Mechanisms of pulmonary fibrosis

Need for an integrated approach

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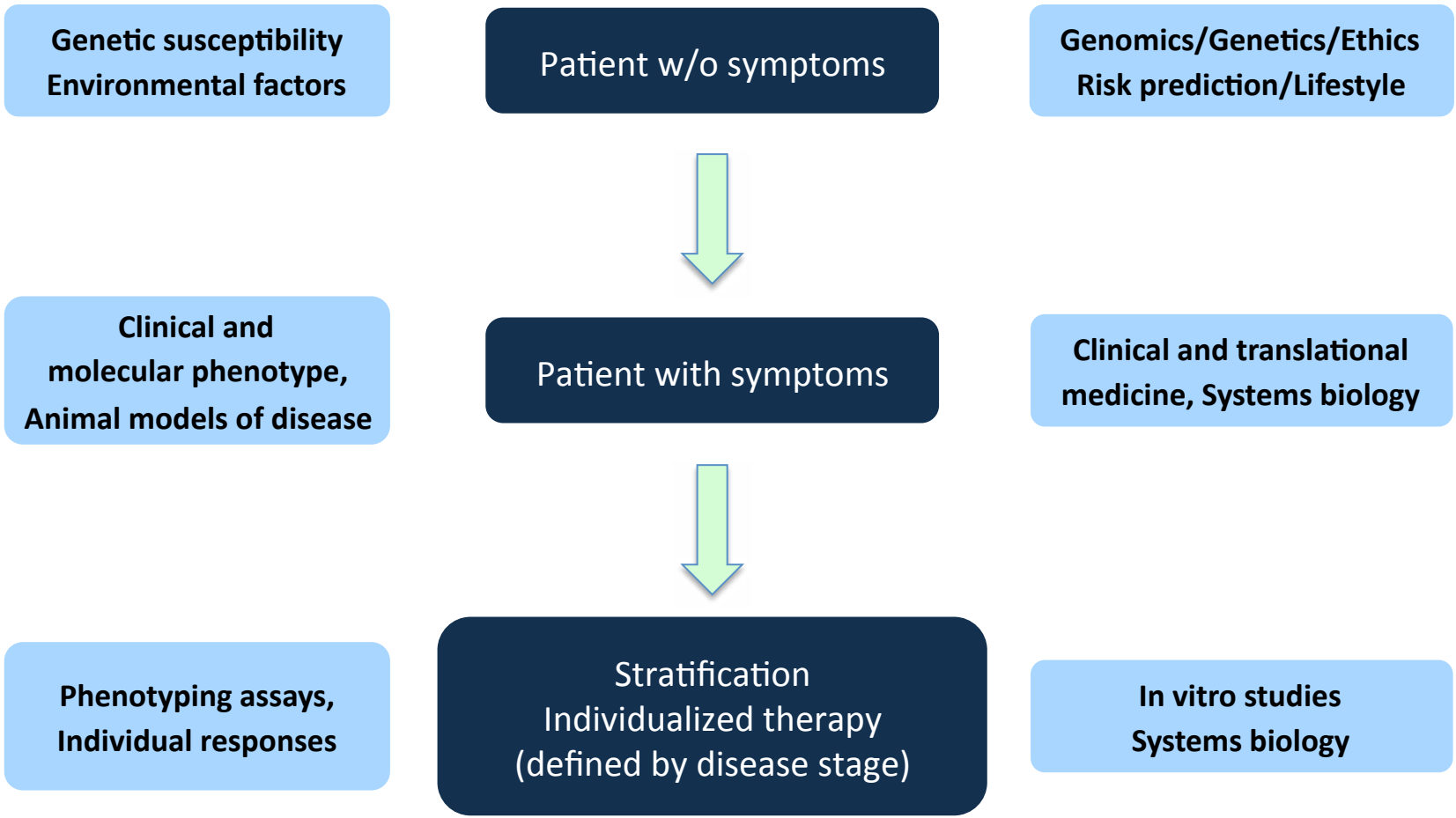
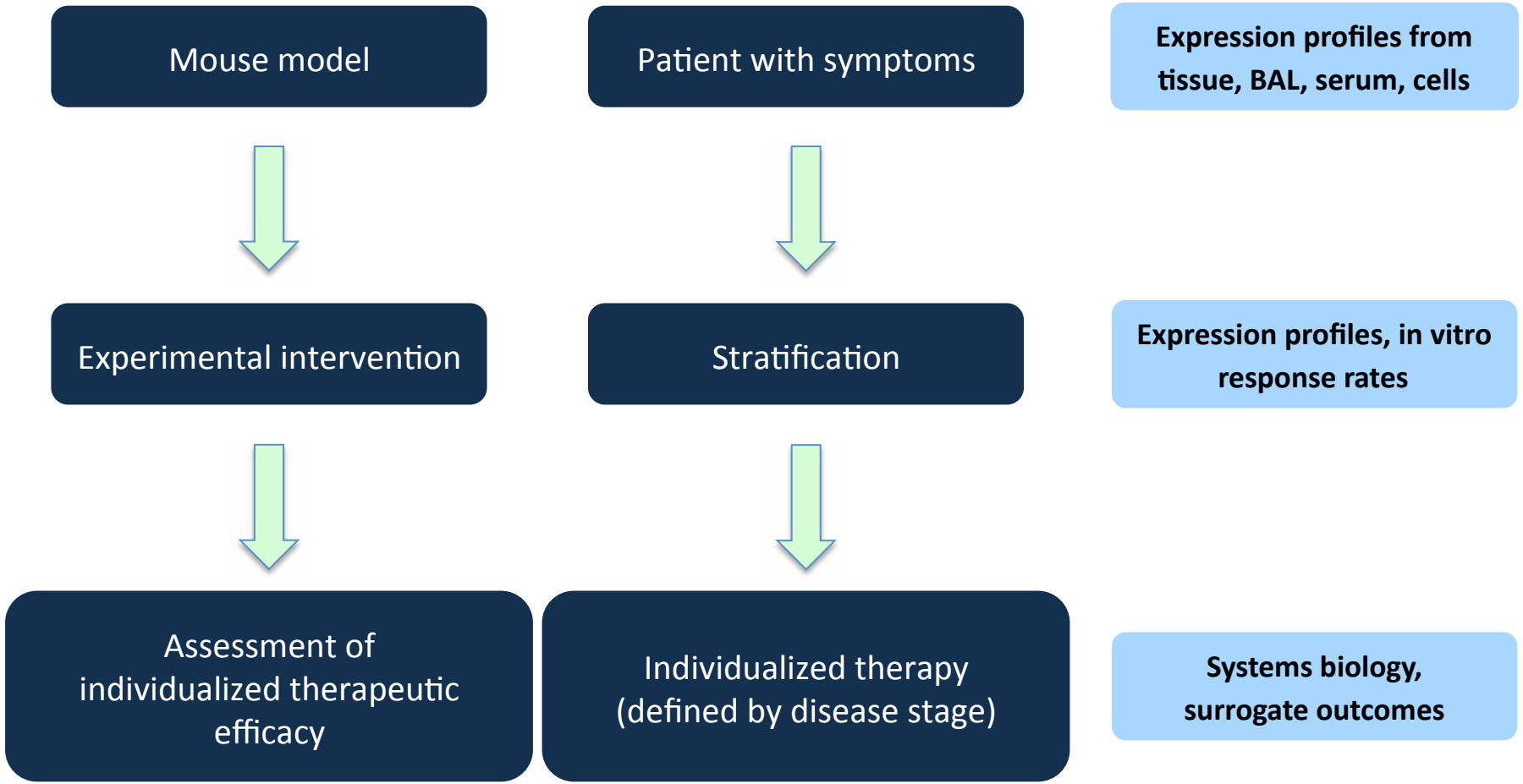
BioMax Symposium, Thursday, May 3, 2012

