21st century disease models

Case study: COPD and severe asthma

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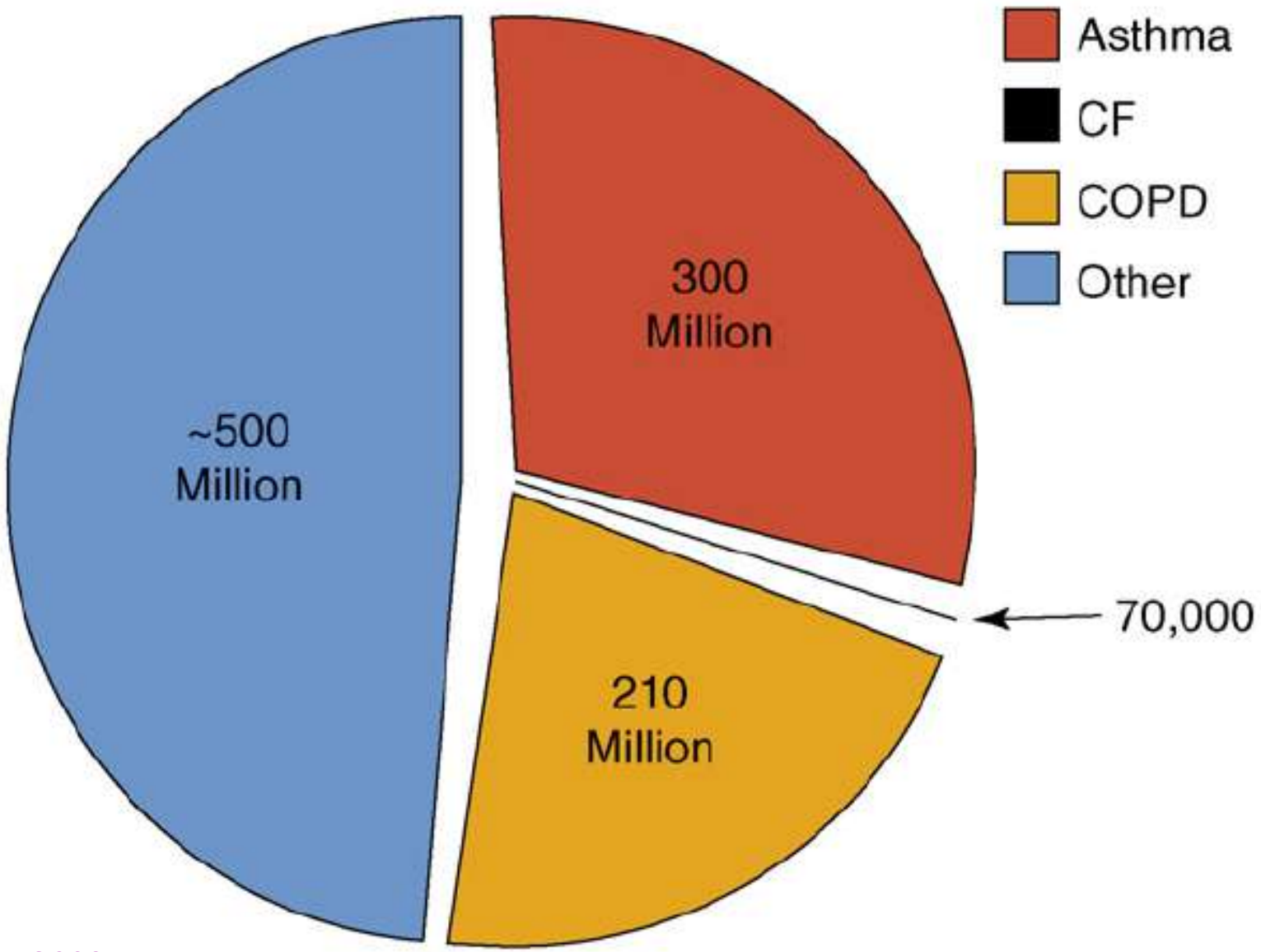
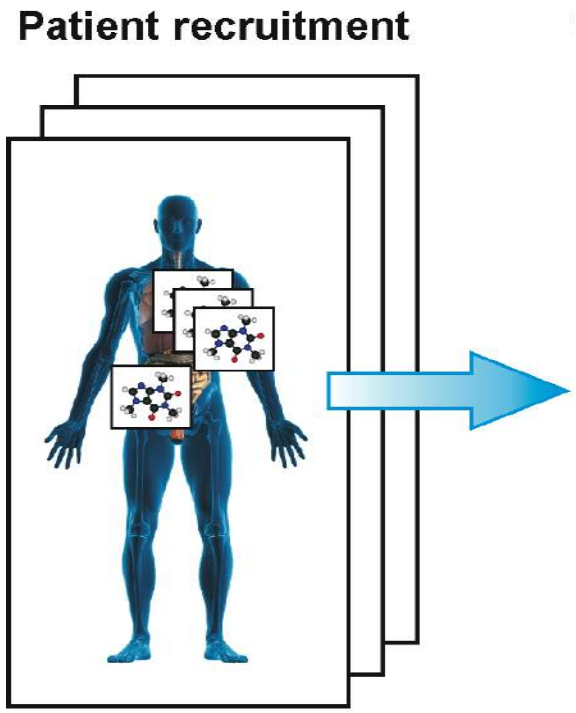
Worldwide prevalence of inflammatory lung diseases



