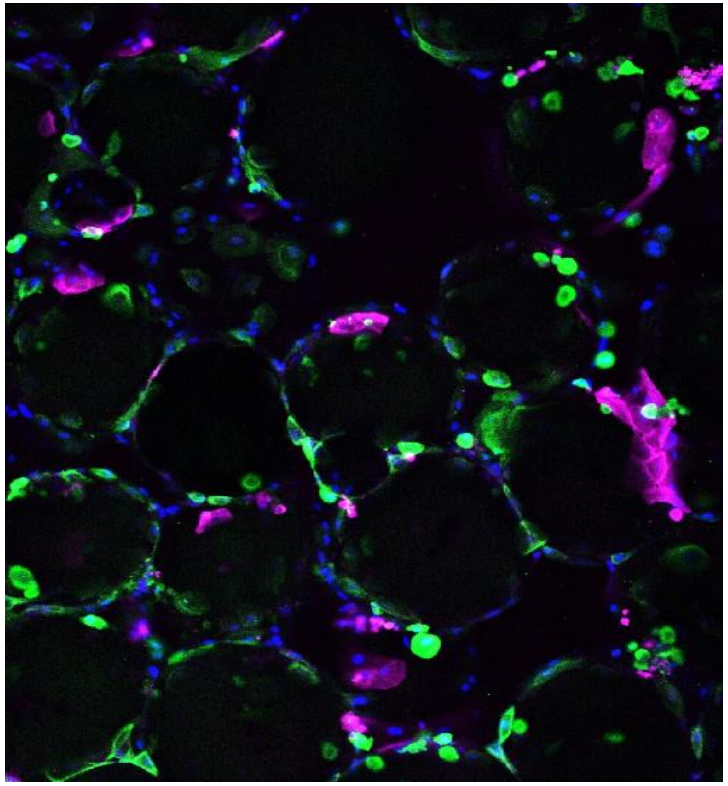
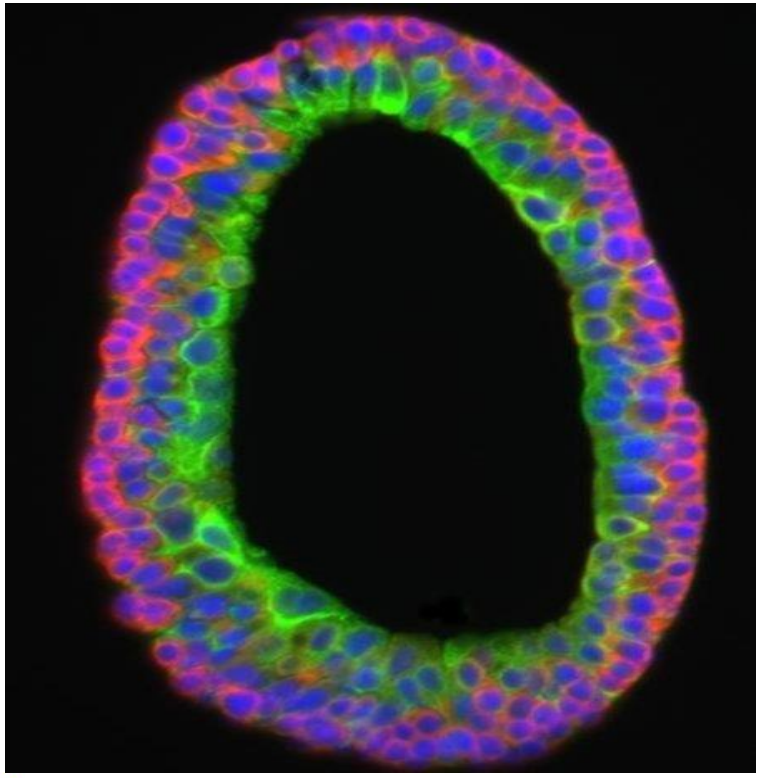
Regenerative Therapies for Lung Diseases