A complex situation



Parallel universes



Idiopathic Pulmonary Fibrosis (IPF)

ATS/ERS definition 2011: "IPF is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause limited to the lungs, occuring primarily in older adults, and associated with a histopathologic and/or radiologic pattern of UIP. IPF diagnosis requires exclusion of other causes of interstitial pneumonias."

The challenge:
IPF – an elusive disease

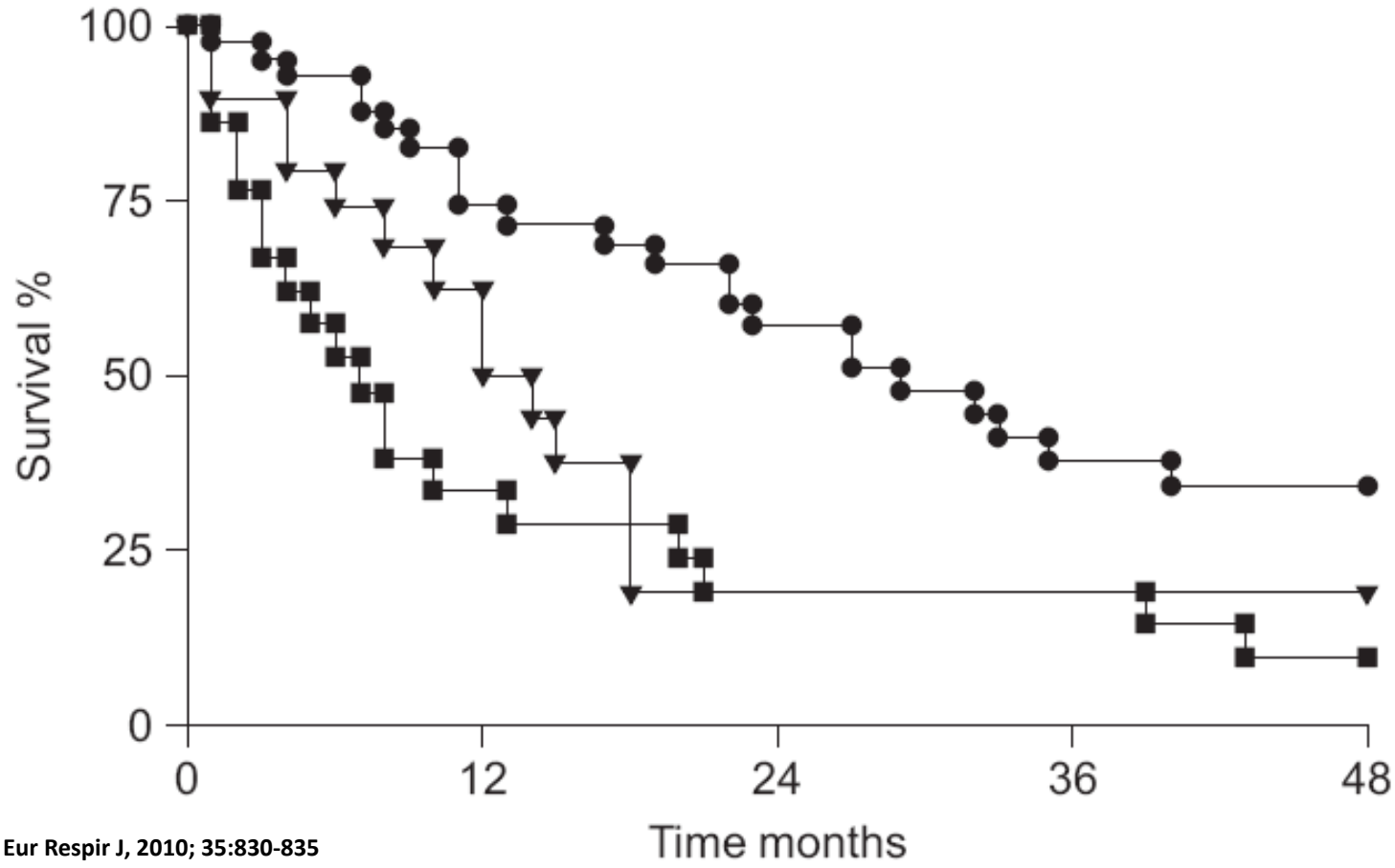
- IPF is a progressive and fatal interstitial lung disease (ILD)
- The natural history of IPF has literally been the same for the last 20 years
- Improving disease understanding has not yet led to translation into clinical practice
- Clinical trials have been unsuccessful (but 3)
- Despite impact of guidelines and consensus recommendations (ATS/ERS 2002), IPF remains a challenge in terms of heterogeneity