Donnelly & Rogers 2008

Severe asthma and COPD: the problem

- Current treatments are insufficient
- All disease is not the same –
  - heterogenous diseases with distinct phenotypes



U-BIOPRED project:

Hypothesis generation

Consensus clustering on clinical features

Smoking (cluster 2) vs non-smoking (cluster 3) of airflow obstruction

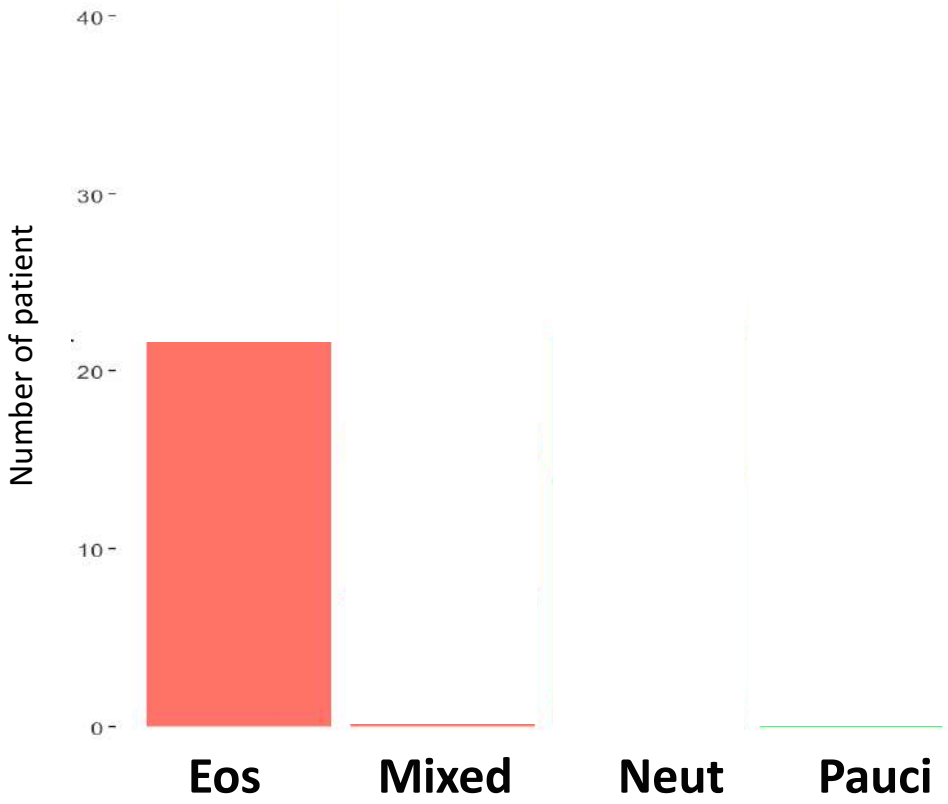
- ***Pathway analysis of cell transcriptomics***

Regulation of actin cytoskeleton (*ITGB1, FN1, ACTN2*)
Fibronectin matrix formation (*ITGB1, FN1)*

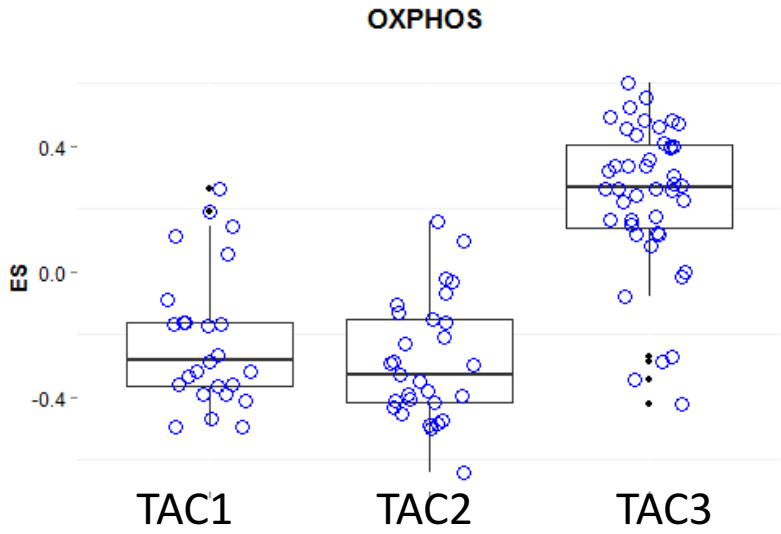
- ***Differentially-expressed proteins in supernatants***