Brigitte Gomperts

October 13th, 2016

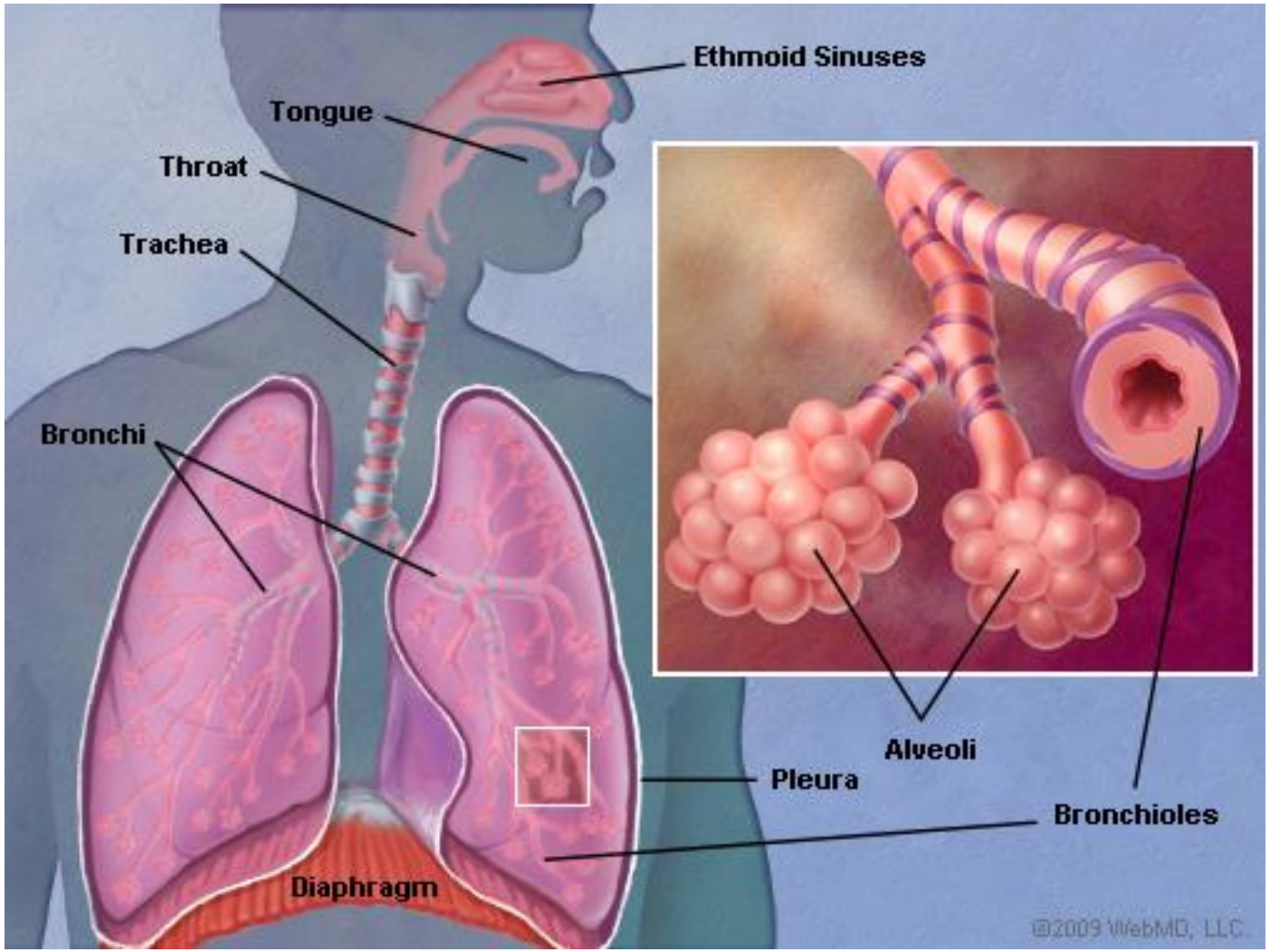
Mattel Children's Hospital UCLA

UCLA Children's Discovery and Innovation Institute

David Geffen School of Medicine

The Lungs Are Structurally and Functionally Complex

Structure

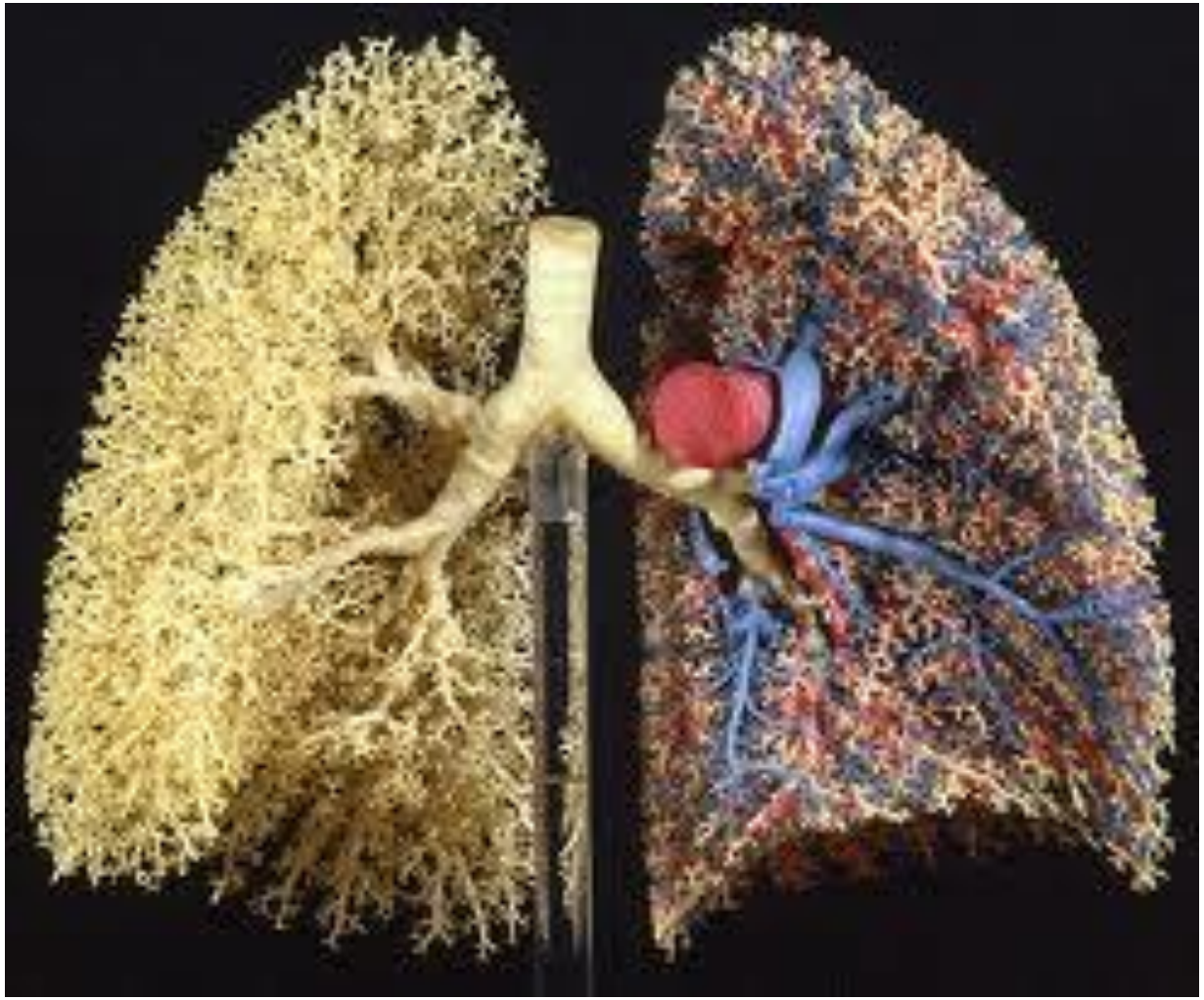


Function

Upper airways:
Host defense by muco-ciliary clearance

Lower airways:
Gas exchange through the respiratory membrane

Complexity of Lung Cells and Diseases



More than 42 different cell types in the lungs:

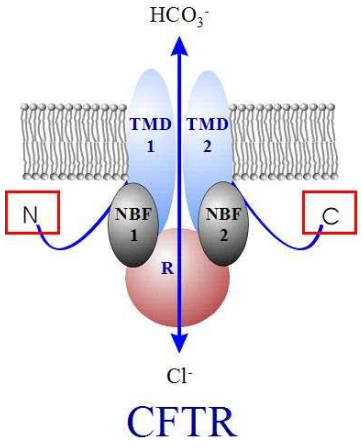
Endothelial cells – 30%
Interstitial cells – 37%
Epithelial cells – 33%
+ Inflammatory cells

Lung diseases affect multiple cell types and impact all anatomical areas of the lung.

Successes and Challenges in Regenerative Therapies for Lung Diseases

	Monogenic Lung Diseases	Complex Lung Diseases
Pathogenesis Understood	✔	✕
Representative Mouse Models	✔	✕
Therapeutic Strategies Identified	✔	✕
Disease Examples	Cystic Fibrosis, Pulmonary Alveolar Proteinosis	Idiopathic Pulmonary Fibrosis, COPD

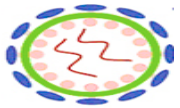
Cystic Fibrosis – Treatment Strategy – Ex Vivo Gene Correction and Transplantation of Airway Stem Cells



Transplantation

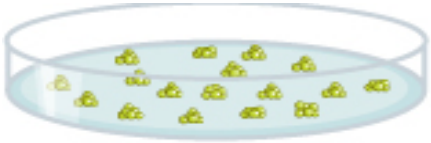
PBMCs

Genetic Reprogramming



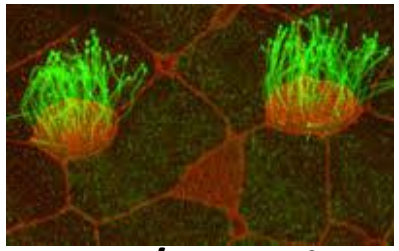
Cmyc
Sox2
Oct4
KLF4

Transfection



Human Induced Pluripotent Stem Cells

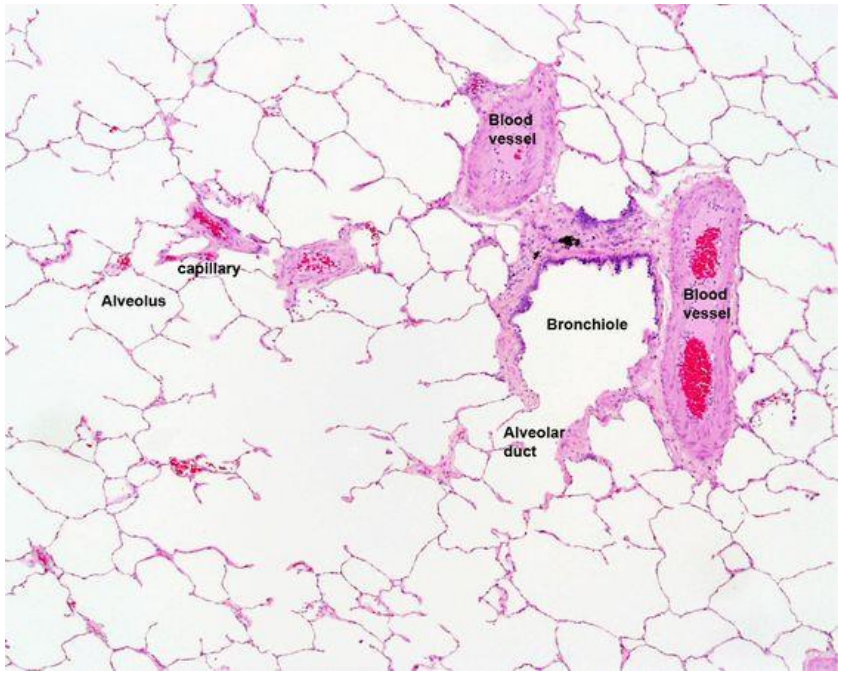
Differentiation and genetic modification