Lung function decline in IPF

4-year-survival of 84 SLB proven IPF patients

- stable disease at 6 months (n=38)
- ▼ marginal decline of FVC (5-10 %) at 6 months (n=23)
- ■ significant decline of FVC (>10%) at 6 months (n=23)

  p<0.005



Zappala et al., Eur Respir J, 2010; 35:830-835

ensive
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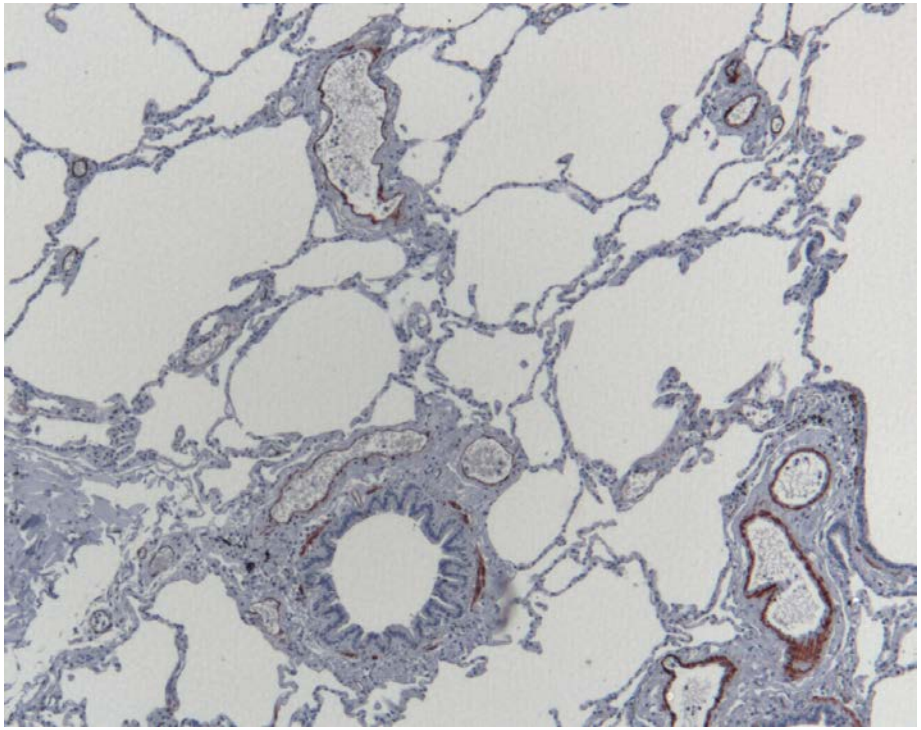
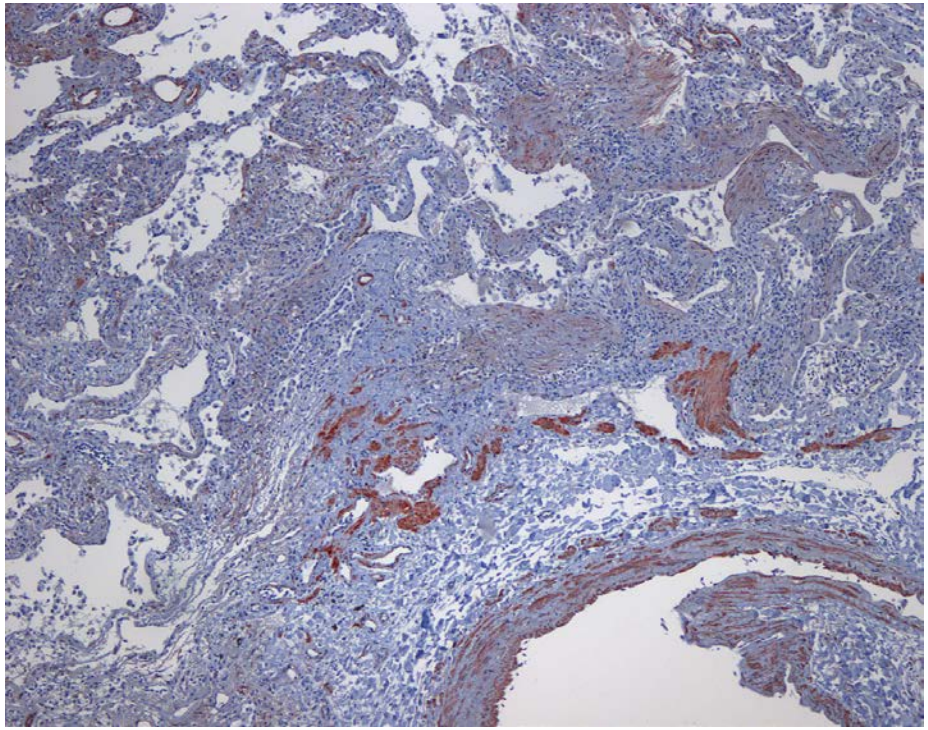
Idiopathic Pulmonary Fibrosis (IPF)



- small alveolar septae, little ECM deposition
- smooth muscle actin expression restricted to the circumference of airways and vessels