LYN: src non-receptor lyn tyrosine kinase
FUT5: Fucosyltransferase 5

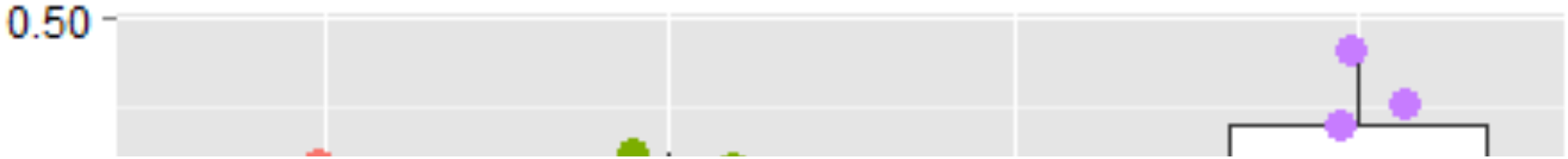
Relationship between sputum inflammatory pattern and the 3 transcriptomic modules



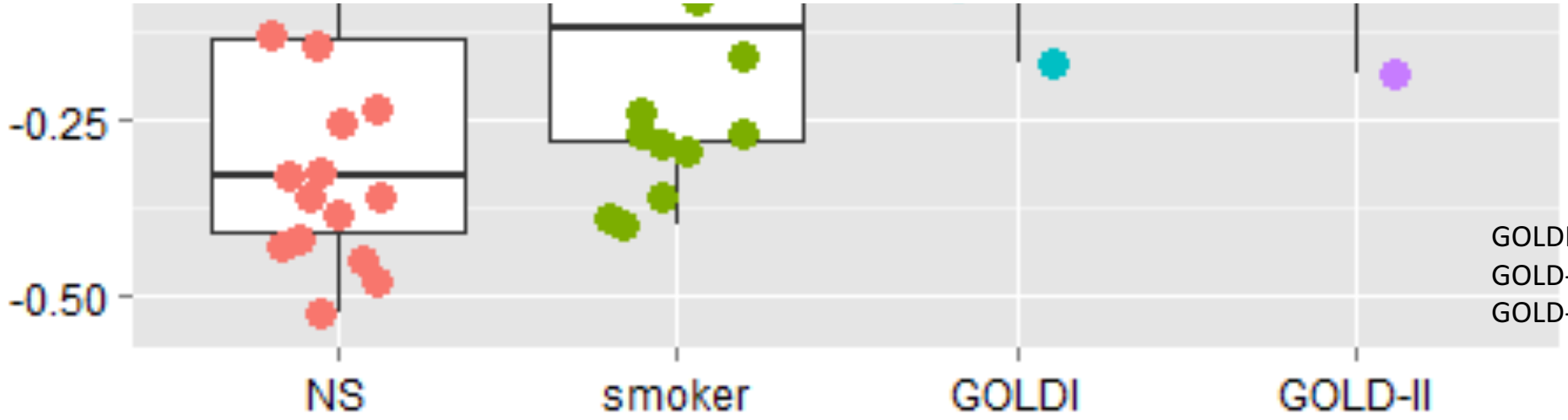
Linked to OXPHOS and ageing and specific macrophage subtypes



TAC3 cluster also enriched in COPD patients



TAC1 enrichment predicts ICS responders in GLUCOLD patients



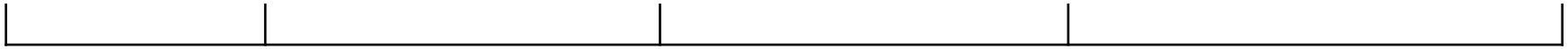
GOLDI-NS	0.32	0.009
GOLD-II-NS	0.41	0.0005
GOLD-II-smoker	0.26	0.045

