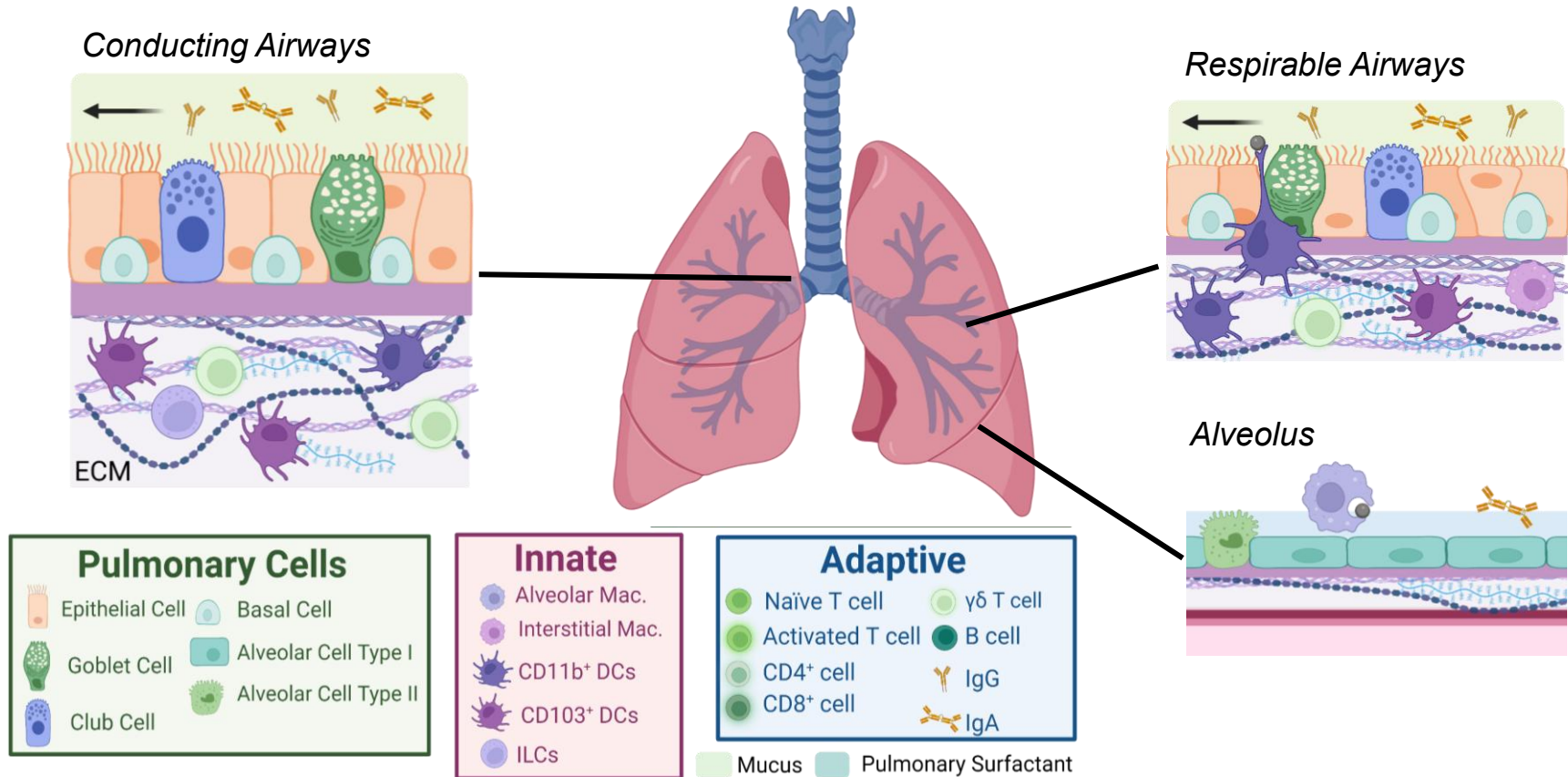
Adobe stock photos; Fromen unpublished



Correct a “bad” response

Direct a “good” response

The absorbance, clearance & immune involvement depends on location



Multiscale challenges in predicting immune response to inhaled products

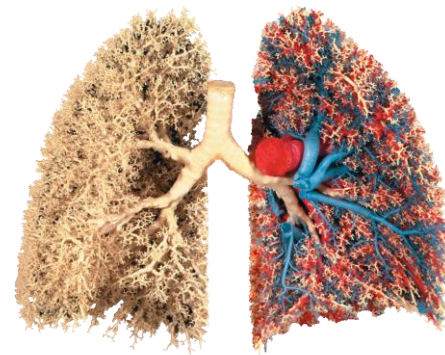
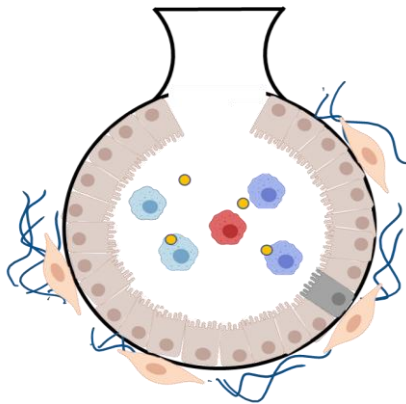
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Targets? Intracellular mechanism?

Microenvironment:
*Cell-cell interactions?
Residence time?*

Tissue Localization:
Where and how much?

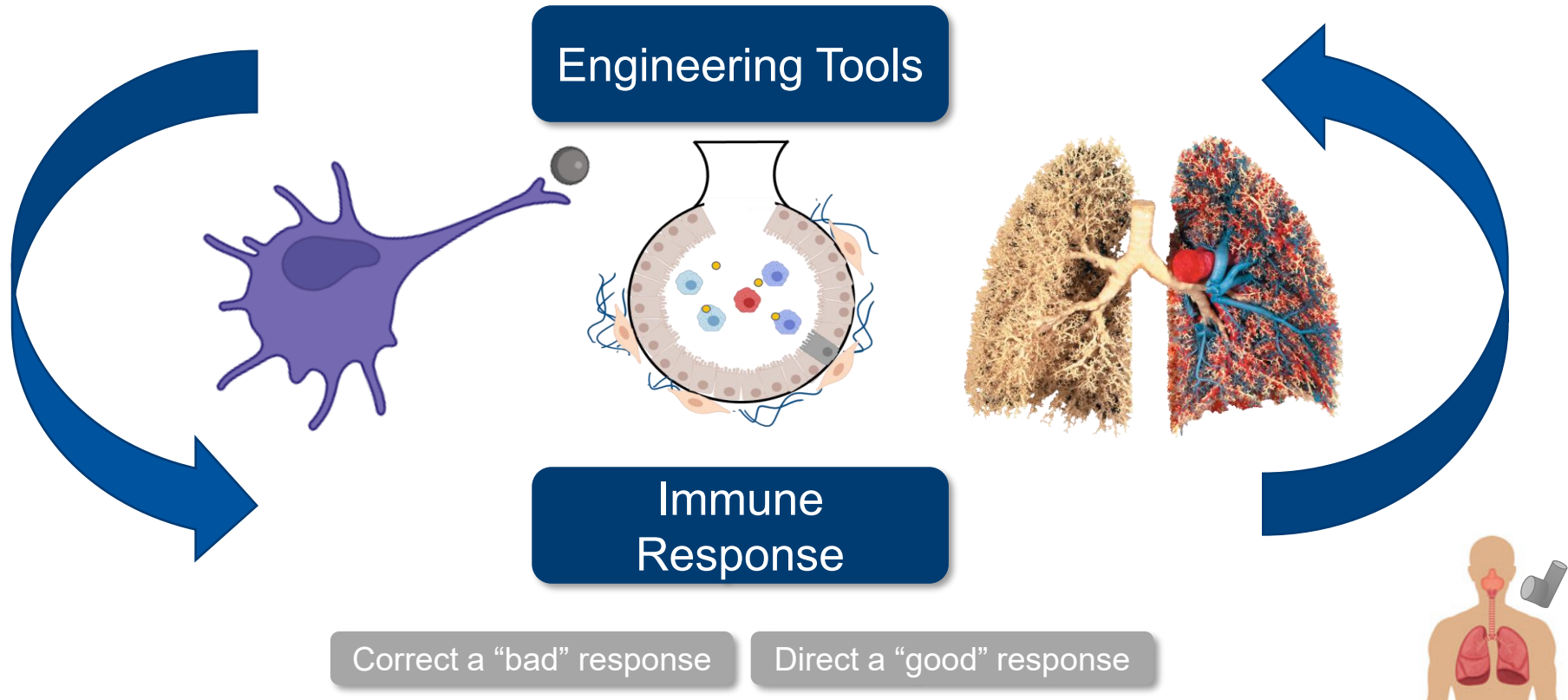


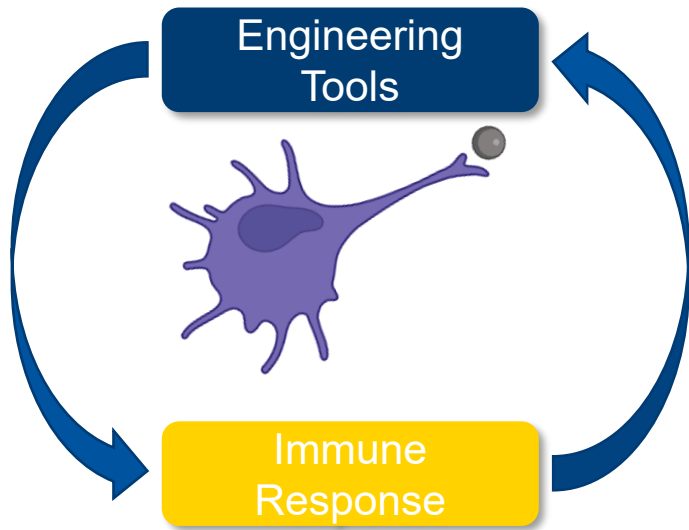
microns



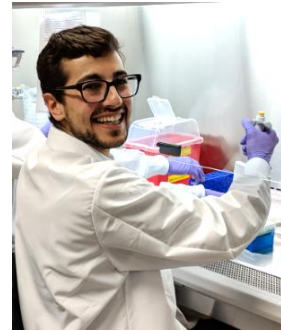
centimeters

Aerosol immune engineering: harnessing the power of the immune system

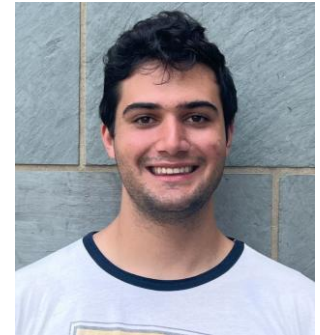




What happens when an innate immune cell internalizes a particle? *(cellular level)*