Lung stem/progenitor cells

expansion

Challenges for Developing Therapies for Complex Lung Diseases



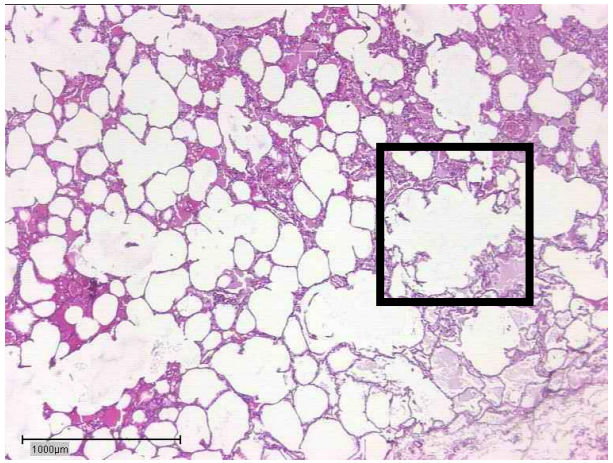
Normal lung

?

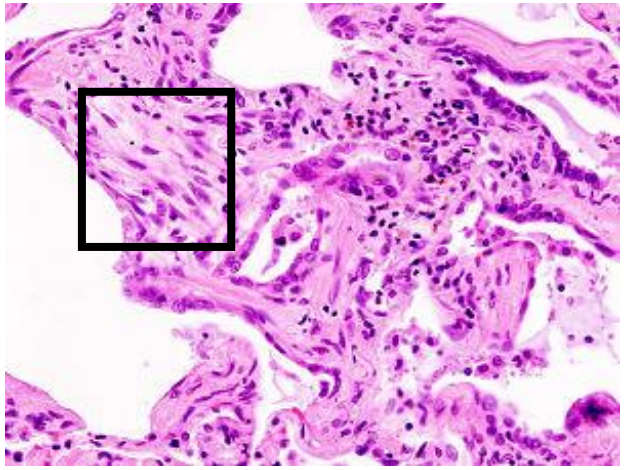
Injury and Repair

Genes + Environment

?