- *inhomogeneous* picture
- small alveolar septae next to massively thickened septae
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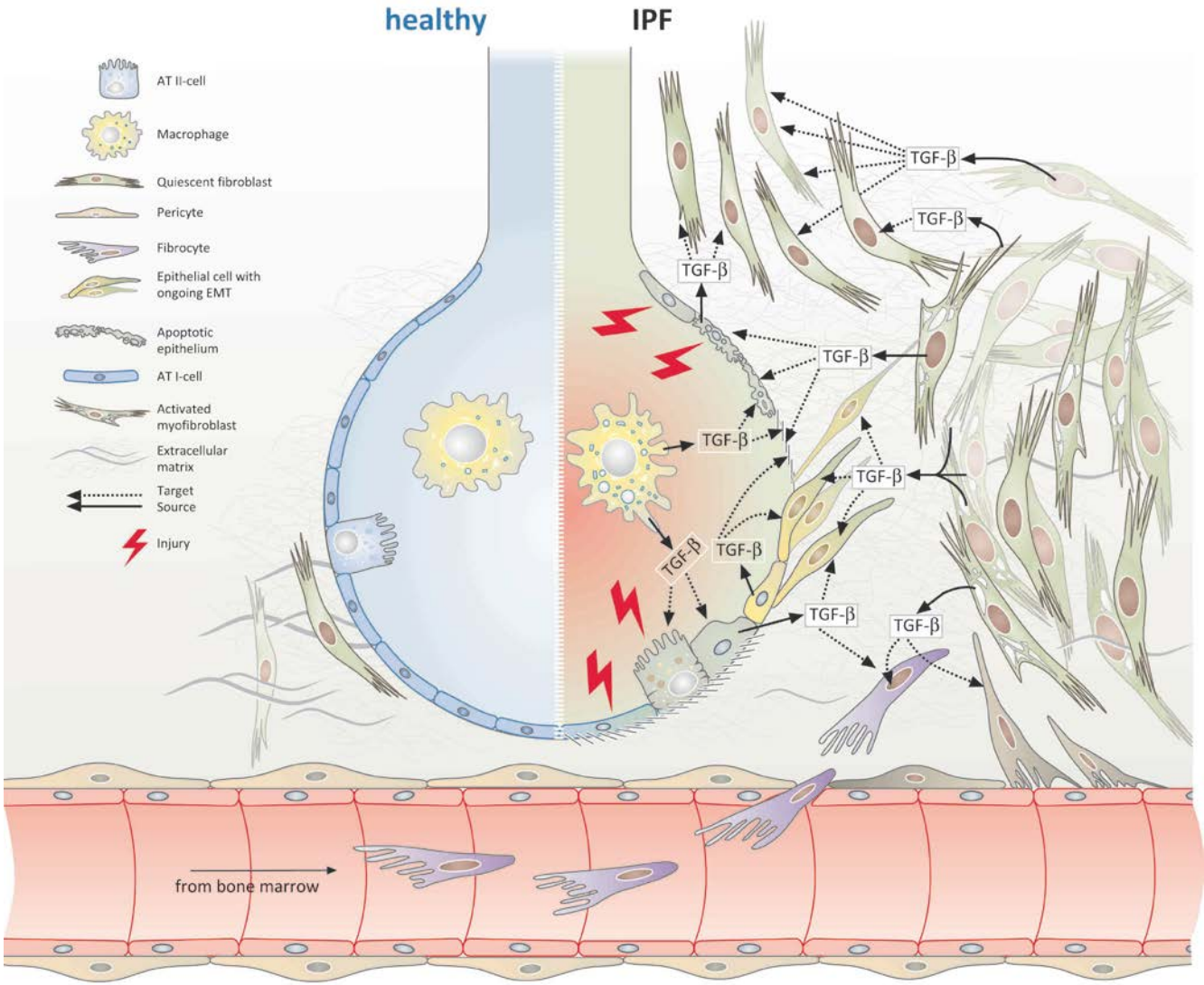
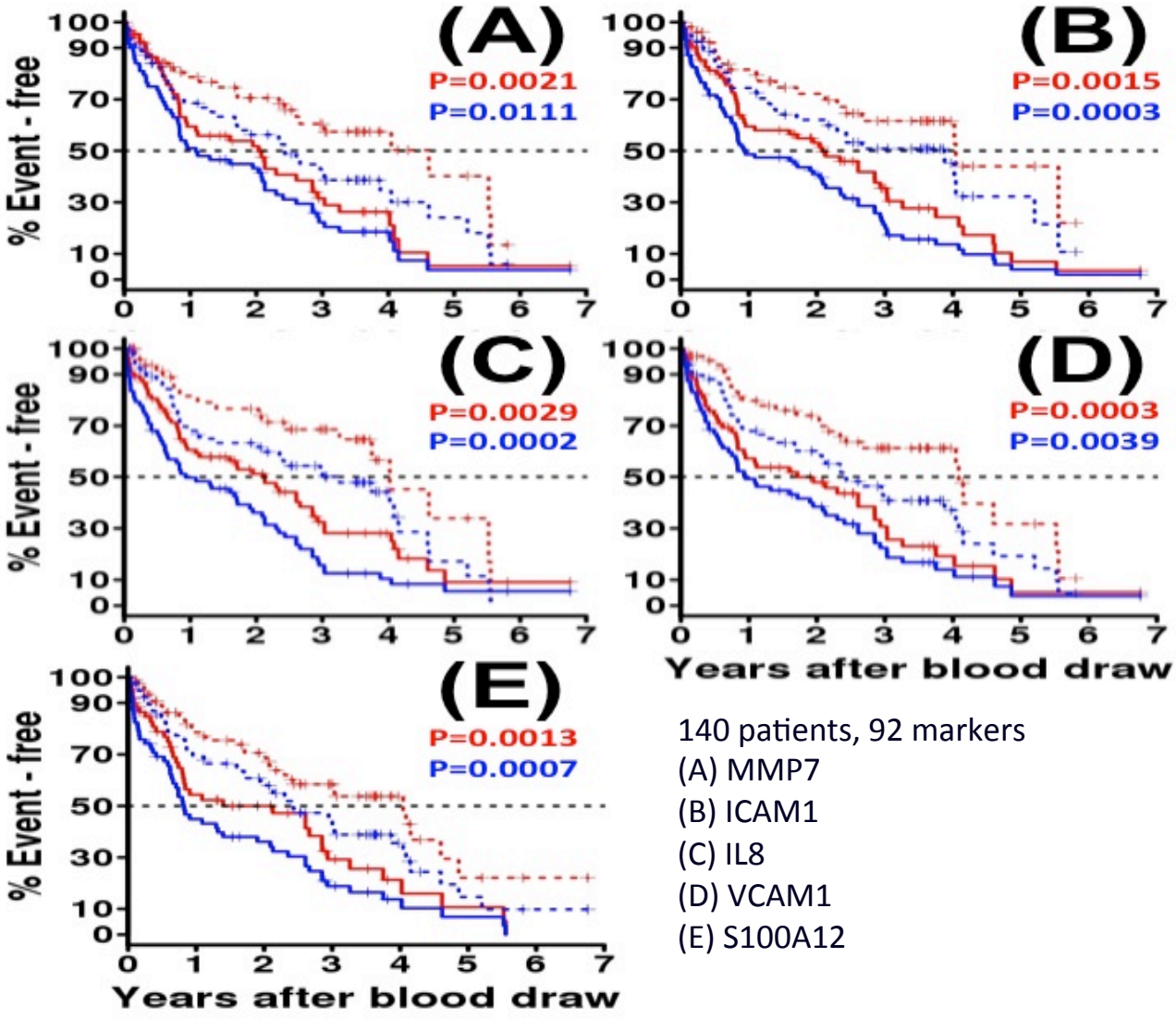