Summary of Transcriptome Modules in asthma from sputum analysis

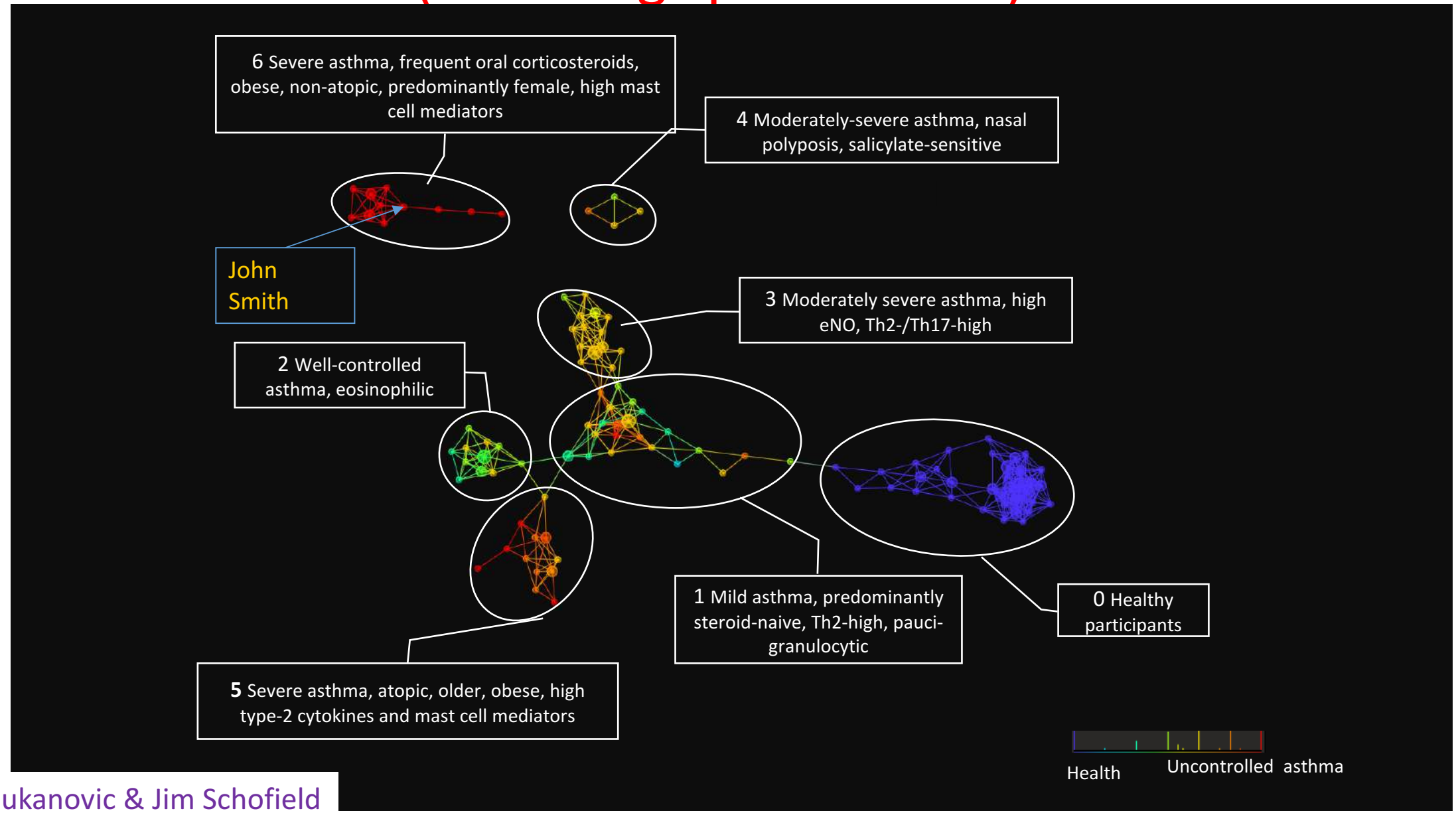
Specific genes characterise each TM and subgroup

TM clustering in sputum used to define blood biomarkers
(IL5RA, VEGFA; GCG, PLA2G2A; CD55, TGFB1, CD22)

Biomarker tests for molecularly targeted therapies are the key to unlocking precision medicine



TDA analysis of 22 clinico-pathological clusters in asthma (including sputum cells)



Ratko Djukanovic & Jim Schofield

Transcriptomic analysis of lung tissue from cigarette smoke induced emphysema murine models and human COPD show shared and distinct pathways

Jeong H. Yun[1,2], Jarrett Morrow[1], Caroline A.Owen[2,3], Weiliang Qiu[1], Kimberly Glass[1], Taotao Lao[1], Zhiqiang Jiang[1], Mark A. Perrella[2,4], Edwin K. Silverman[1,2], Xiaobo Zhou[1,2]*, Craig P. Hersh[1,2]*