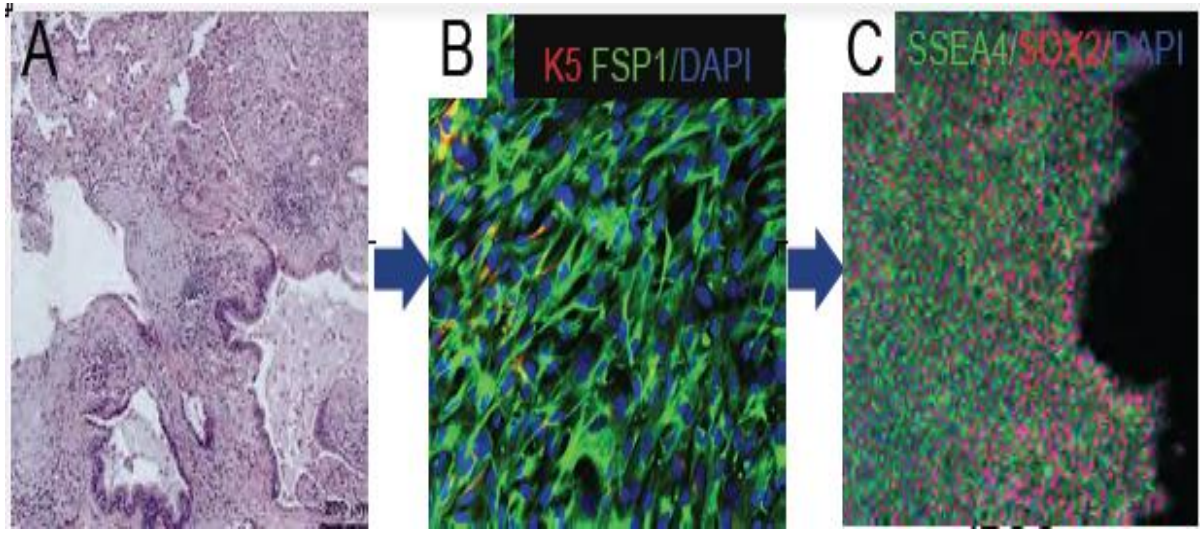


COPD



IPF

Modeling Complex Disorders – Using iPSCs from Familial IPF Patients to Model IPF



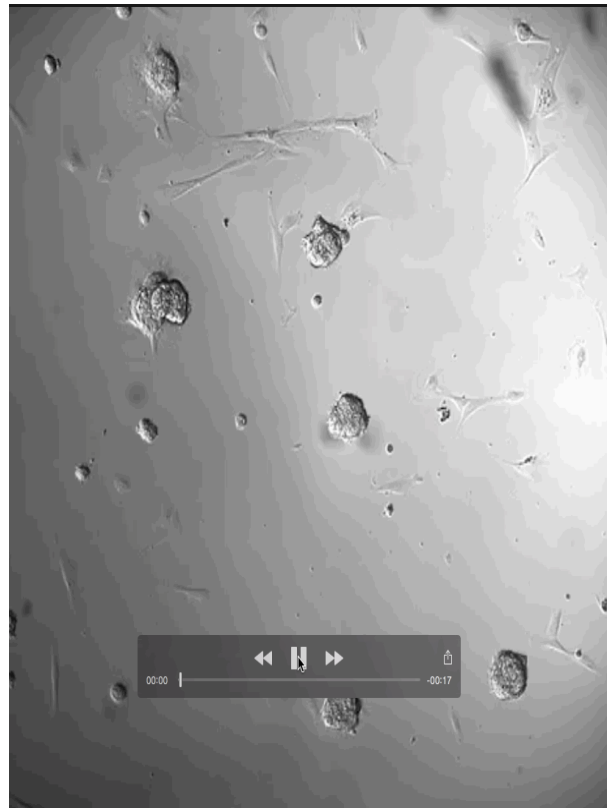
IPF Tissue

IPF lung fibroblasts

iPSCs derived from IPF lung fibroblasts

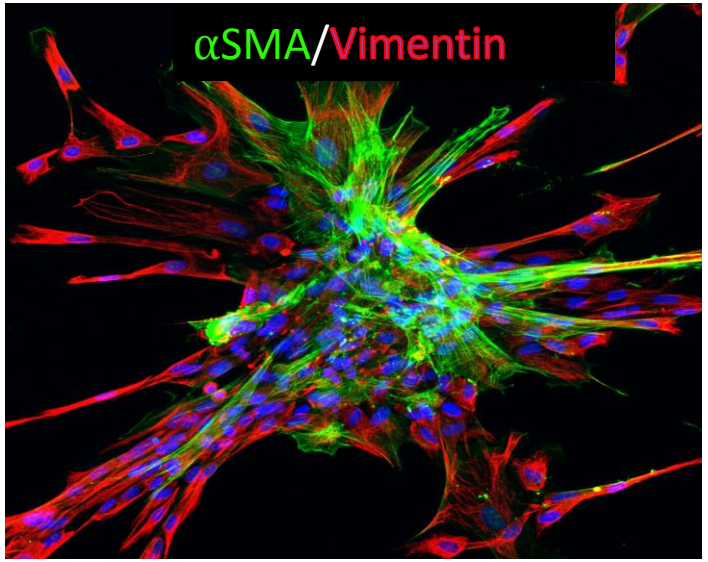
Day 4

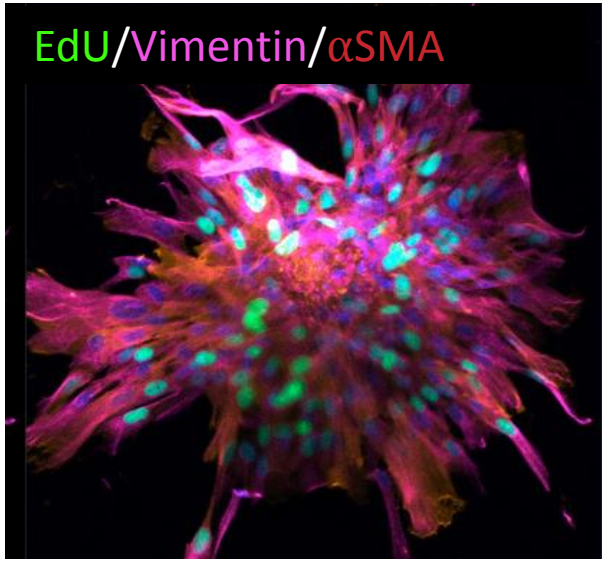
Day 13

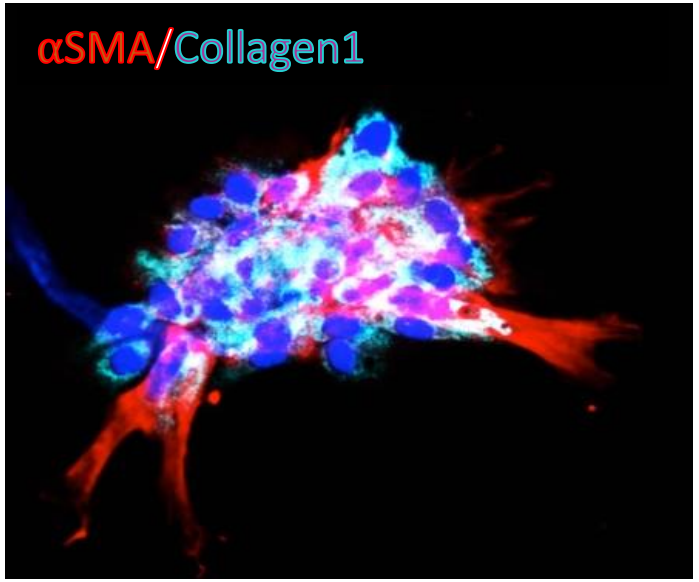


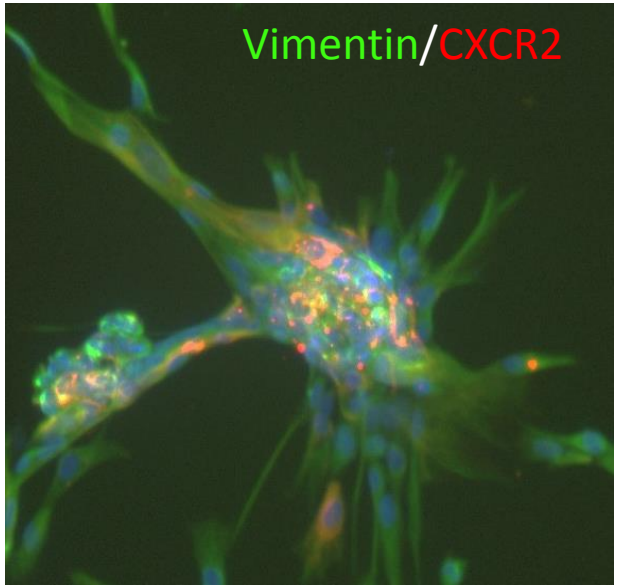
Preethi Vijayaraj

Patient-Derived iPSCs Model Fibrosis in a Dish





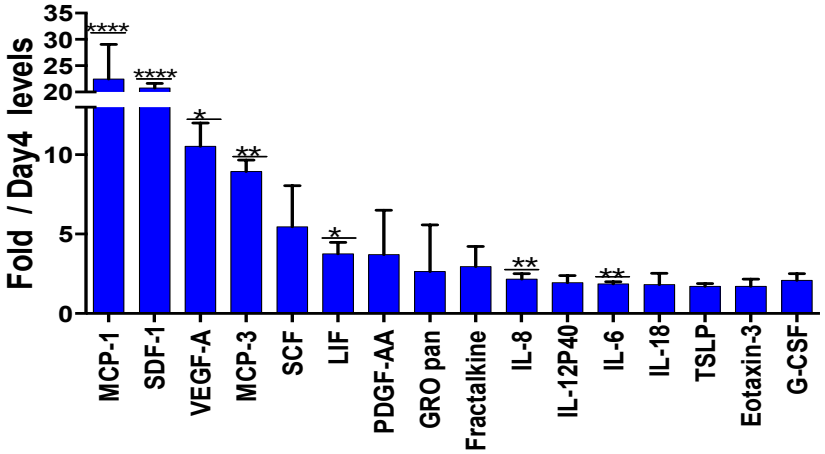