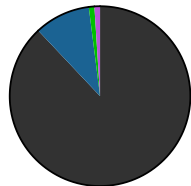
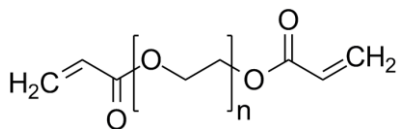
Bader Jarai



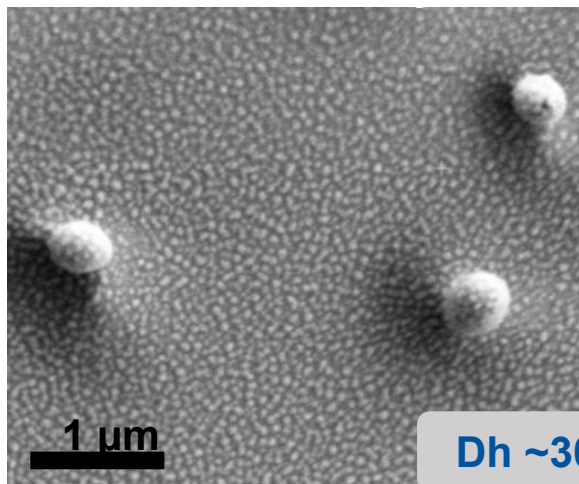
Michael Trautmann-Rodriguez

PEGDA “Immunologically Inert” Particle Platform

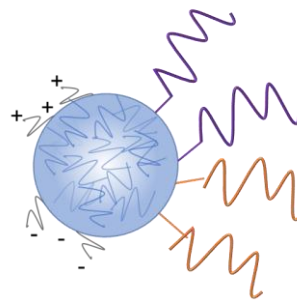
Poly(ethylene glycol)
diacrylate (PEGDA)



88% PEGDA₇₀₀
10% CEA
1% FITC
1% Photoinitiator

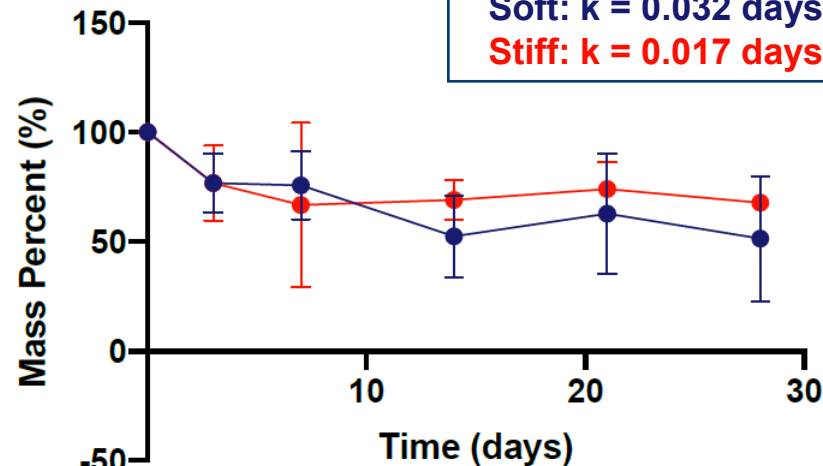


Dh ~300 nm



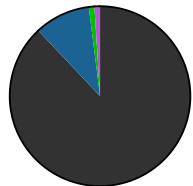
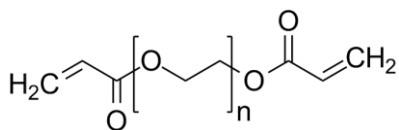
First Order Kinetics
 $\ln([\text{NP}]/[\text{NP}_0]) = -k \cdot t$

Soft: $k = 0.032 \text{ days}^{-1}$
Stiff: $k = 0.017 \text{ days}^{-1}$

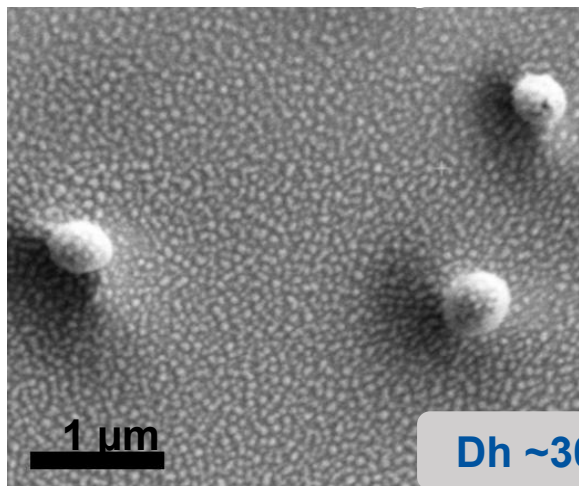


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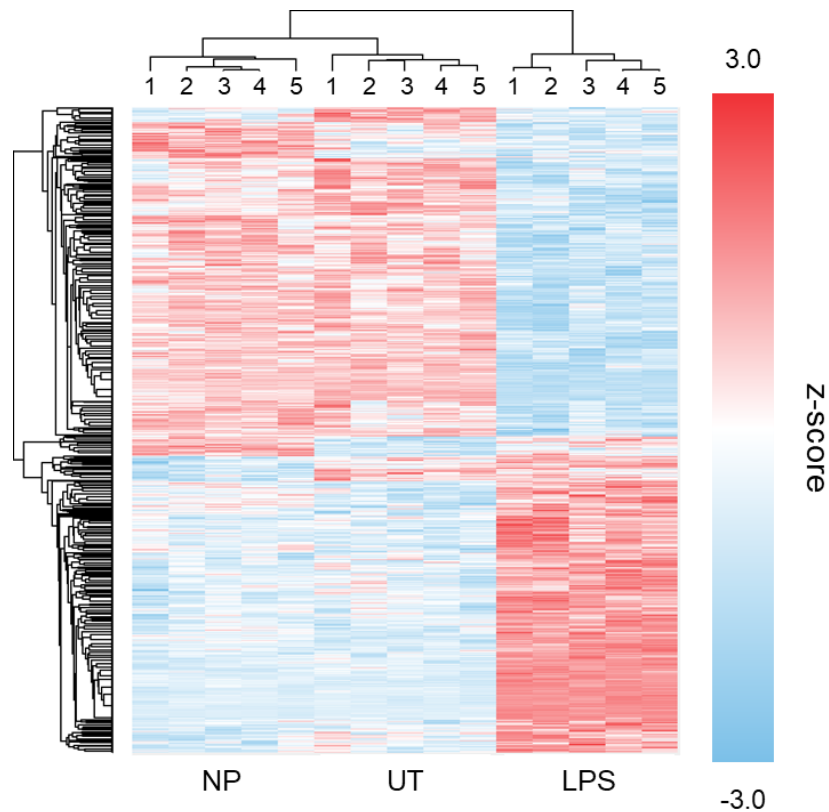
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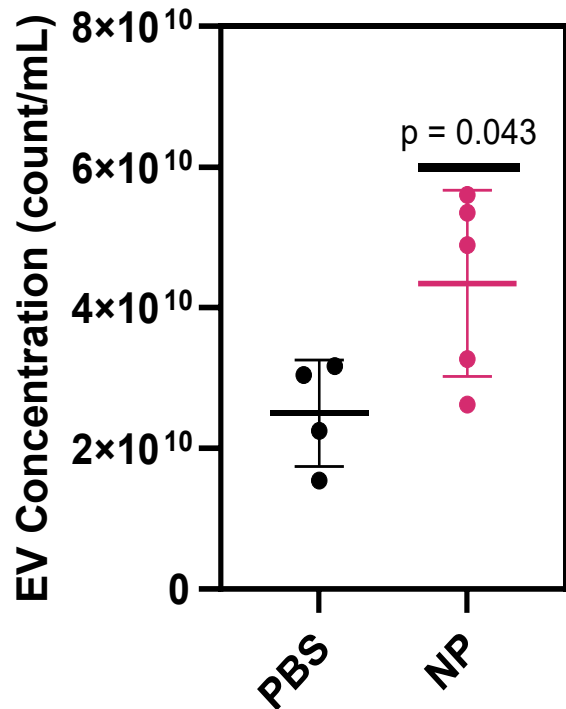
88% PEGDA₇₀₀
10% CEA
1% FITC
1% Photoinitiator



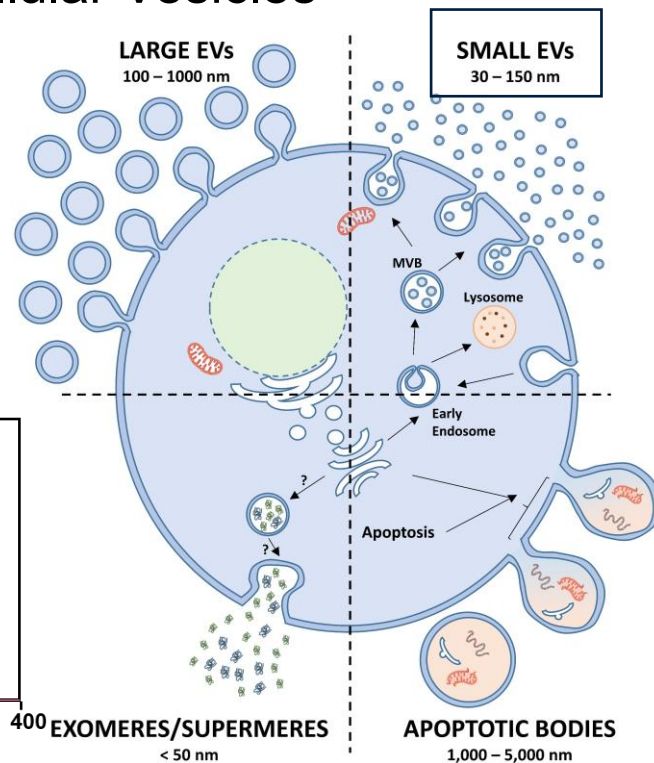
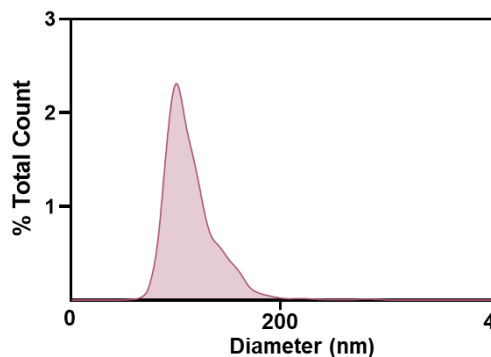
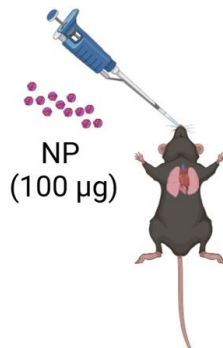
Dh ~300 nm