*contributed equally

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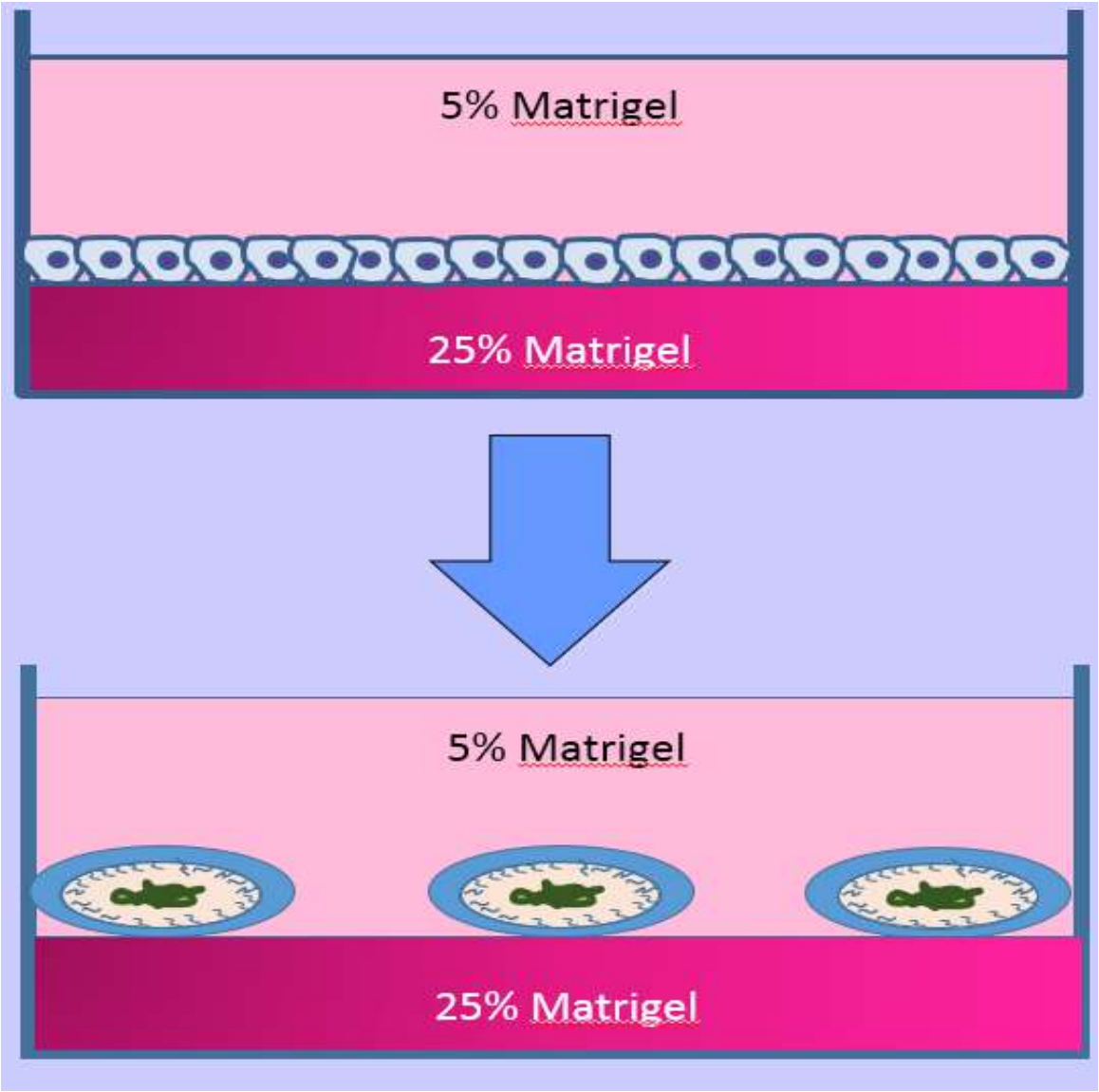
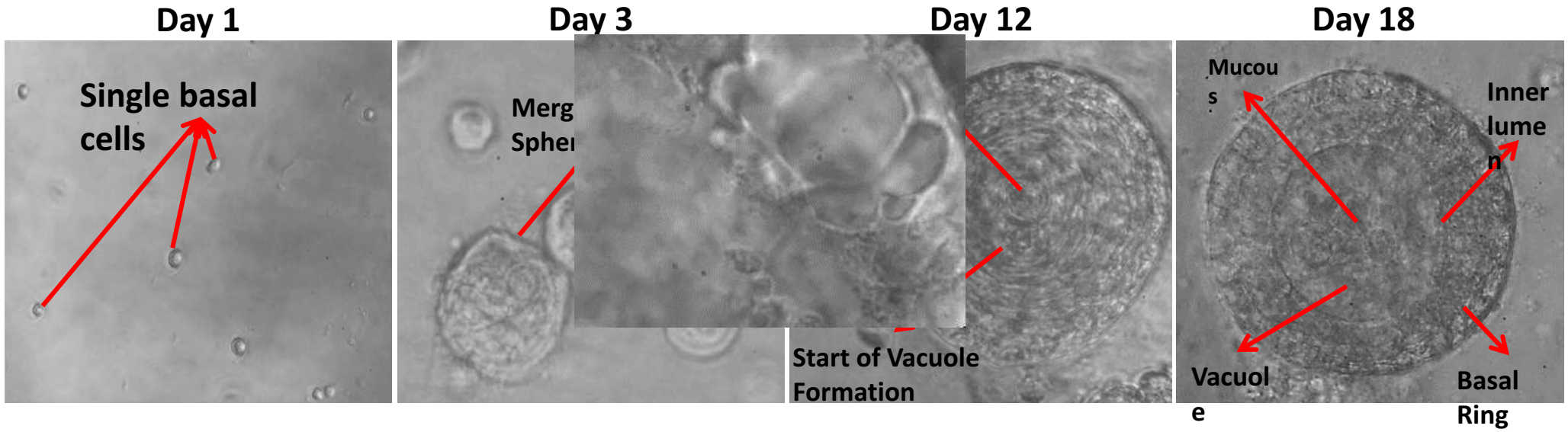
Schematic of Bronchosphere Culture