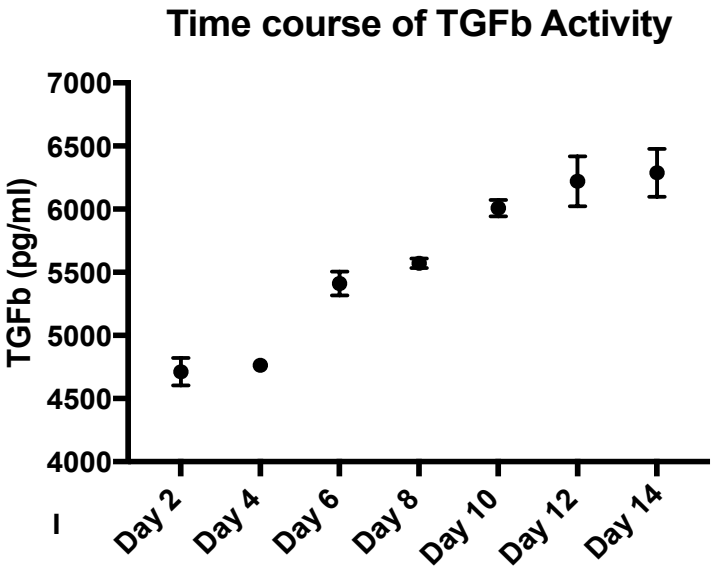
Preethi Vijayaraj

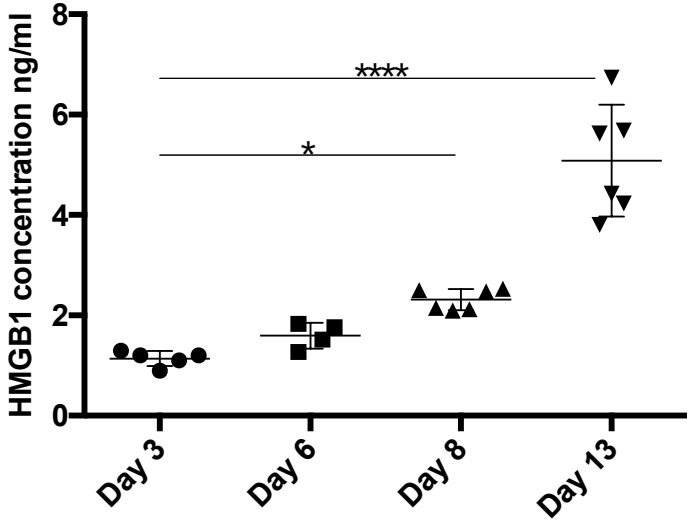
Patient-Derived iPSCs Model IPF

Cytokine and Chemokine Production

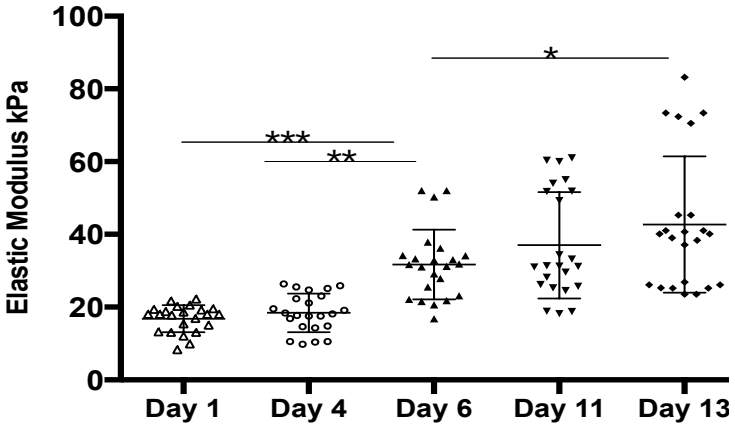


Activation of TGFβ





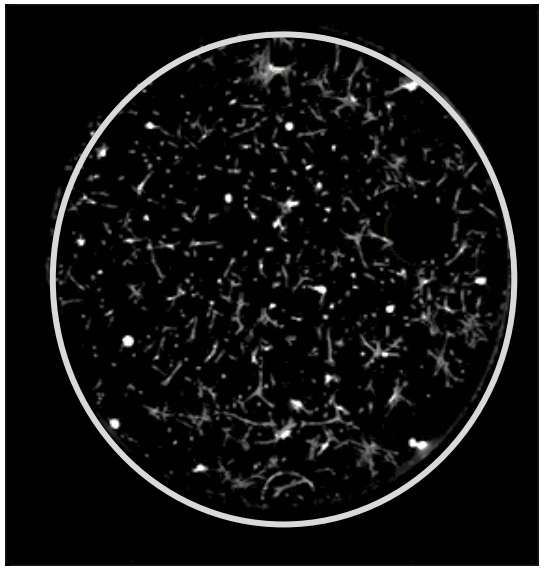
Damage Associated Molecular Pattern



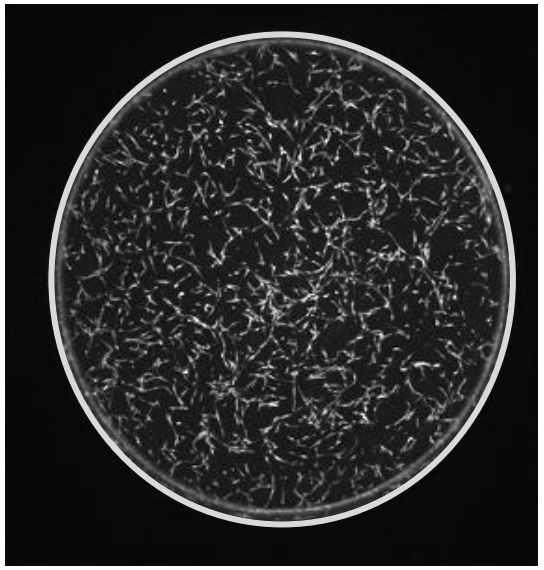
Atomic Force Microscopy

Phenotypic Drug Screening for IPF

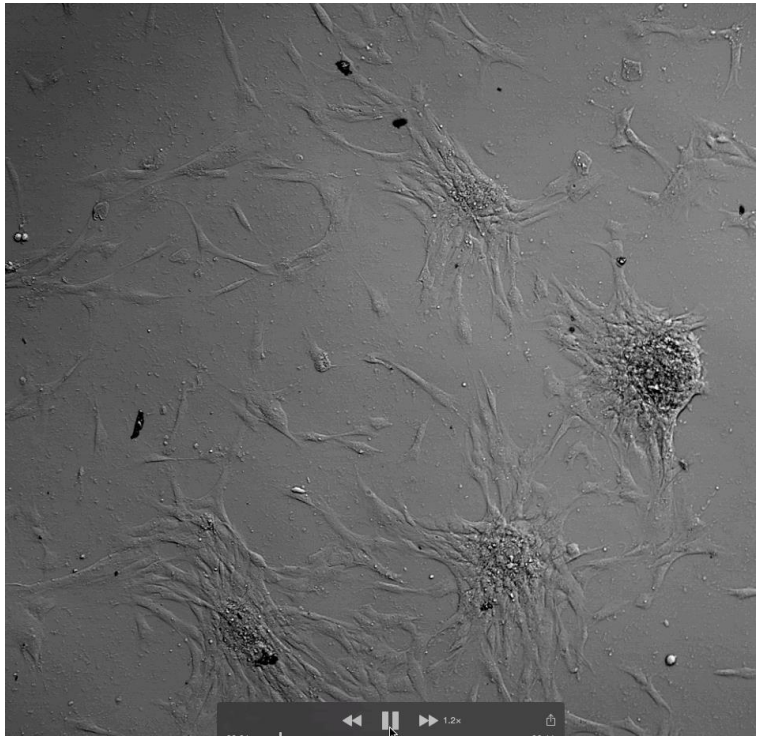
1% DMSO



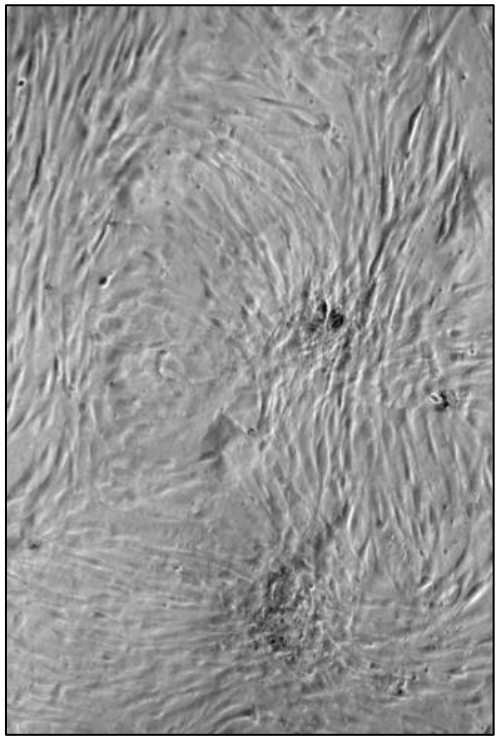
Compound X



Compound X - reversal (24 hrs)