NP dosage produces an abundance of Extracellular Vesicles

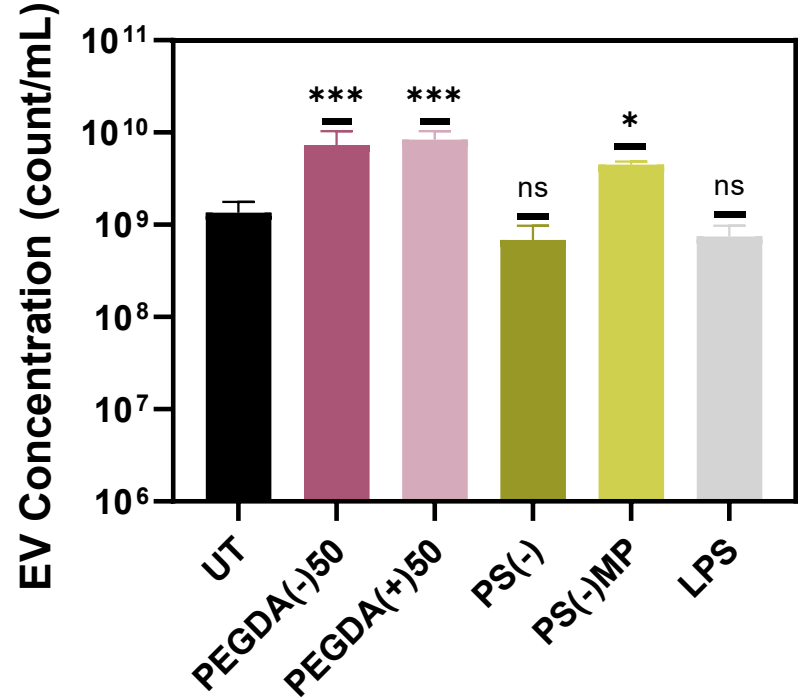
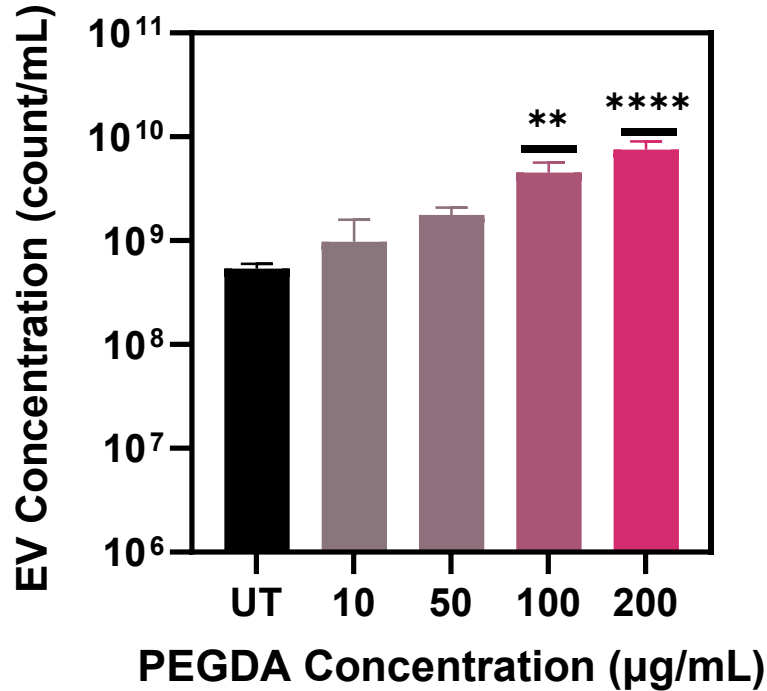


C57BL/6J, female 4-6 wks
24 hr NP dose (100 ug/mouse), n=5

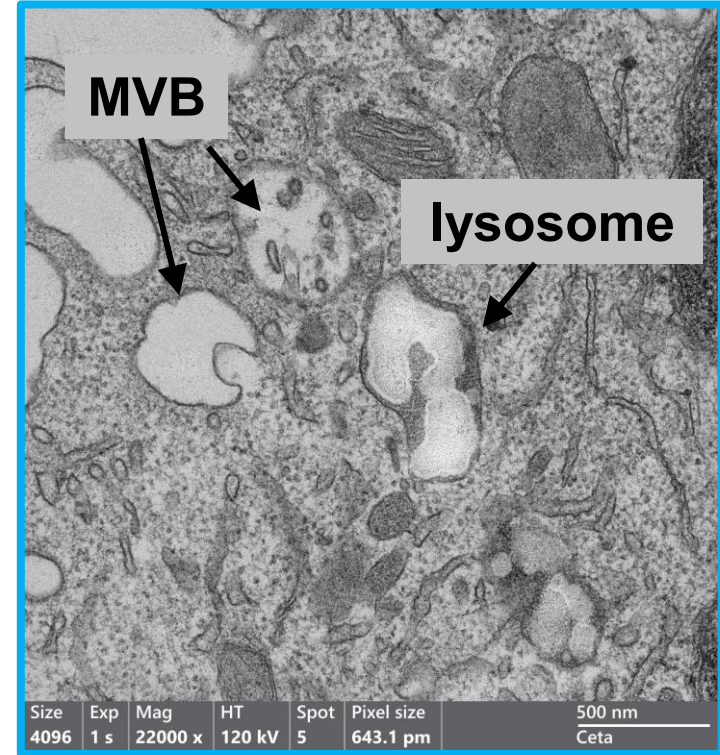
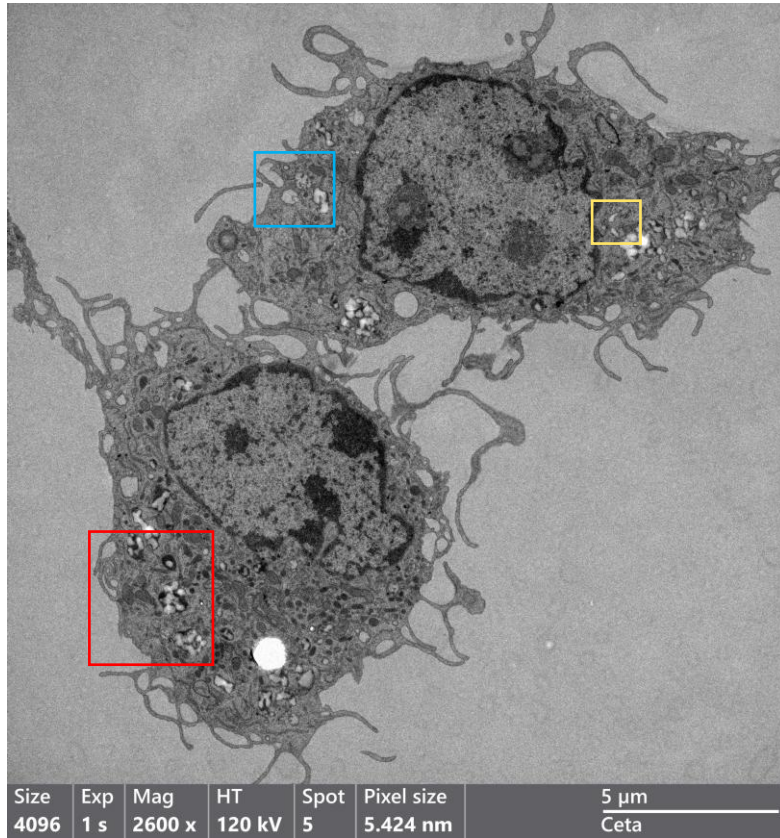


Macrophage small EV secretion dependent on phagocytosis

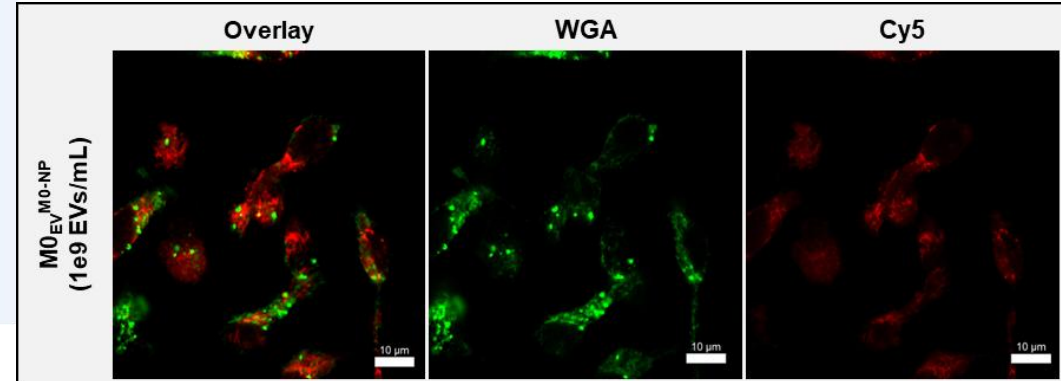
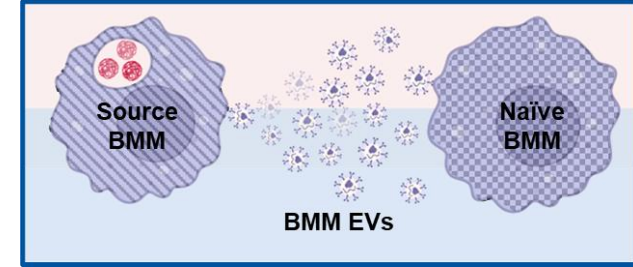
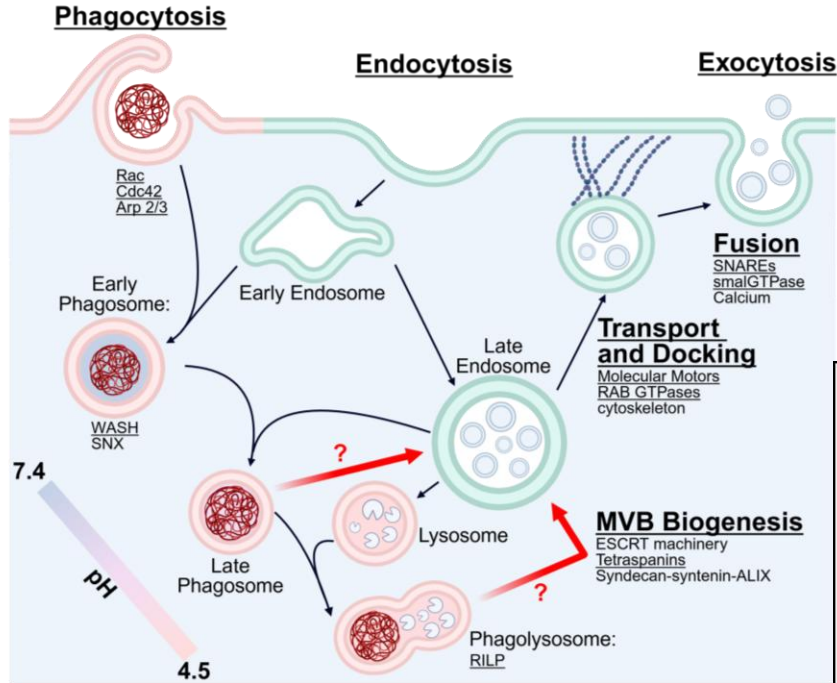
BMM EV Secretion