Plus stiffening agent

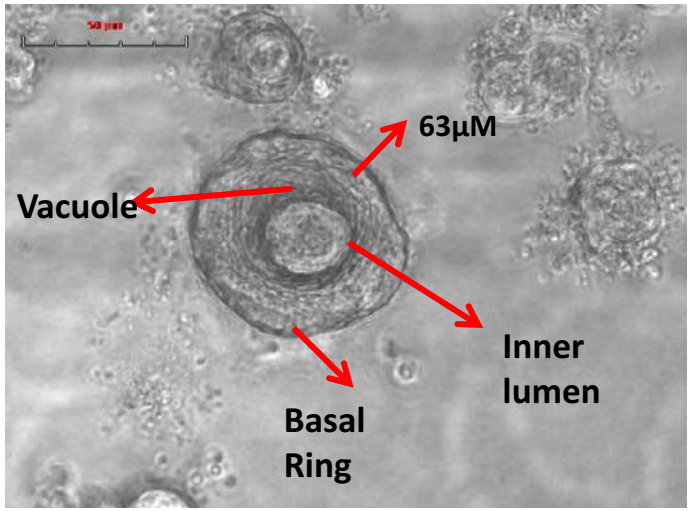
NHBE Bronchosphere Development

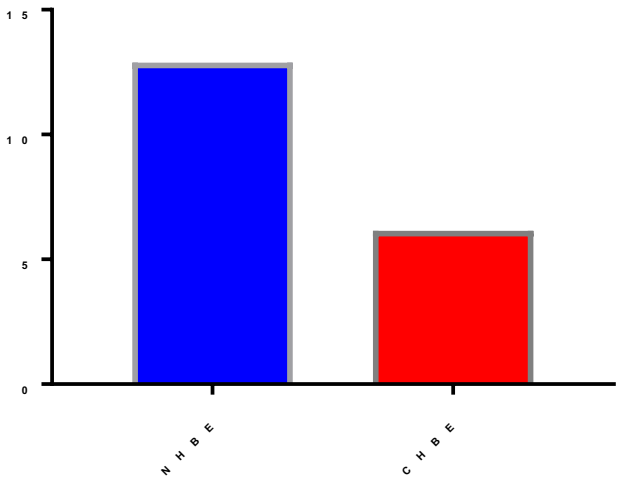


Basal Cells **Spheroids** **Intermediate Spheroid** **Bronchosphere**

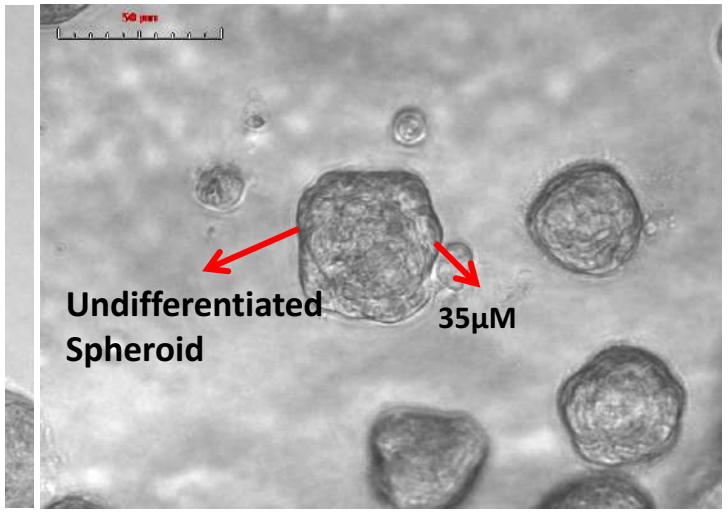
Basal cell marker positive ($P63^+$, $NFGR^+$ and $ITGA6^+$)