CPC Comprehensive Pneumology Center

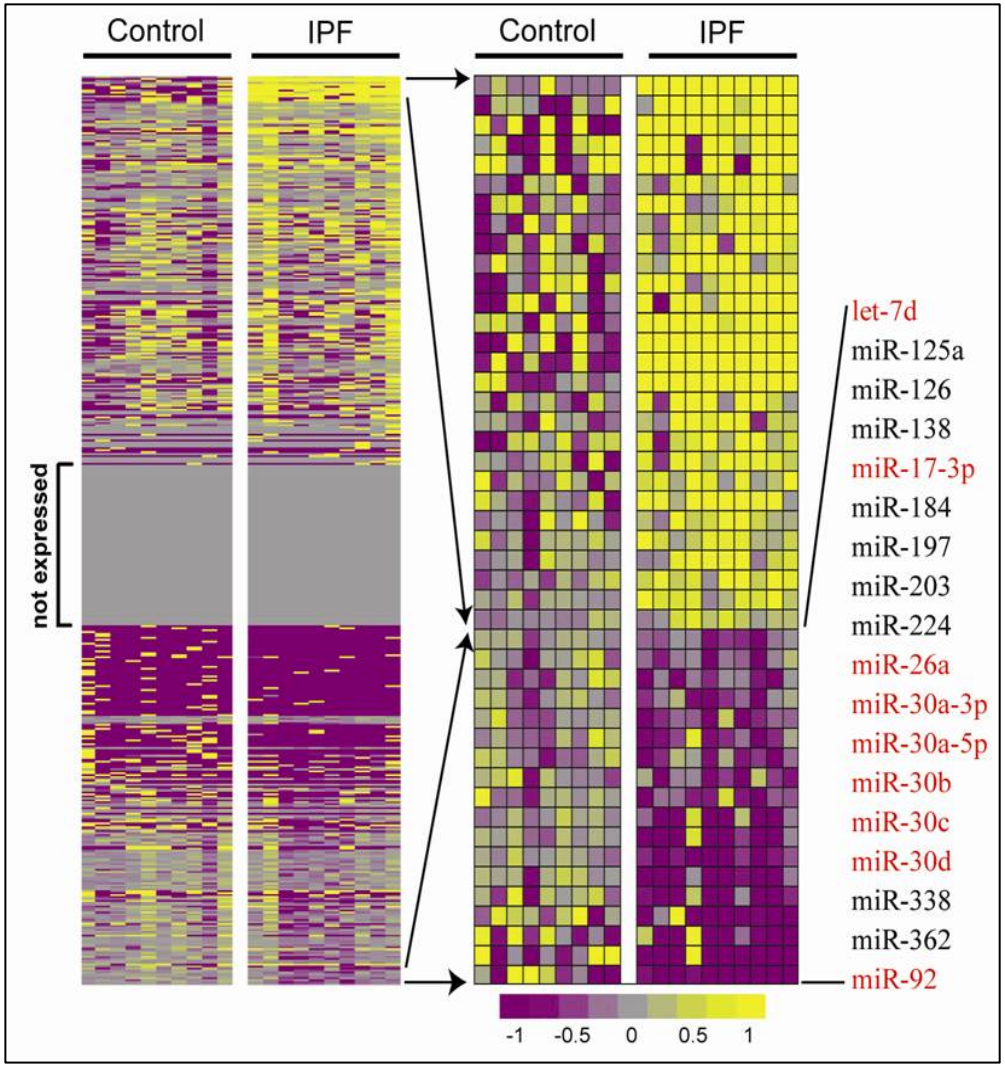
Peripheral blood proteins are predictive of outcome



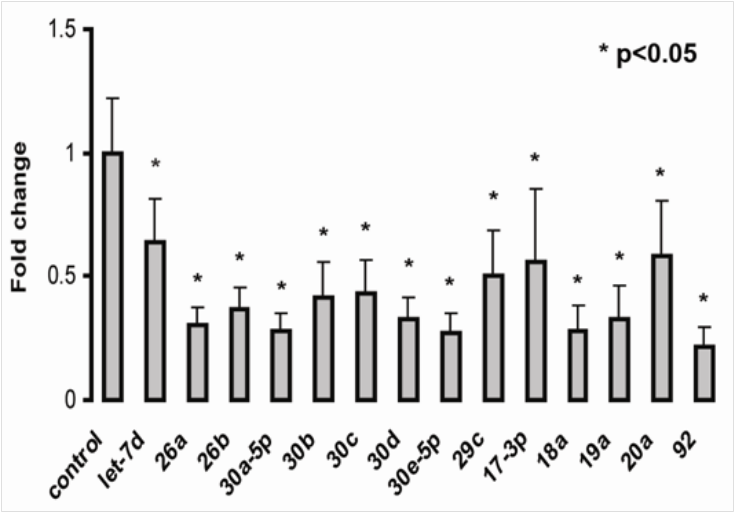
140 patients, 92 markers
(A) MMP7
(B) ICAM1
(C) IL8
(D) VCAM1
(E) S100A12