Macrophage small EV secretion follows intracellular MVB formation



Propagation of signals using phagocytosis and small EV biogenesis



Multiscale challenges in predicting immune response to inhaled products

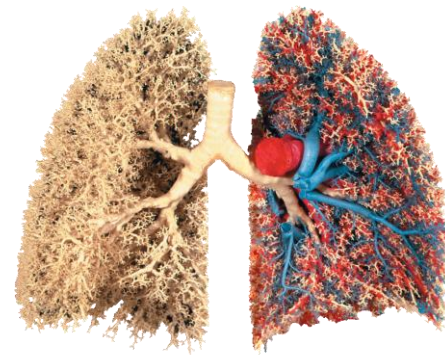
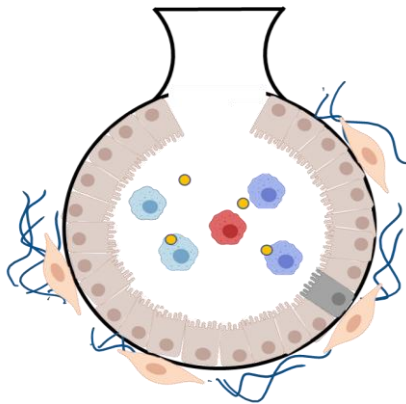
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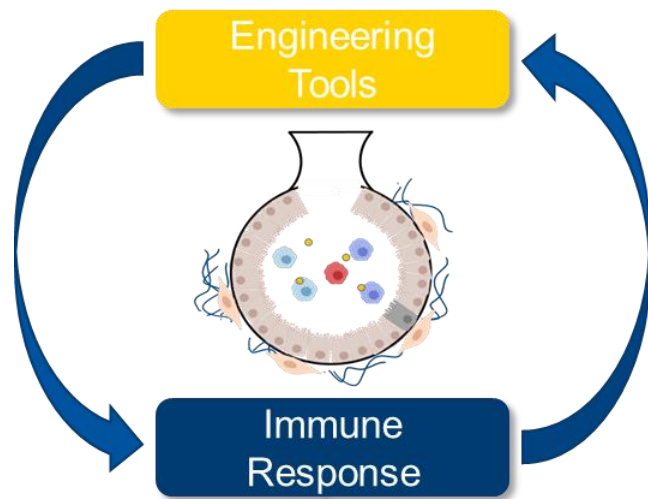
Tissue Localization:
Where and how much?



microns



centimeters



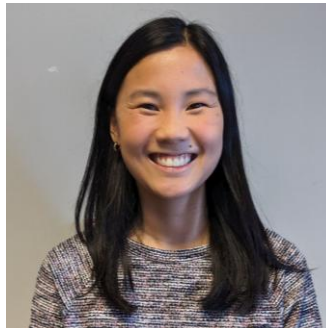
How does the microenvironment regulate cell response? *(population level)*



April Kloxin



Kartik Bomb



Jodi Graf

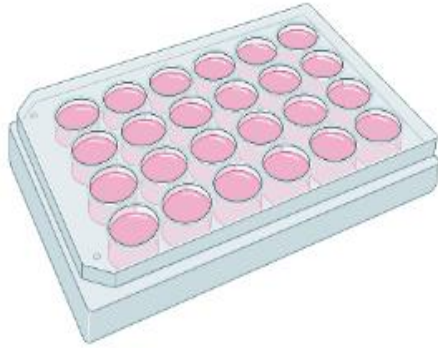


Emma Sudduth

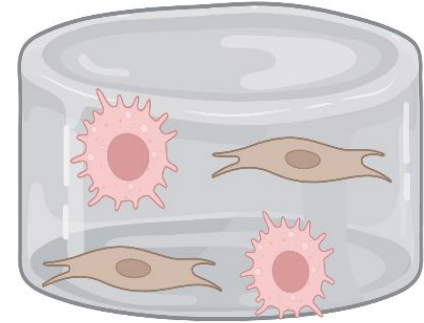


Lina Pradhan

Moving toward 3D *in vitro* hydrogel modeling to improve biological relevance

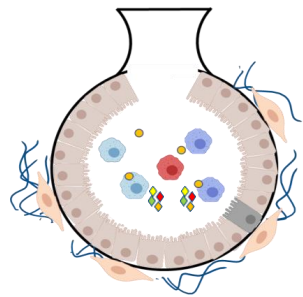


Tissue culture plastic: 3 GPa



Lung Tissue: ~5 kPa

High throughput Hydrogel Platform to probe microenvironment effects



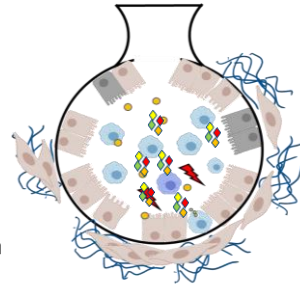
Healthy Lung Alveoli



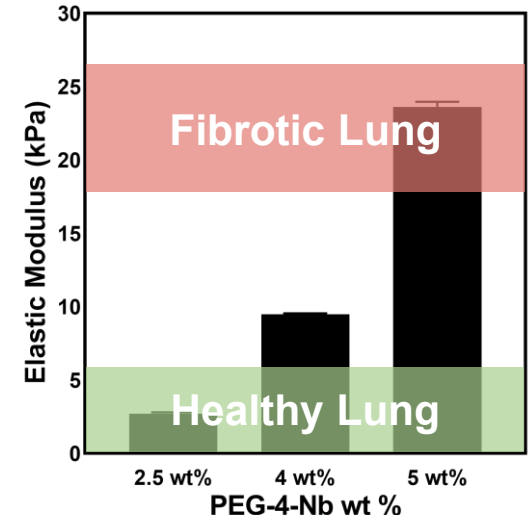
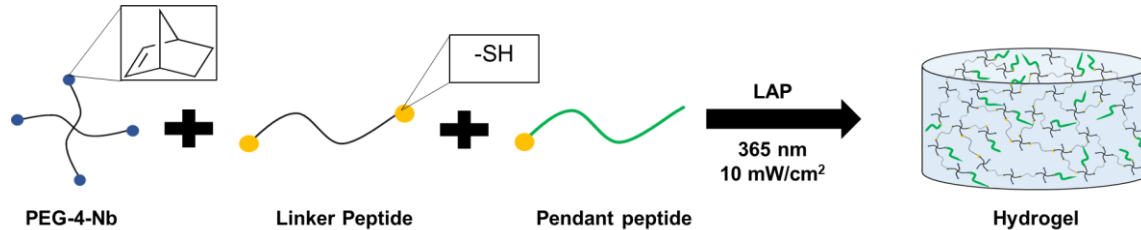
Healthy lung
E~ 1.5 – 5 kPa