NHBEC

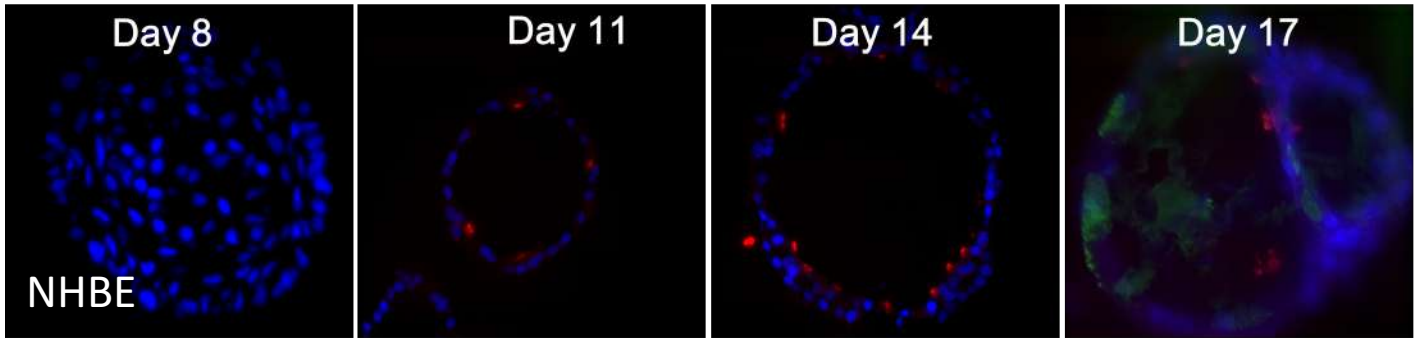




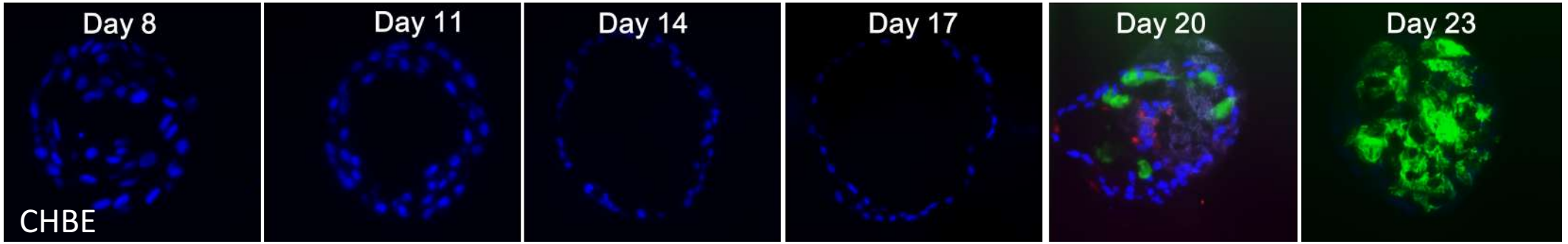
CHBEC

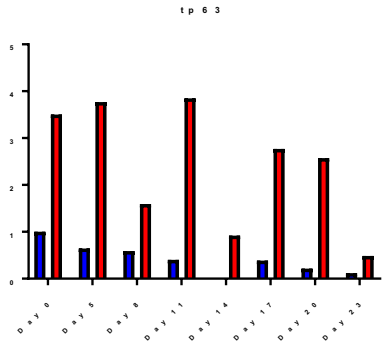


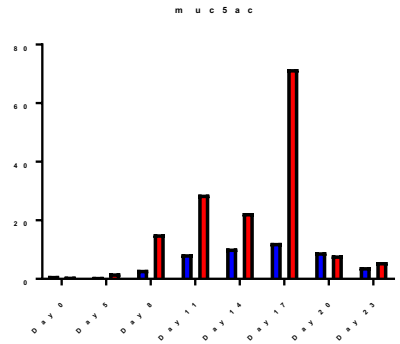
Gene Expression During Bronchosphere Development