Richards et al., AJRCCM 2011

microRNAs are differentially expressed in IPF

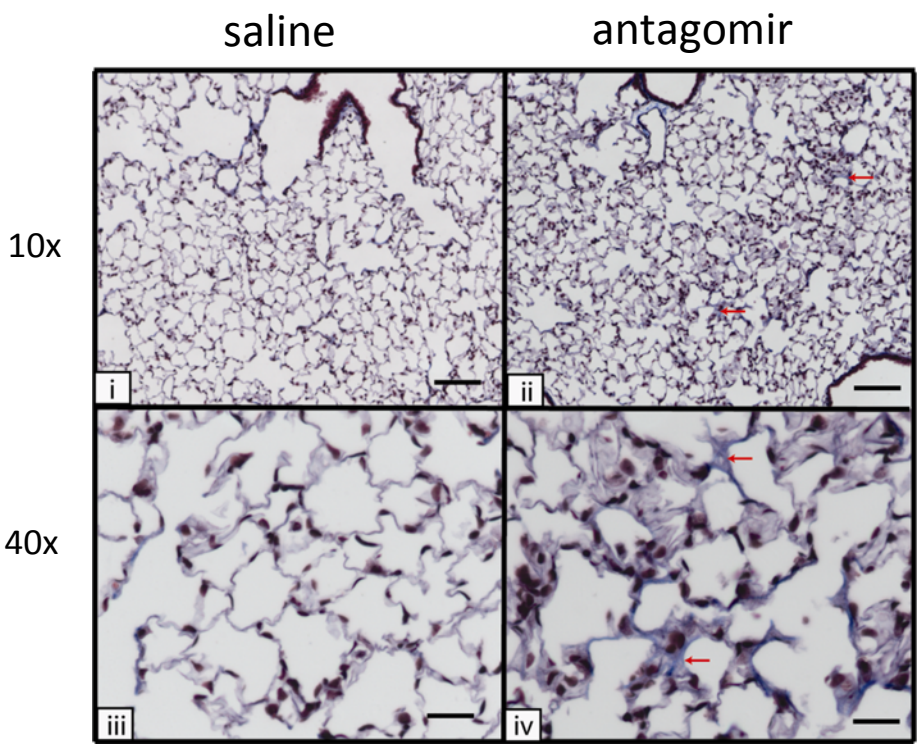


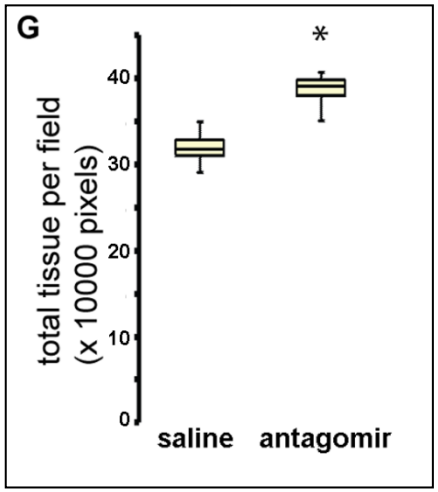
Platform: Agilent
10 IPF and 10 control tissues

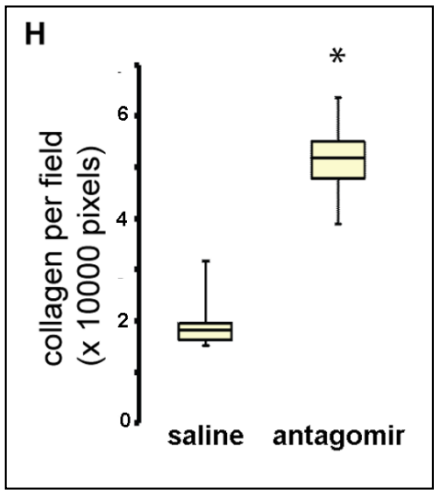


Pandit et al., AJRCCM 2010

let-7d inhibition causes alveolar septal thickening and collagen deposition in the lung