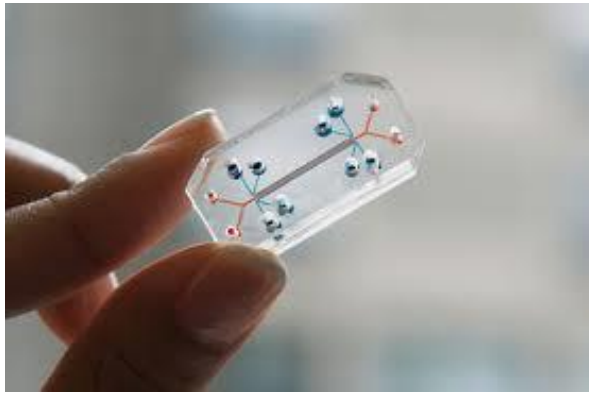


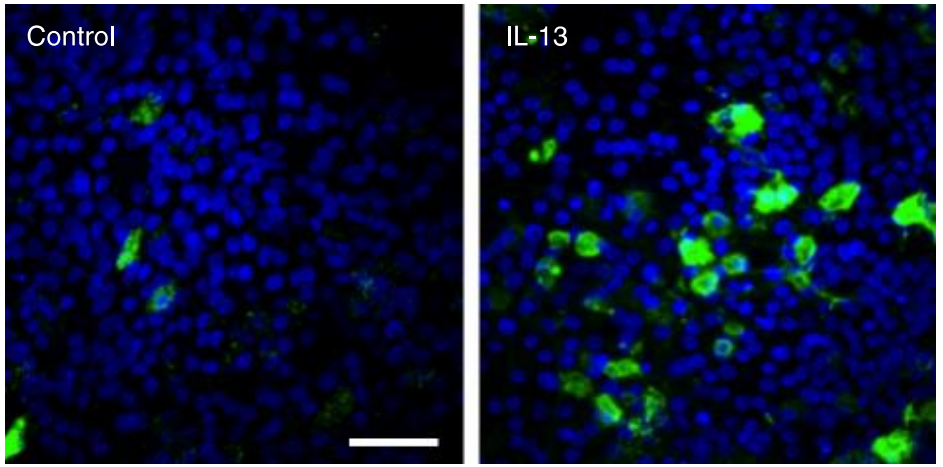
Compound X reversal (48 hrs)



Bioengineering Lungs – Lung on a Chip
Building lung structure and function

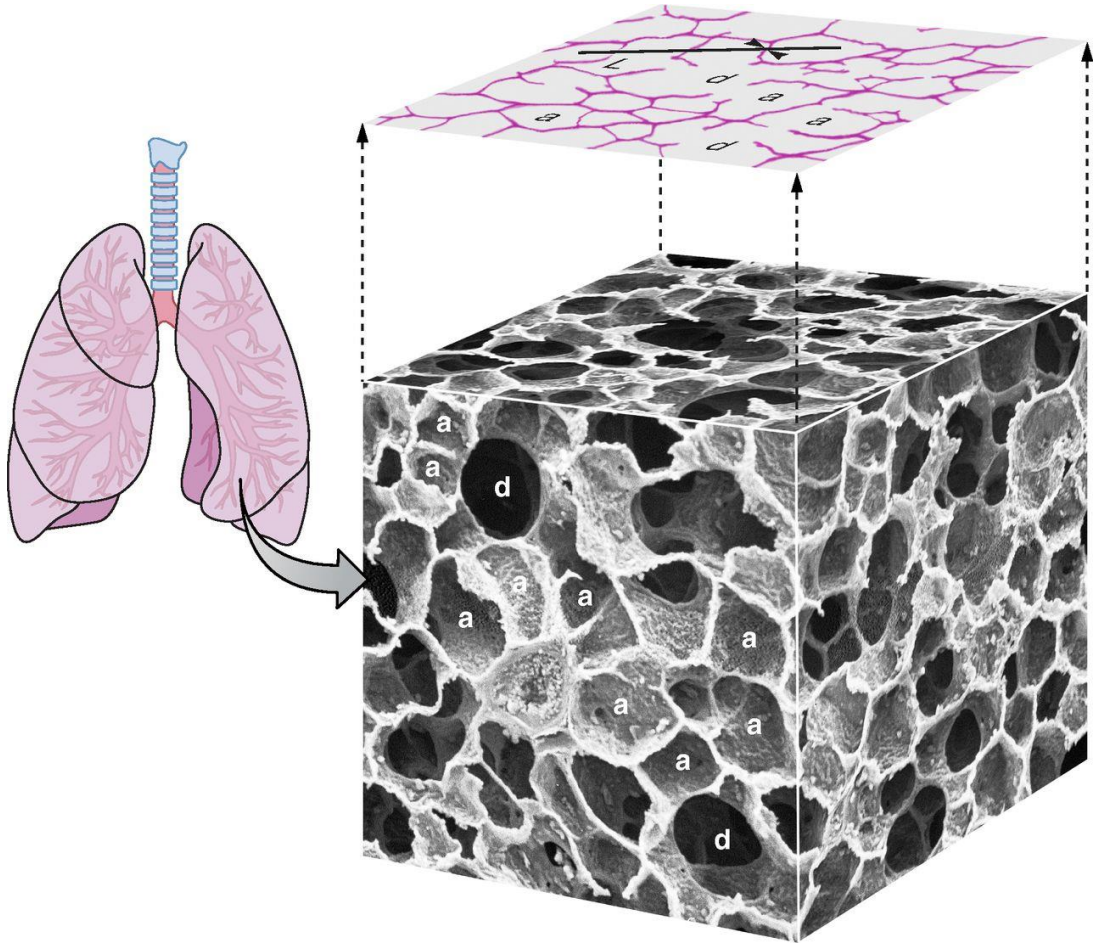
- Primary cells seeded in microfluidics device
- Two chambers: epithelial and endothelial
- “Breathing movements” allow for cyclic stretch
- Multiple pathologic states modeled: asthma, COPD, airway response to injury, etc.
- Platform for drug/toxin screen



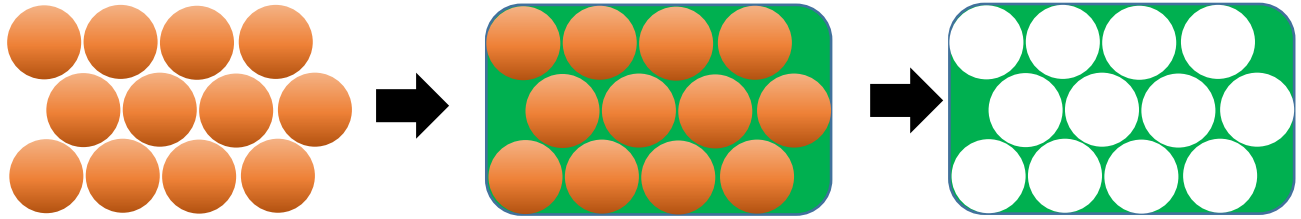


Benam KH et al, *Nature Methods*; 13 (2): 151-160

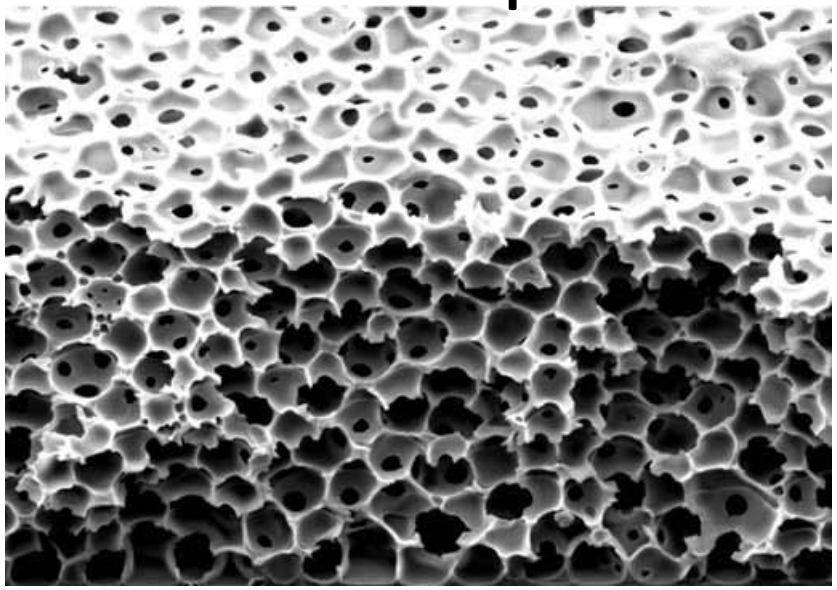
Mimicking Lung Architecture – The Importance of 3D