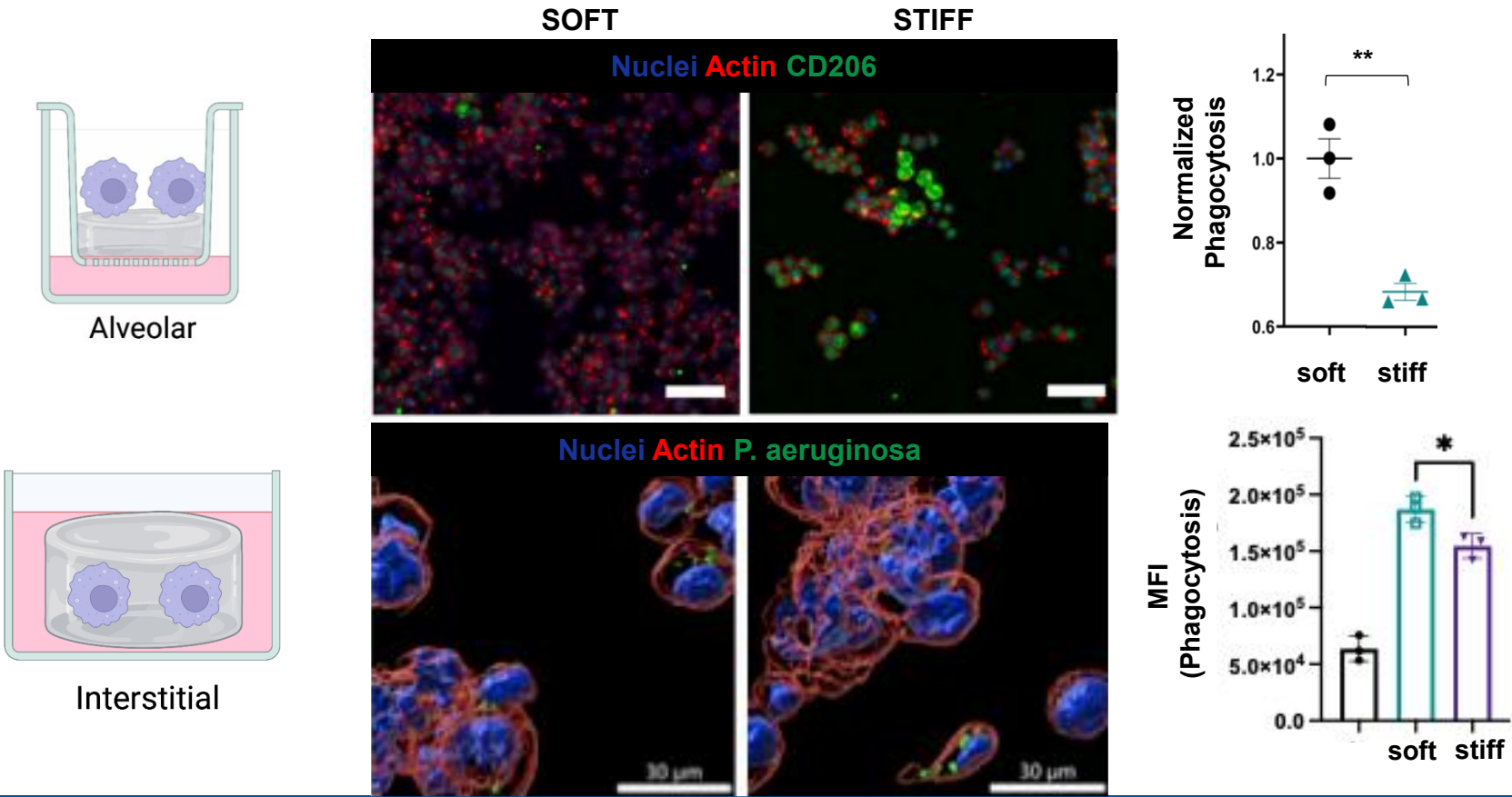
Fibrotic lung
E~ 20 – 25 kPa



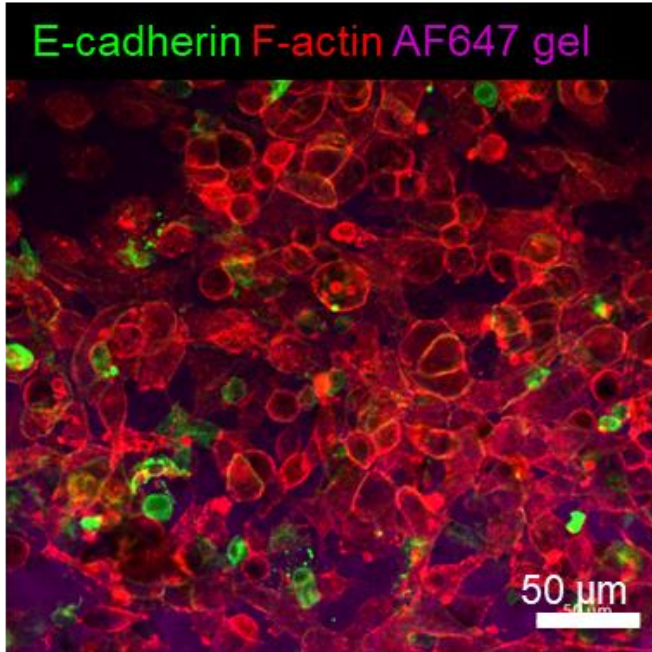
Fibrotic Lung Alveoli



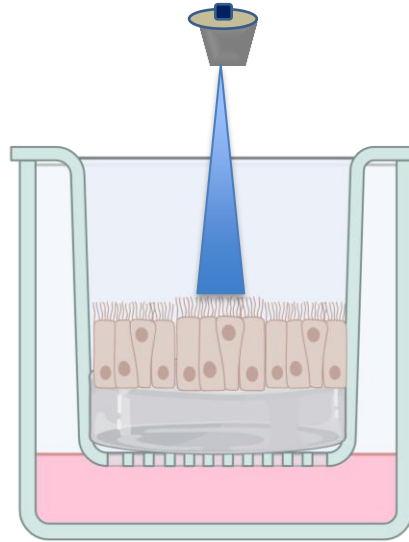
Macrophage phagocytosis is impaired in stiffer microenvironments



PEG-based hydrogels facilitate advanced epithelial cultures

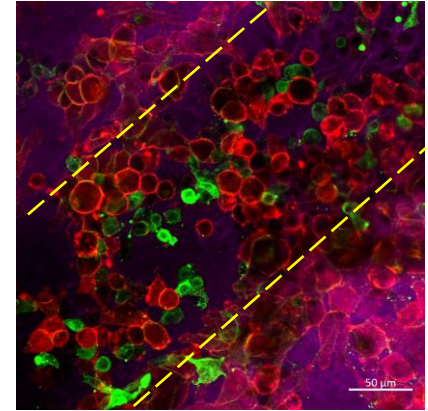


Controlled light exposure

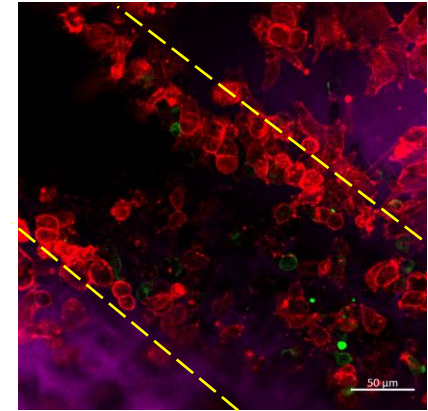


Epithelial cells
(A549; Calu-3 & HBEs)

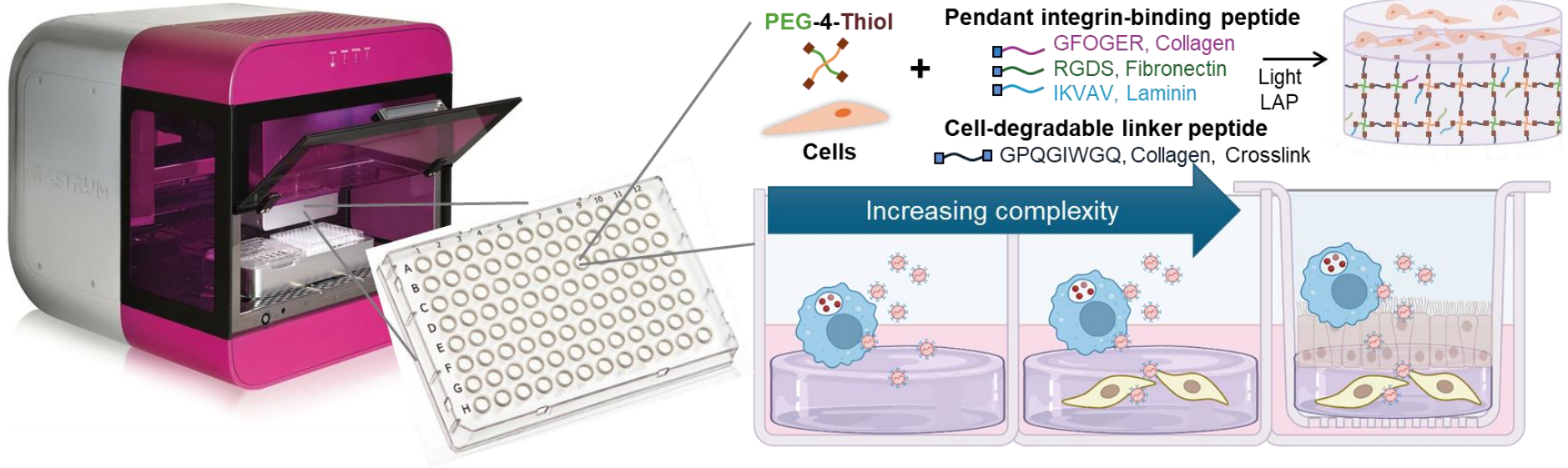
Day 5 PI 50 μm



Day 5 PI 100 μm



Future opportunities in integrated multicellular ALI cultures on lung ECM



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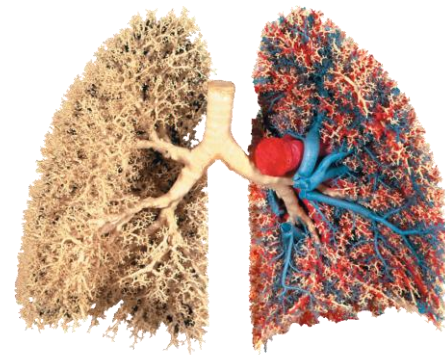
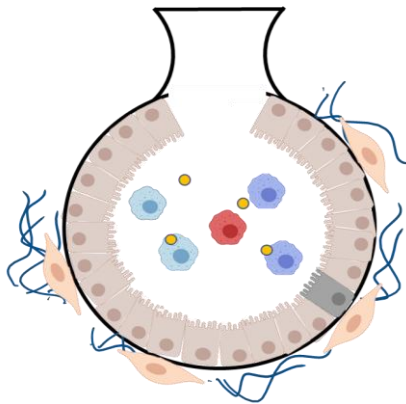
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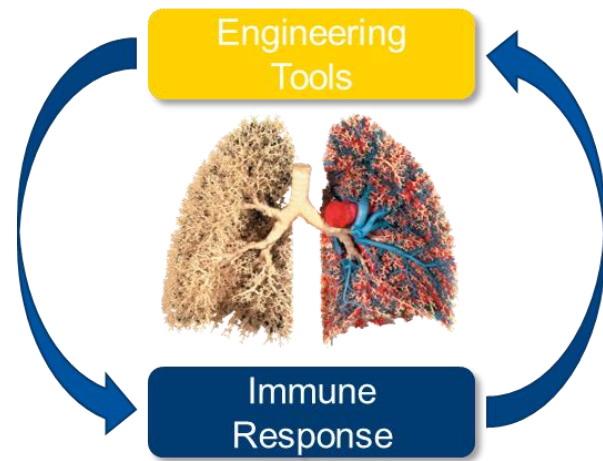
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Where and how much?



microns



centimeters



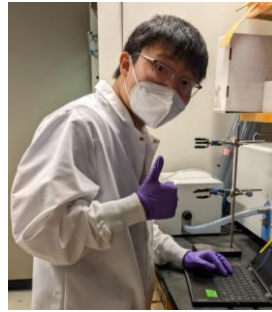
Where do inhaled therapeutics go? *(tissue level)*