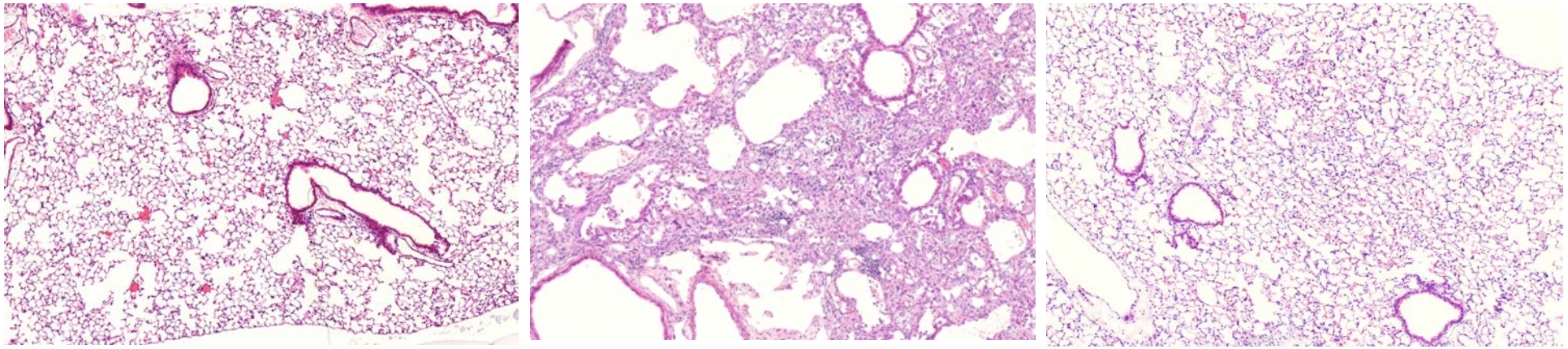






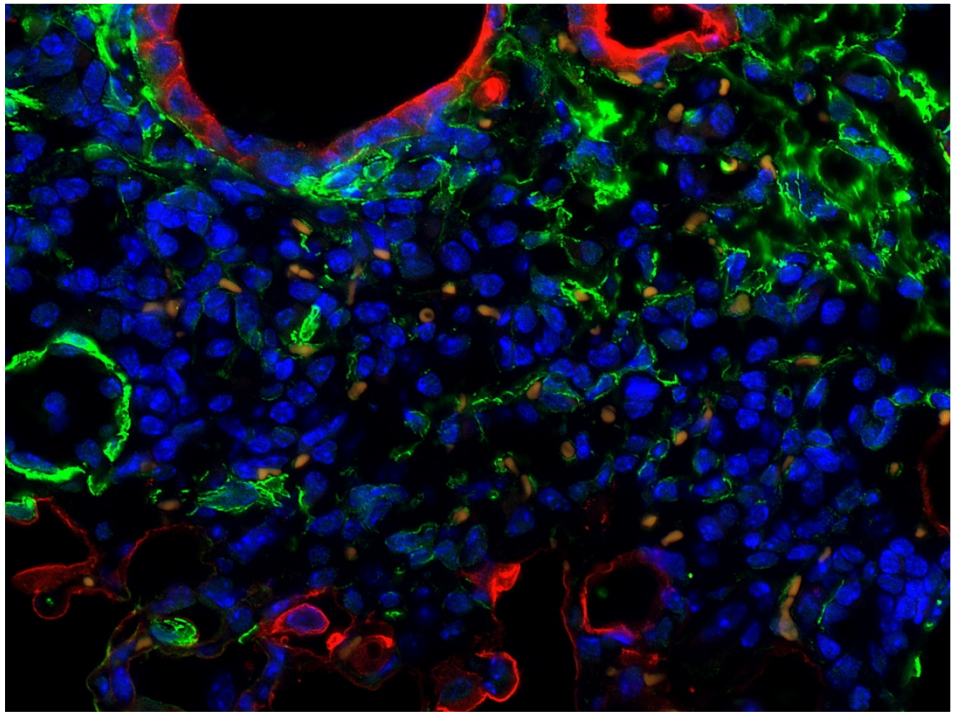
Pandit et al., AJRCCM 2010

Bleomycin-induced Pulmonary Fibrosis

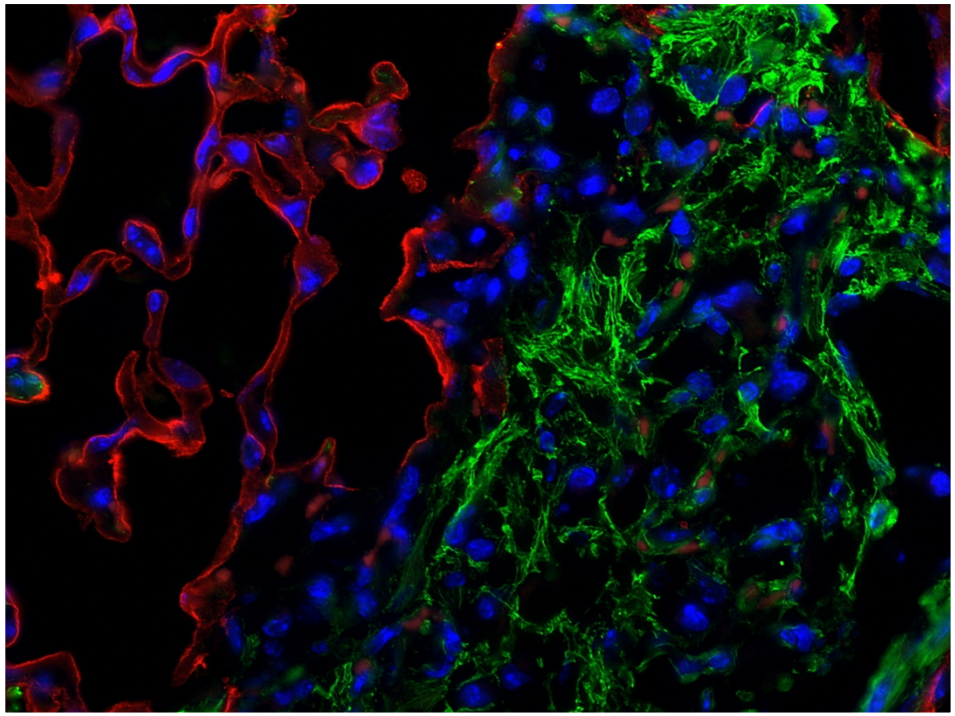


Bleomycin-induced Pulmonary Fibrosis

DAPI, αSMA, Aq5

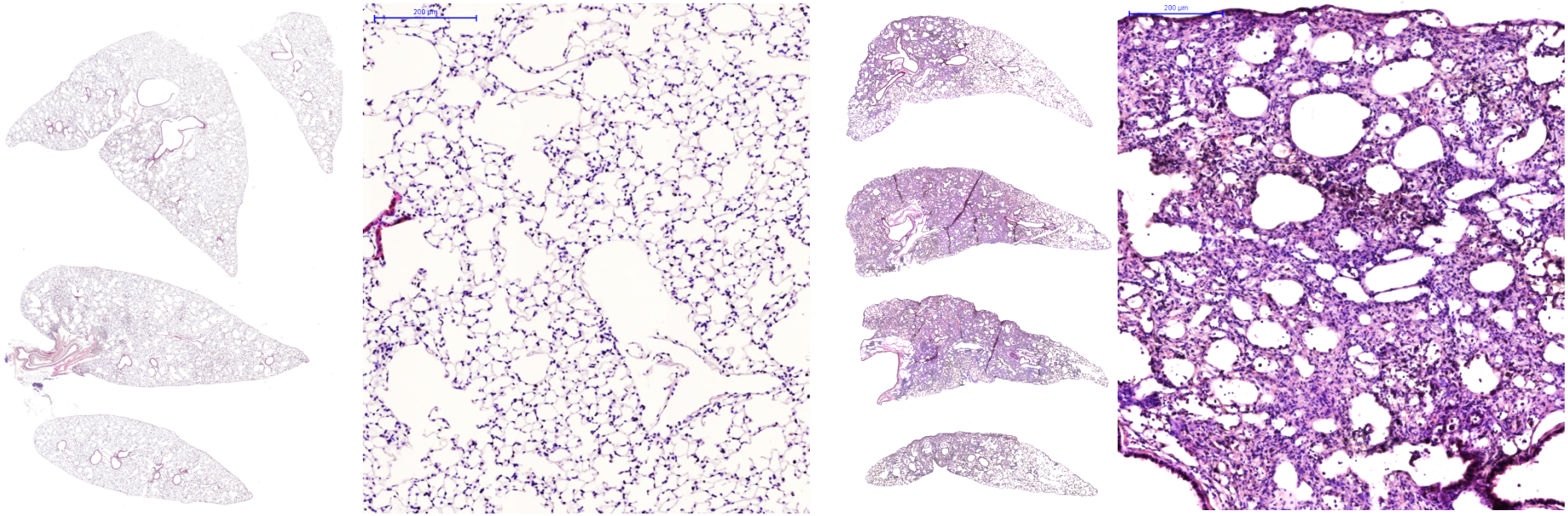


small airway

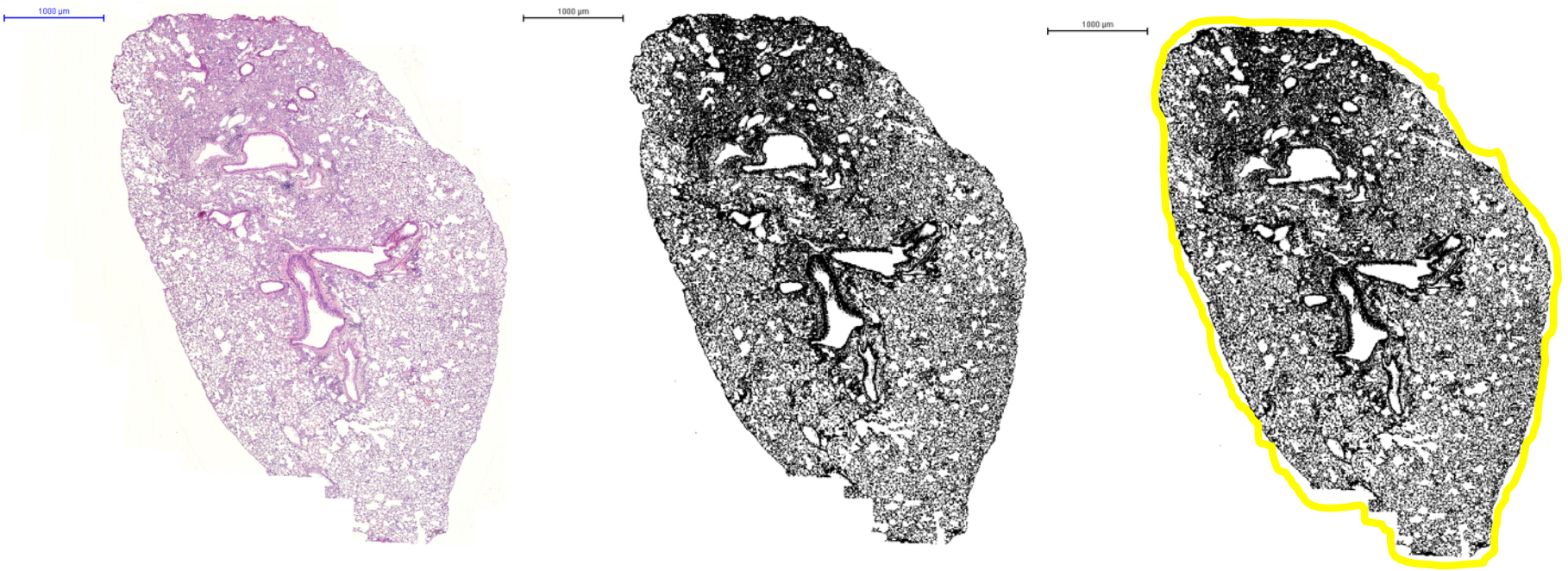


alveoli