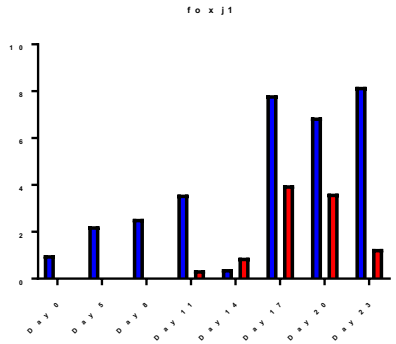


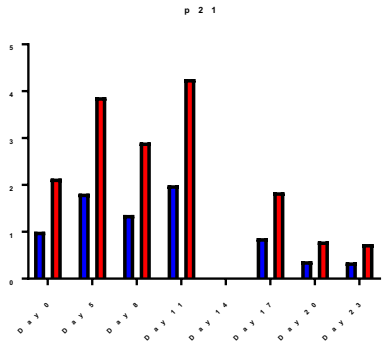
Representative staining of bronchosphere sections- α-tubulin (cilia), goblet cell (MUC5AC and DAPI (nucleus) from day 2-17 (NHBE) and 8-23 (CHBE) to show luminal development. Bronchospheres replicate features of human airway lumen.

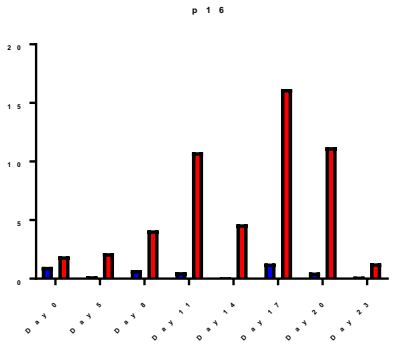








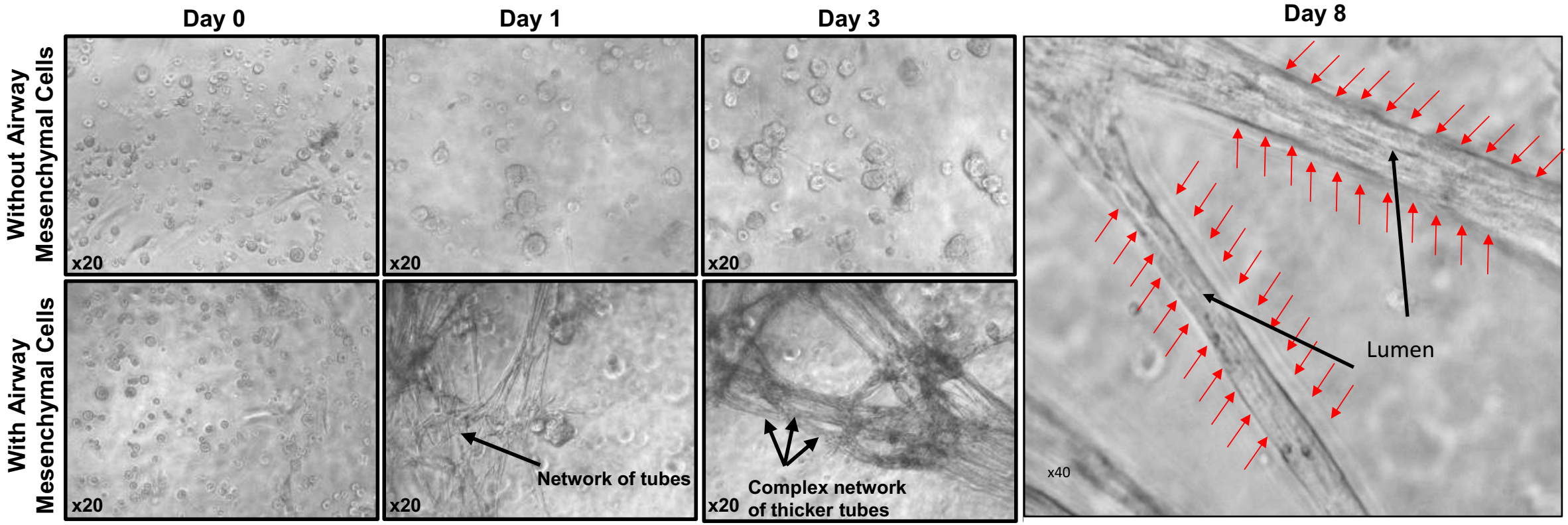




Bronchotubules/organoid formation

ASM, fibroblasts or stem cells. Tubules contract with acetylcholine

Stiffness essential as maintains structure – allows time to produce own matrix



Tank Guney, Sharon Mumby, Sean Ojo

The future

- Precision medicine is a rapidly developing field in respiratory medicine
- Integration of large datasets over time can:
  - refine patient subsets,
  - indicate mechanisms to enable targeted therapy
- Analysis at the target site important for subphenotyping patients before examination of blood biomarkers
- Better models for mechanistic studies and PoC drug studies
- Need to translate to point of care

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