Emily Kolewe



Ian Woodward



Yinkui Yu



Dominic Hoffman

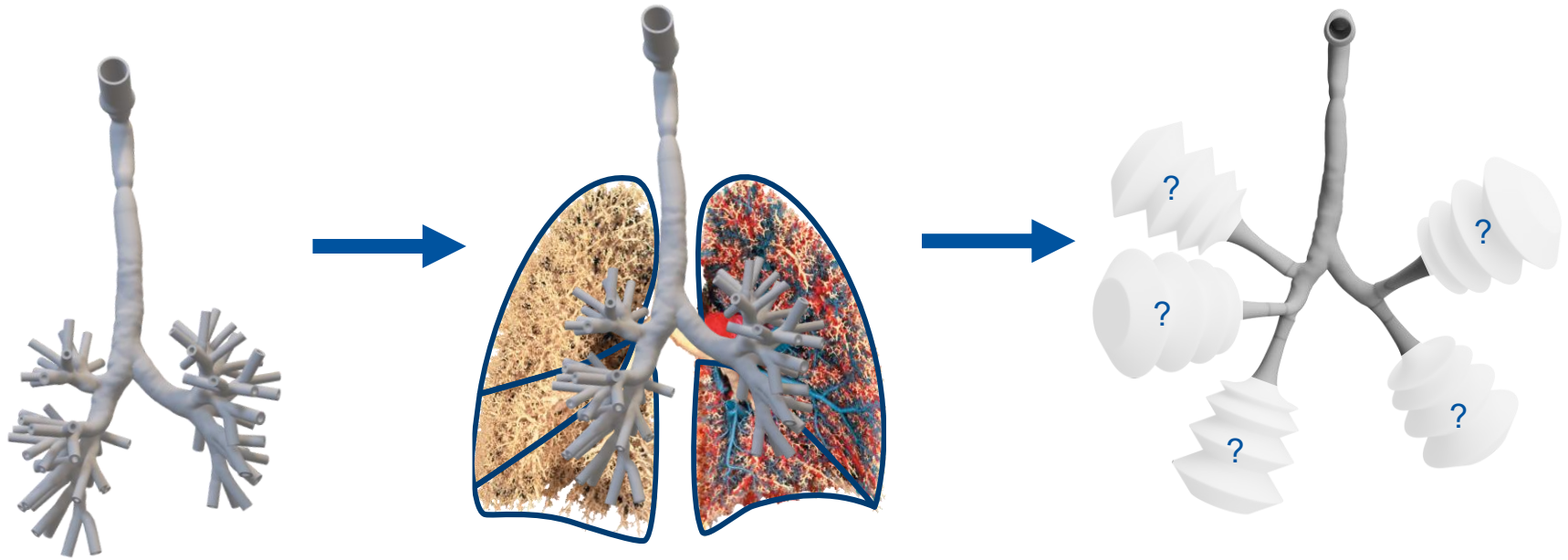


Katie Austin

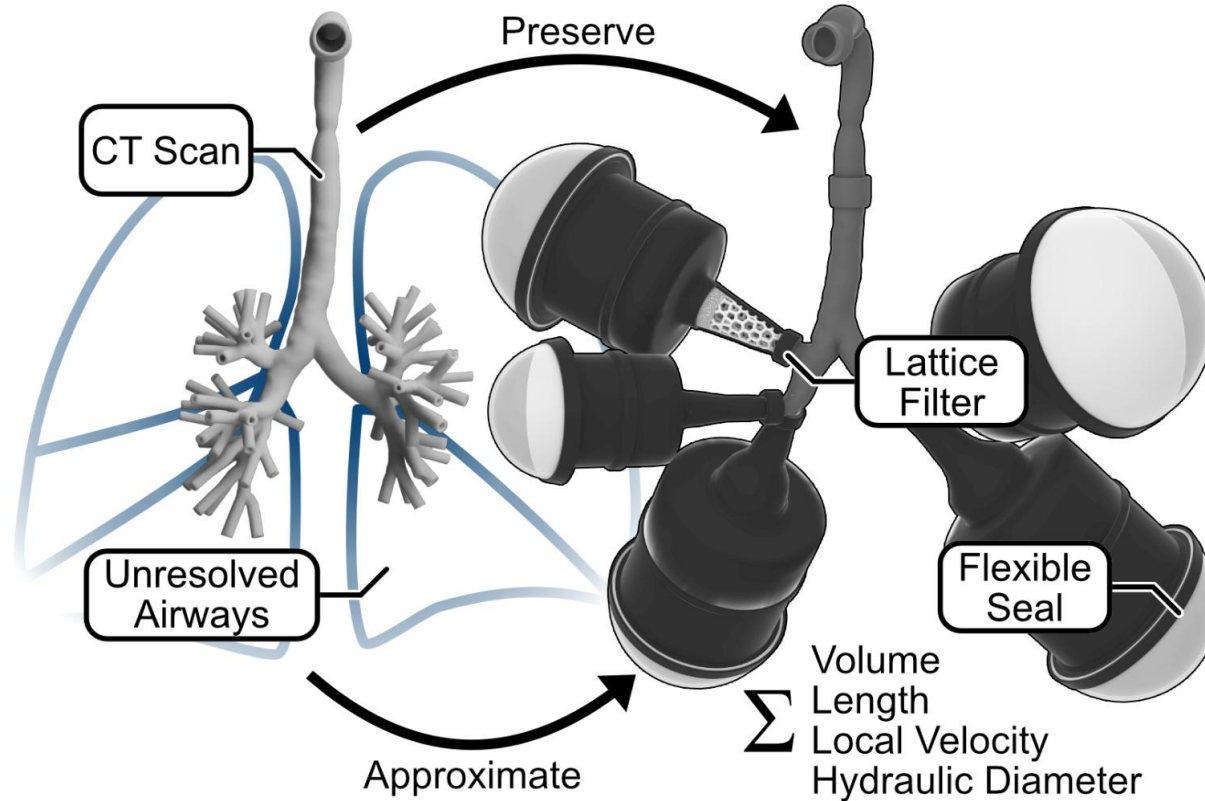


Logan Whitesel

Building a physical full-volume dynamic airway for spatial deposition



TIDAL: Total inhalable deposition in an actuated lung



Spatial Collection

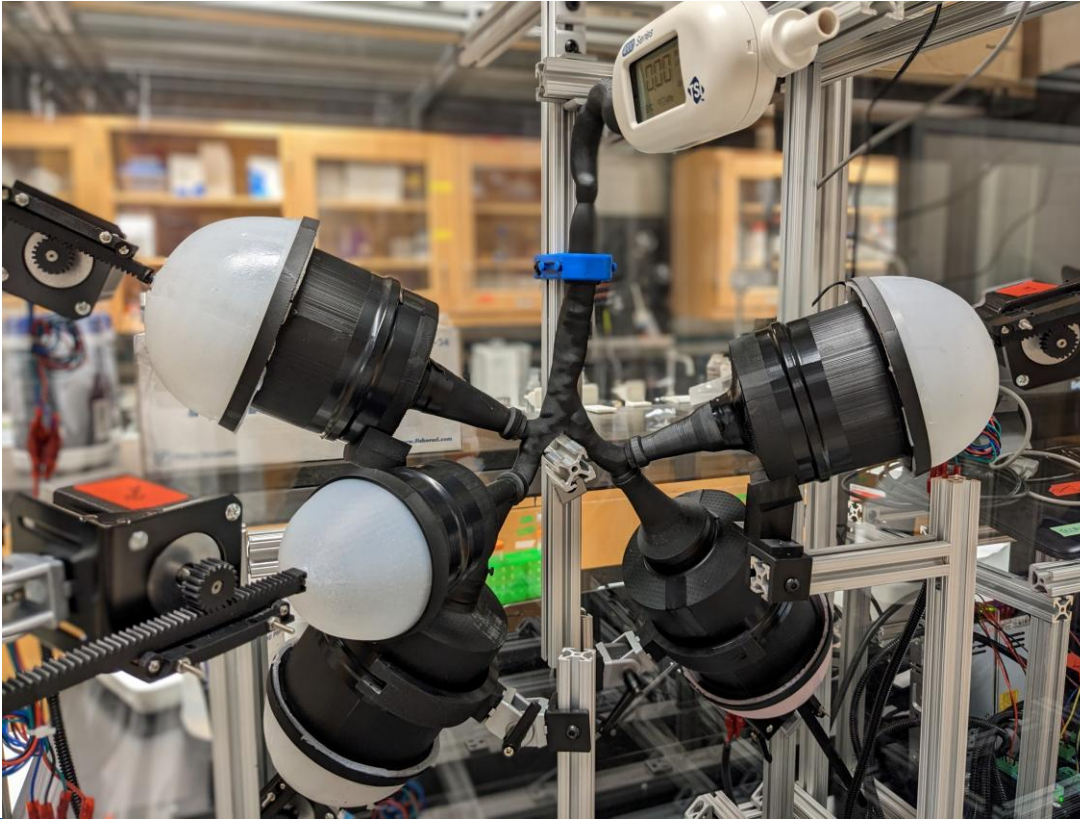
Full Lung Volume

Full Inhaler Dose

Breathing Dynamics

Modular

TIDAL: Total inhalable deposition in an actuated lung



Spatial Collection

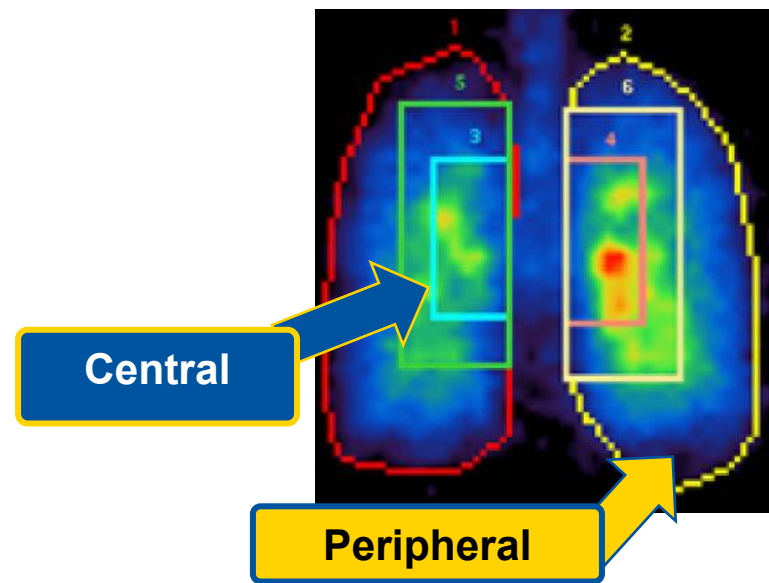
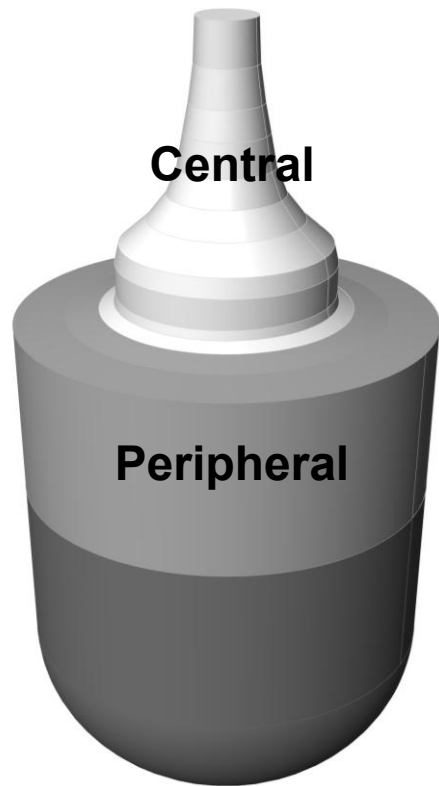
Full Lung Volume

