How single-cell biology is reshaping our understanding of pulmonary fibrosis

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Disclosures

- Grants/Contracts: NIH/NHLBI, Department of Defense, Department of Veterans Affairs, ThreeLakes Foundation, Boehringer Ingelheim, Bristol-Myers-Squibb
- SAB/Consulting: APIE, ARDA

Idiopathic Pulmonary Fibrosis is an awful disease



Current IPF therapies modestly slow disease progression and are poorly tolerated





Richeldi et al. NEJM 2014.

Epithelial injury and dysfunctional repair is central to IPF pathogenesis – but how?



Step 1: Building the IPF Cell Atlas



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114,396 cells20 PF Lungs10 Control

Habermann et al. *Science Advances* 2020. 6:eaba1972

Step 1: The IPF Cell Atlas – novel progenitor cells







Habermann et al. *Science Advances* 2020. 6:eaba1972

Step 1: The IPF Cell Atlas

KRT17+ "aberrant basaloid cells" exhibit most of the "hallmarks" of IPF lungs



Step 2: Integrating genetics and single cell genomics



Natri et al. Nature Genetics 2024.

A subset of eQTL have disease-context specific regulatory effects



Natri et al. Nature Genetics 2024.

Disease-interacting eQTL are enriched within motifs for stress-induced transcription factors



Step 3: Modeling disease biology ex-vivo





FLEX-seq resolves perturbation conditions that phenocopy IPF-associated cellular reprogramming



Step 4: Leveraging archival samples





Early IPF High Risk Cohort@VUMC



Defining the Molecular Pathogenesis of Early Pulmonary Fibrosis





Nick Banovich Annika Vannan



Spatial transcriptomics



Unsupervised hierarchical clustering distinguishes ILA progression outcomes



UMAP1



FLEX-seq of archival FFPE blocks



Step 5: Spatial contextualization of diseaseemergent cellular phenotypes



Vannan et al. bioRxiv 2023. [in-revision]



Deciphering cellular diversity of pathologic features



Imaging-based spatial methods allow use of cellagnostic methods to explore "niche" evolution



Vannan et al. bioRxiv 2023. [in-revision]

Characterizing progressive airspace dysregulation



Vannan et al. *bioRxiv* 2023. [in-revision]

Aberrant epithelial cell detachment on the "leading edge" of fibrosis



One Xexium slide generated data on more cells than our entire sc-eQTL dataset

Summary Decoding Cel	ll Segmentation Analysis	Image QC			
Key Metrics ③					
628,8 Number of cells of	60 detected Media	80 an transcripts per cell	184.7 Nuclear transcripts per 100 µm²	98,240,321 Total high quality decoded transcripts	
Custom panel: 34 TMA – 17 samples	13 genes s Seg	Segmentation Methods 💿			
	Cells	Cells segmented by boundary stain		22,138 (19.4%)	
	Cells	Cells segmented by interior RNA stain		478,375 (76.1%)	
	Cells	segmented by nucleu	s expansion (5.0 µm) 2	28,347 (4.5%)	
	Total	cells detected	e	528,860 (100%)	

Cellbound looks promising to improve segmentation



Cellbound enhances segmentation fidelity, especially for irregularly shaped cells



Acknowledgements

- Vanderbilt Lung Fibrosis Research group
 - Margaret Salisbury, MD
 - Scott McCall MD, PhD
 - Jason Gokey, PhD
 - Ana Serezani, PhD
 - Erin Wilfong, MD/PhD
 - Carla Calvi

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- Taylor Sherrill
- Merced Malabanan, PhD
- Ujjal Singha, PhD
- Frank Kamga, PhD
- Rafi Fernandez, MD, PhD
- David Nichols
- David Han
- Isabella Gaona
- Luca DiGiovanni
- Abigail Dietrich
- Daphne Mitchell
- Lisa Lancaster & ILD clinical team
- Coordinators and study nurses

VUMC collaborators

- Jennifer Sucre (Neonatology) & BOLD Center
- Ciara Shaver, Julie Bastarache, Lorraine Ware (Pulmonary)
- Matthew Bacchetta (Cardiac Surgery) & Lung Transplant Program
- Bradley Richmond (Pulmonary)
- John Phillips & Joy Cogan (Pediatric Genetics)
- Qi Liu & colleagues (Biostatistics)
- VANTAGE
- Sam Bailin, John Koethe, Celestine Wanjalla (ID)
- Vineet Agrawal, Anna Hemnes (Pulmonary HTN)
- Ravi Shah (Cardiology)
- U. Michigan
 - Tim Blackwell
 - Yang Liu
- Translational Genomics Research Institute
 - Nick Banovich
 - Annika Vannan
- St. Vincent's Research Institute (Melbourne)
 - Davis McCarthy
 - Ruiqian Lyu
- Cornell
 - Anna Podolanczuk
 - Renat Shaykiev











Pulmonary Fibrosis

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Vanderbilt Institute for Clinical and Translational Research

Boehringer Ingelheim, Cellgene/BMS

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