Inverse Opal Generation

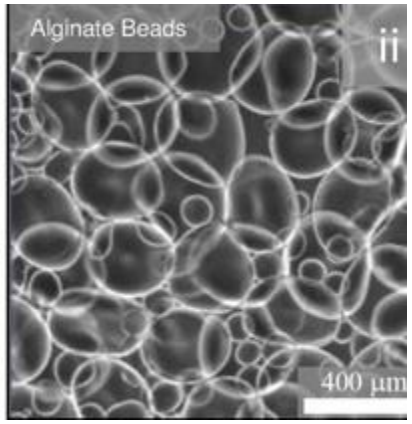


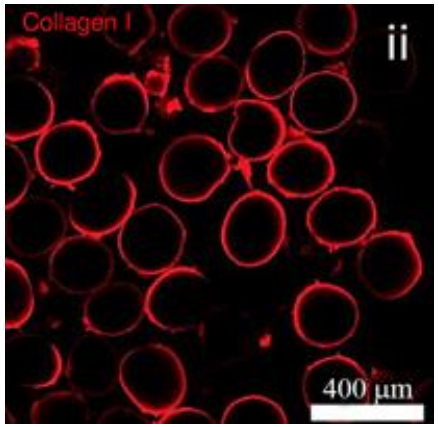
Inverse Opal

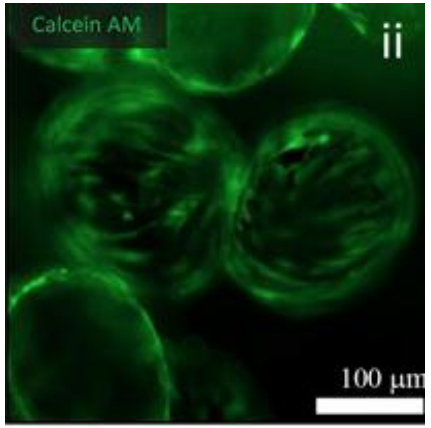


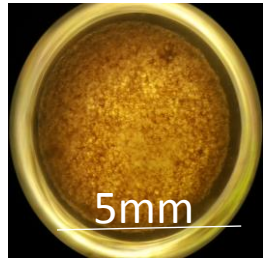
Bruce Dunn
Dan Wilkinson

Bioengineering Lungs Using 3D Scaffolds

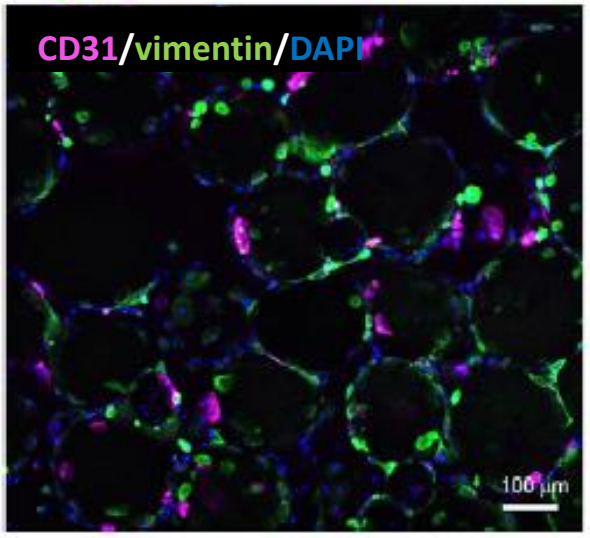




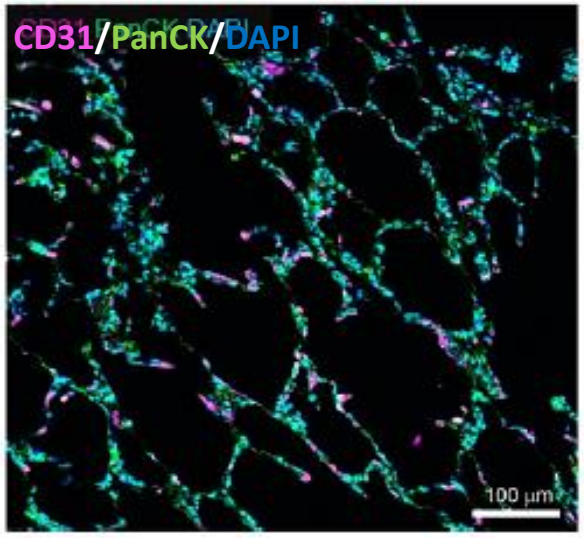




Beads and lung fibroblasts spinning at 4rpm in bioreactor



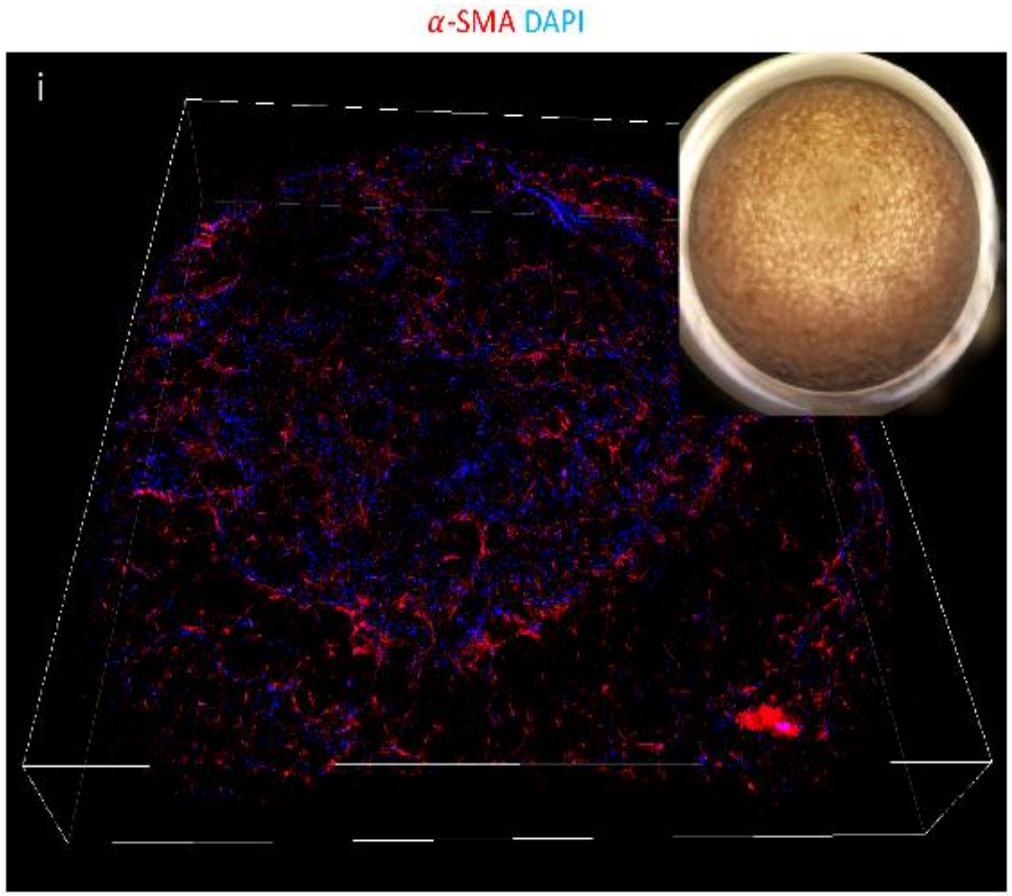
Bioengineered lung



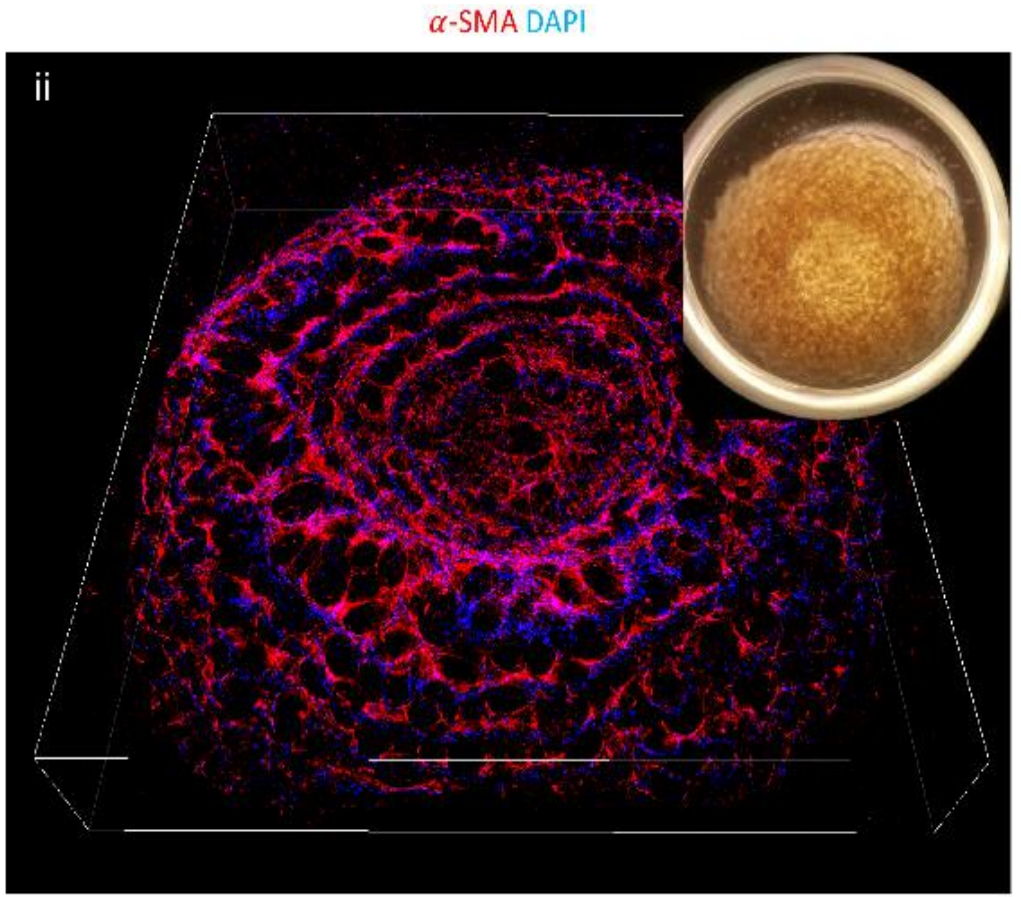
Normal human lung

Wilkinson D et al,
Stem Cells Translational Medicine 2016