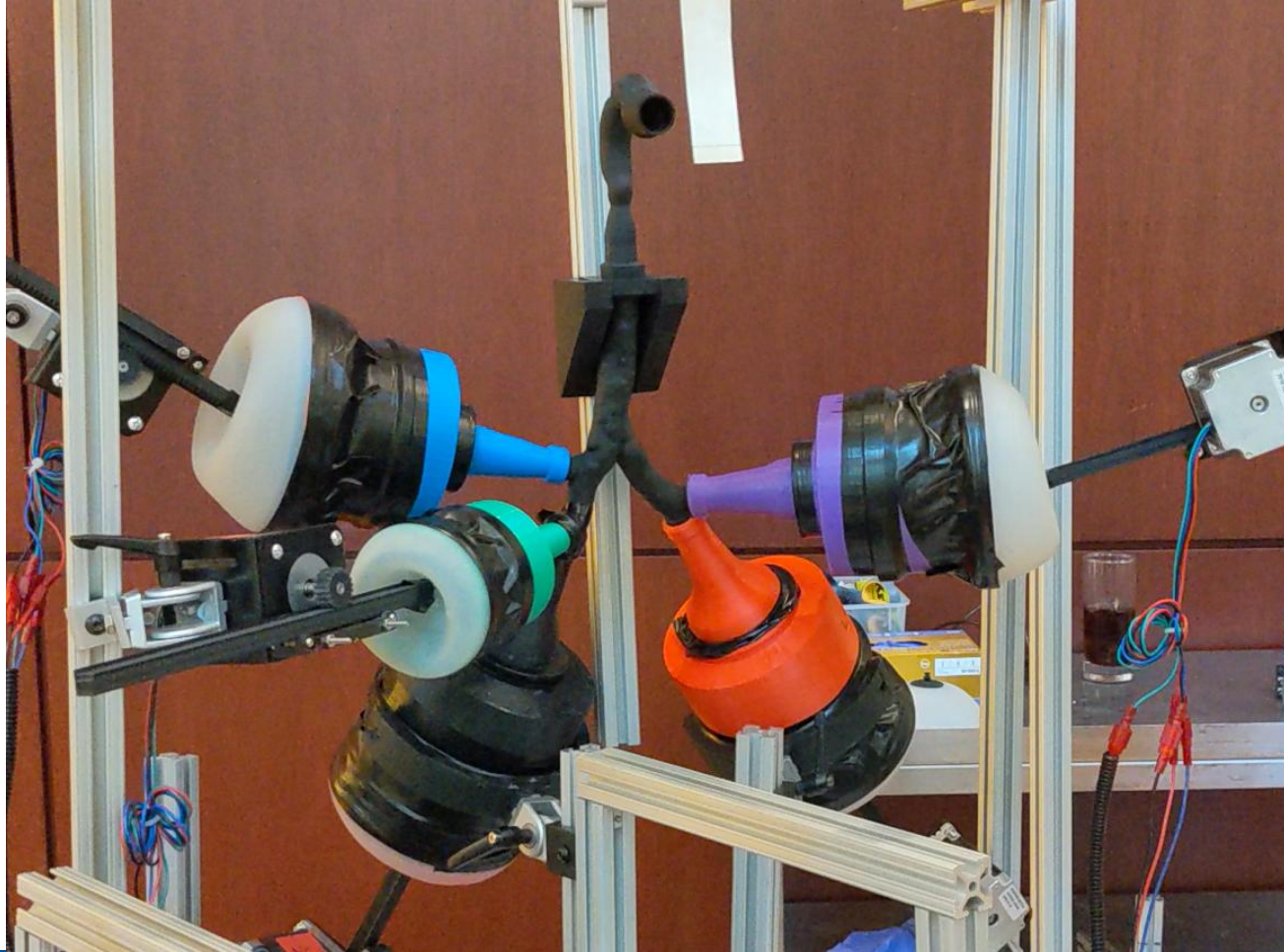
Full Inhaler Dose

Breathing Dynamics

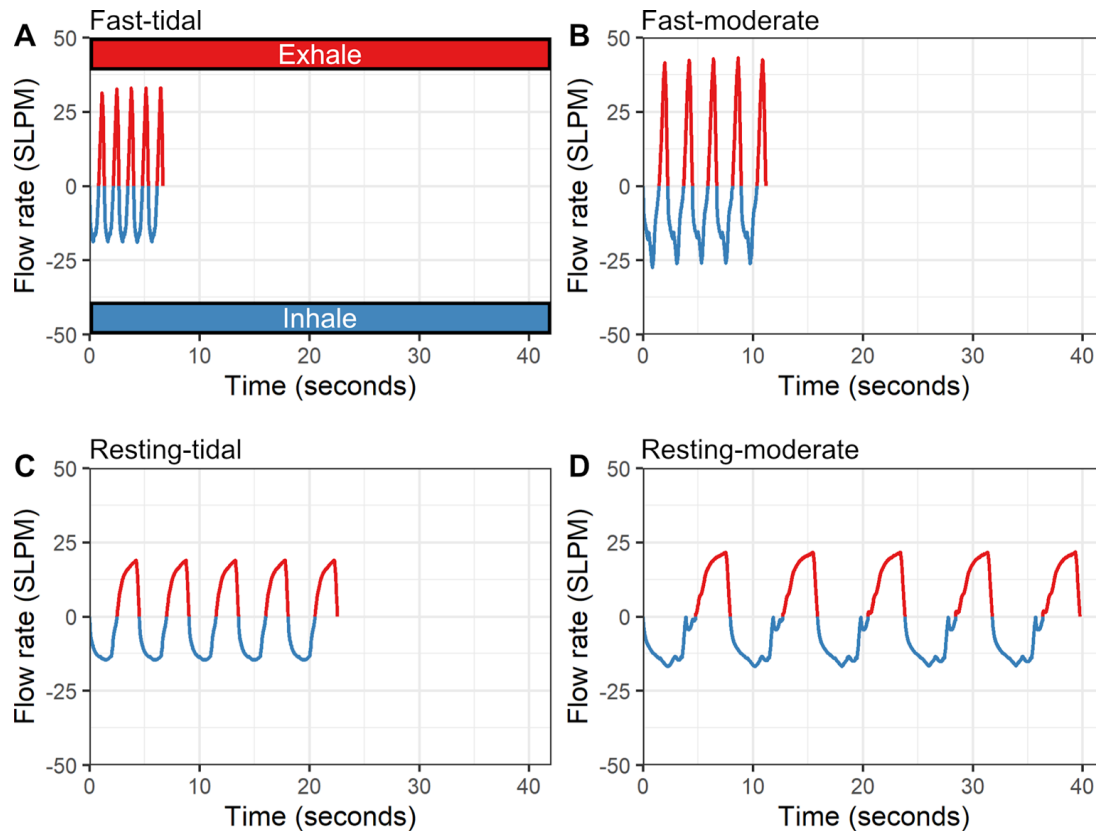
Modular

Spatial collection enabled by tunable “filters”

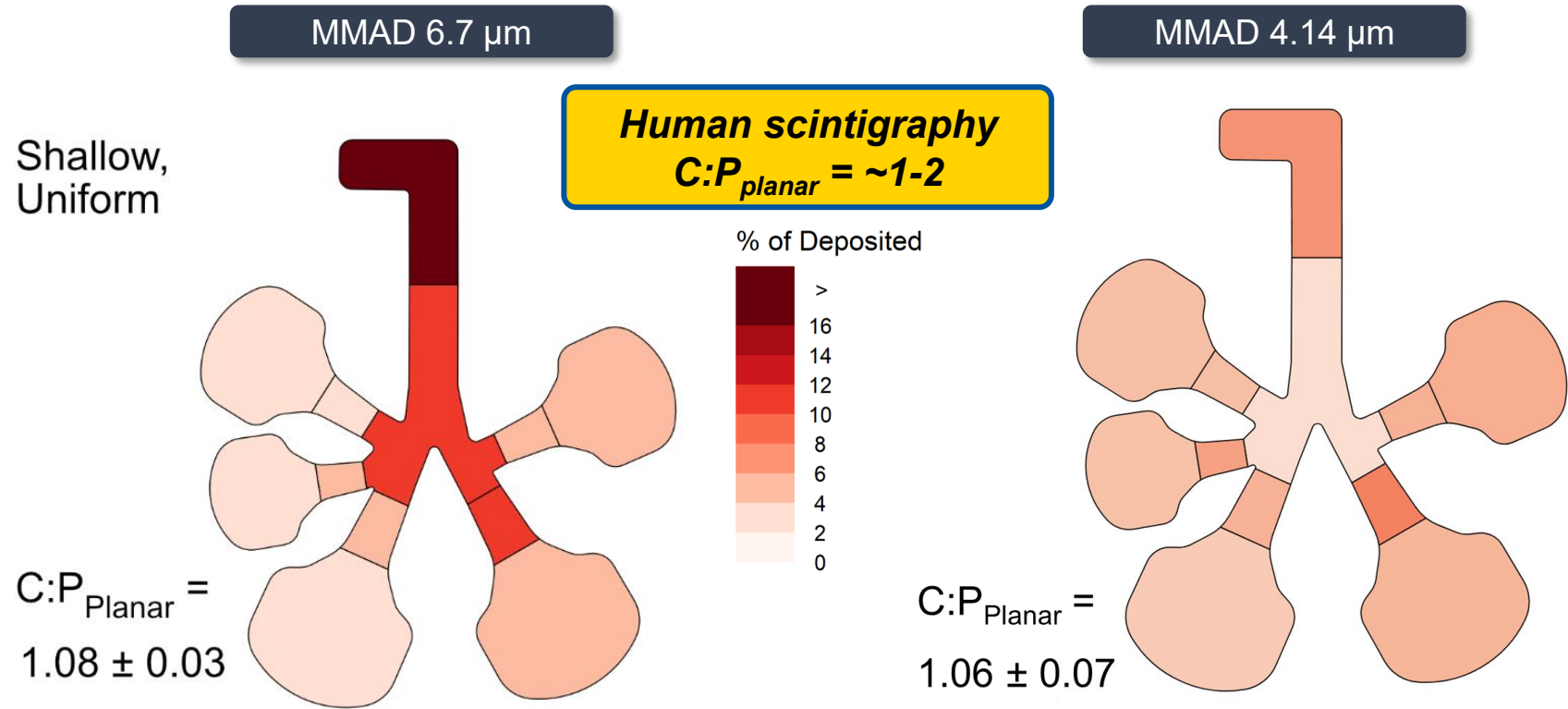




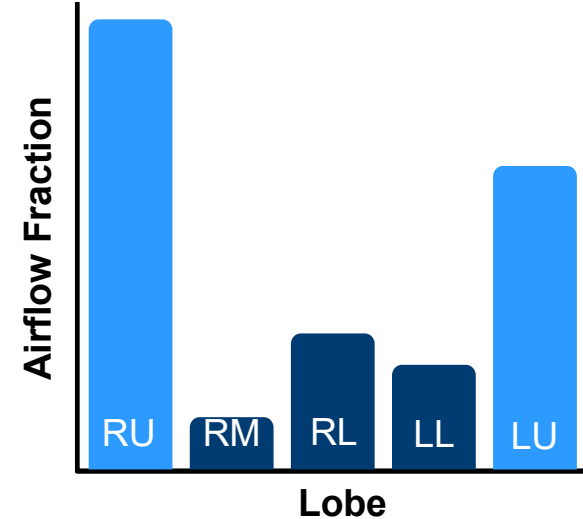
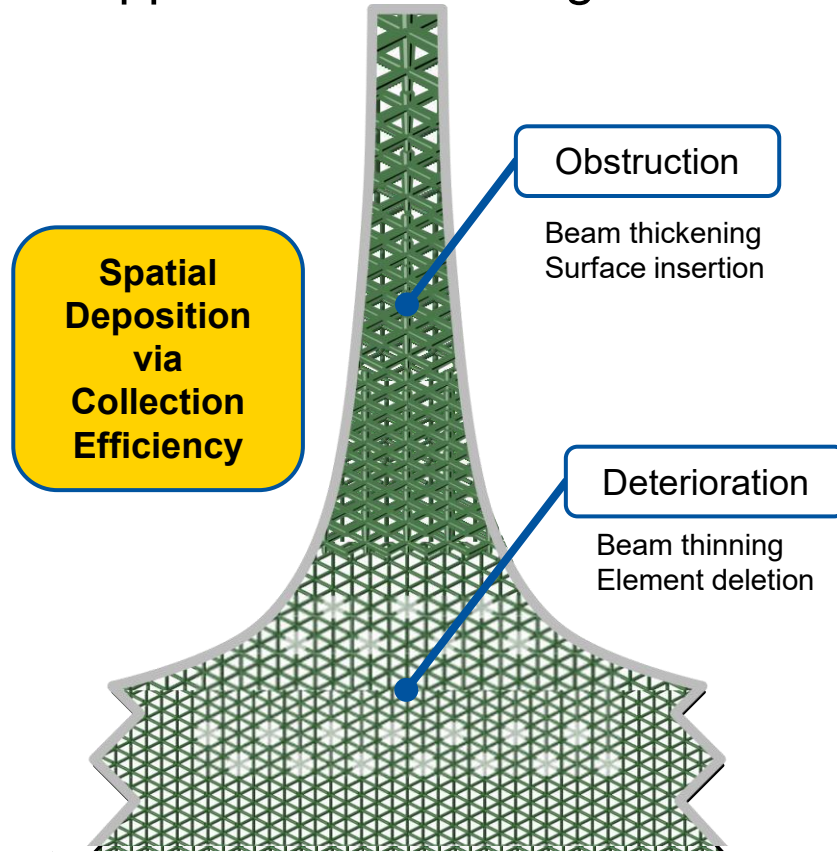
A wide range of physiologically relevant breathing patterns achievable