Using 3D Bioengineered Lung Tissue for Disease Modeling and Drug Discovery

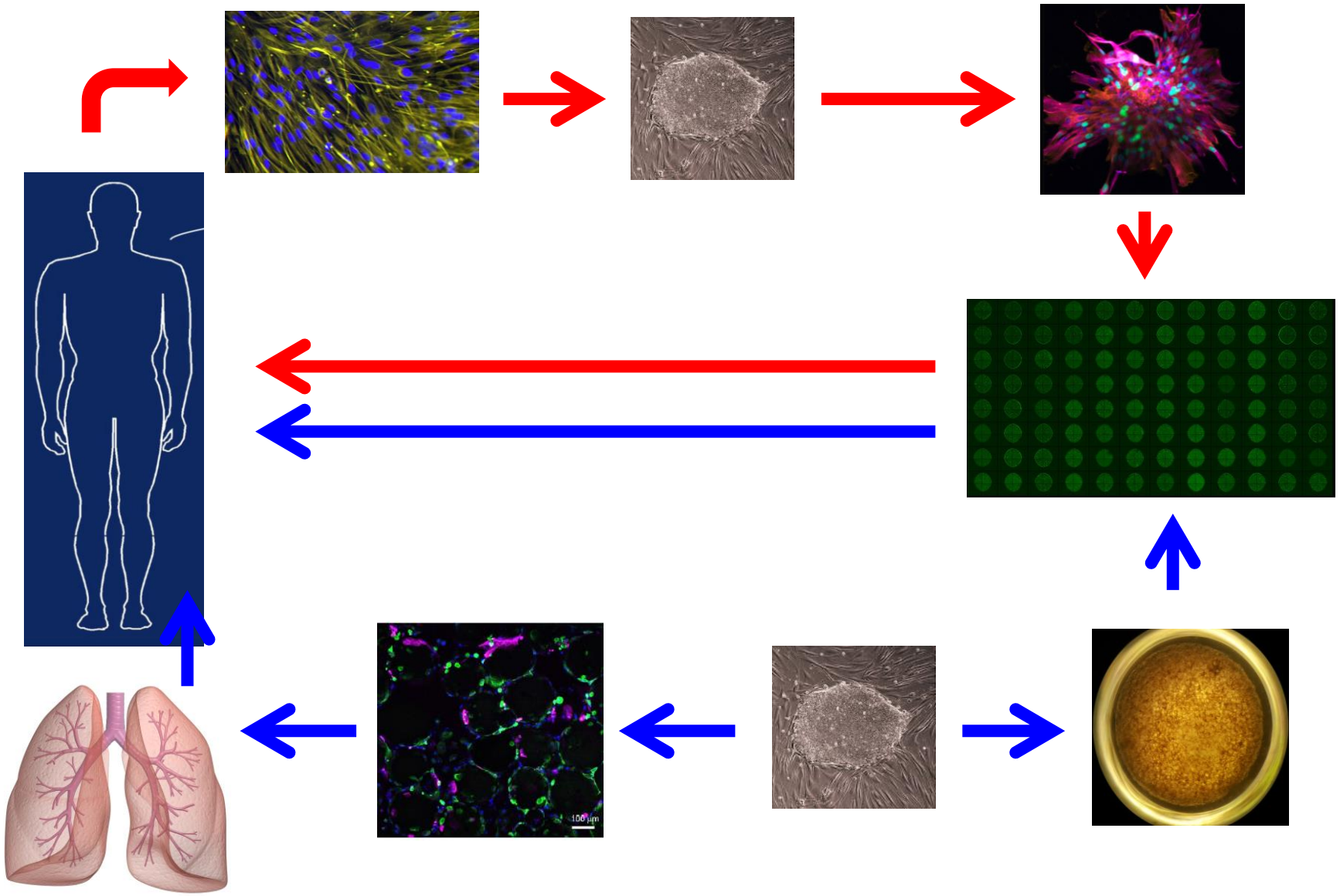


No TGFβ



TGFβ

Summary – Pathways to the Clinic for Complex Lung Diseases



Acknowledgements

Gomperts lab:

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Bharti Bisht
Jackie Alva
Kelly Darmawan
Ashley Hope

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CIRM CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE
National Heart Lung and Blood Institute
Tobacco-Related Disease Research Program TRDRP Research for a Healthier California
Congressionally Directed Medical Research Programs CDMRP Department of Defense
CONCERN FOUNDATION