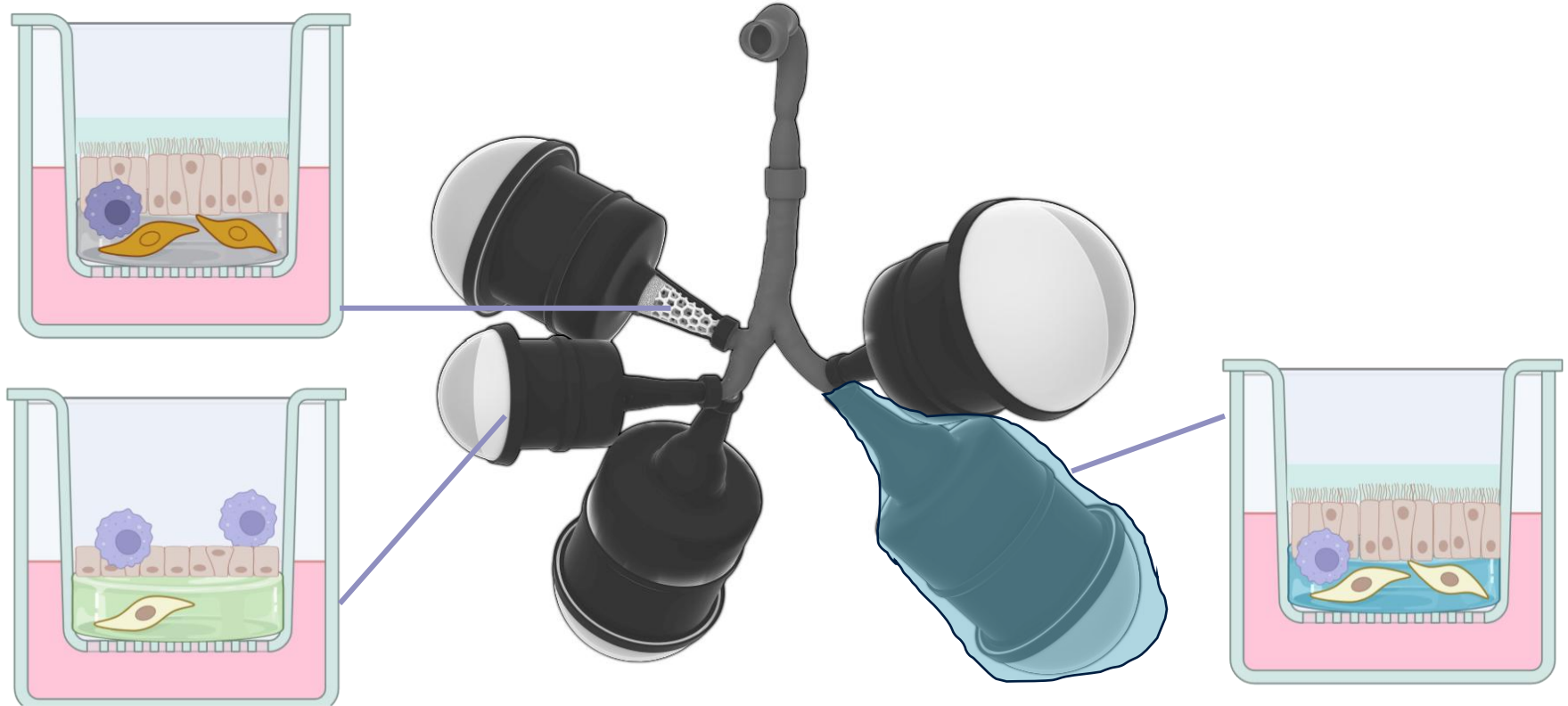
Capturing spatial deposition with TIDAL and validating to a healthy adult



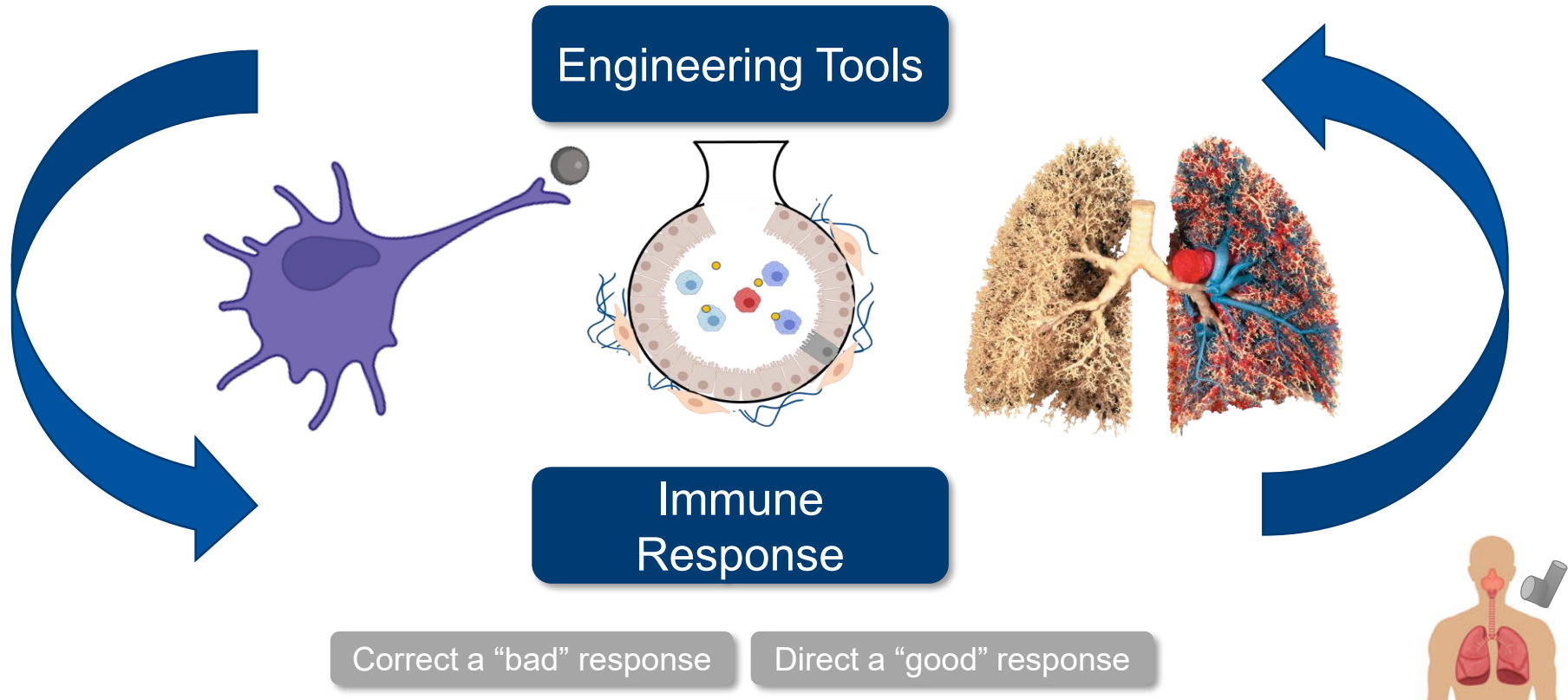
Future opportunities to design lattices to mimic disease



Building an integrated workflow to assess disease-specific responses



Aerosol immune engineering: harnessing the power of the immune system





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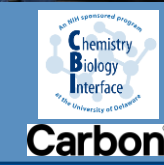
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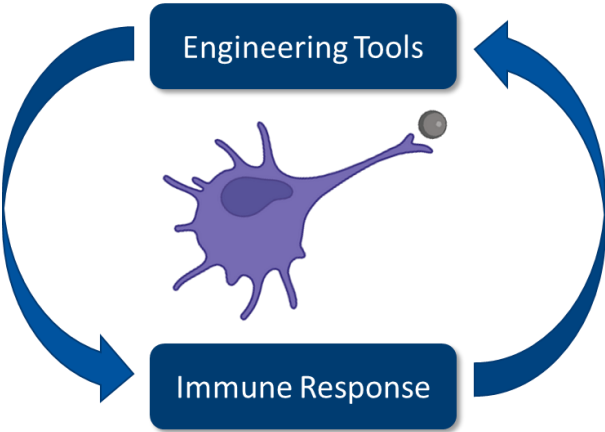
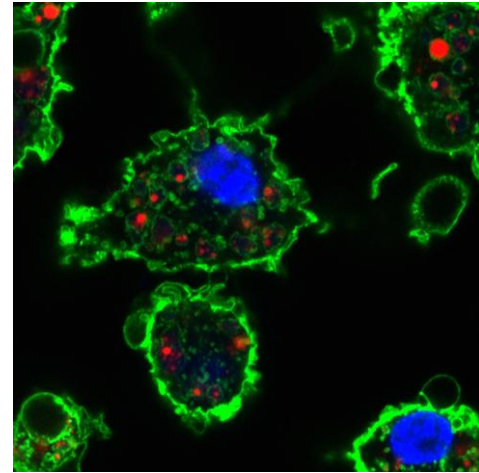
@cathy-fromen
 @FromenLab



Thank you!

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<https://sites.udel.edu/cfromen/>



FROMEN LAB



UNIVERSITY OF
DELAWARE



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@cathy-fromen