Fibrosis quantification by software analysis



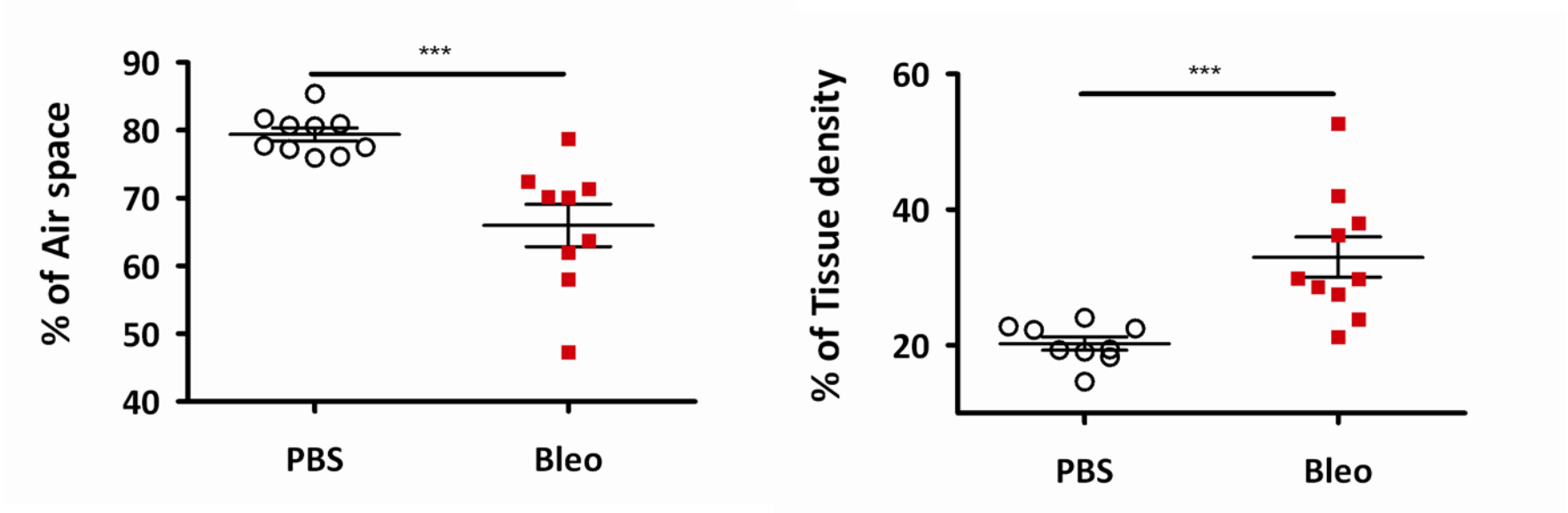
Quantification method



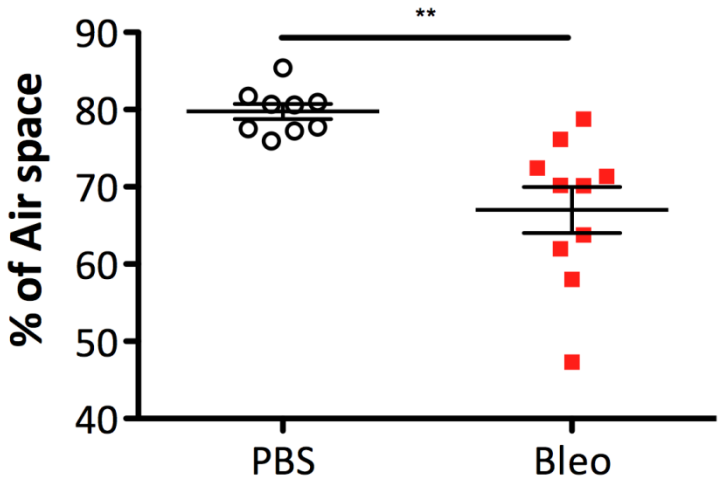
- Each image is analyzed separately upon conversion to 8-bit
- Whole lung is selected for area measurement
- Percentage of tissue density is obtained

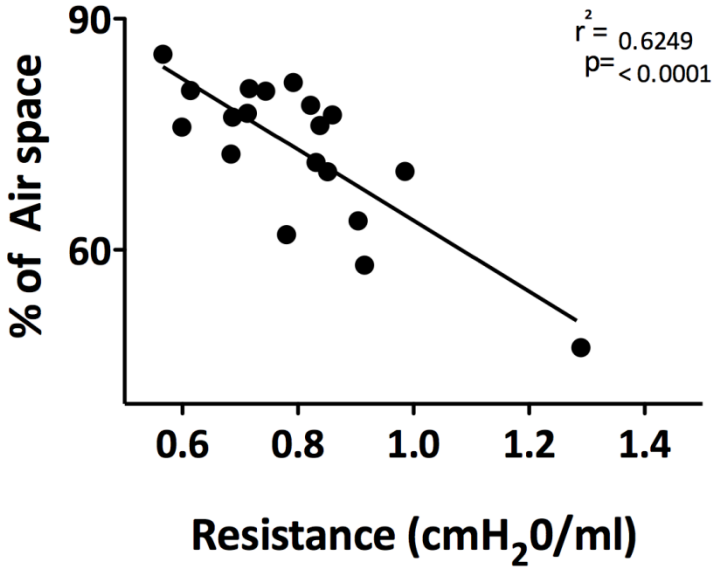
Unbiased software based fibrosis quantification

Day 14



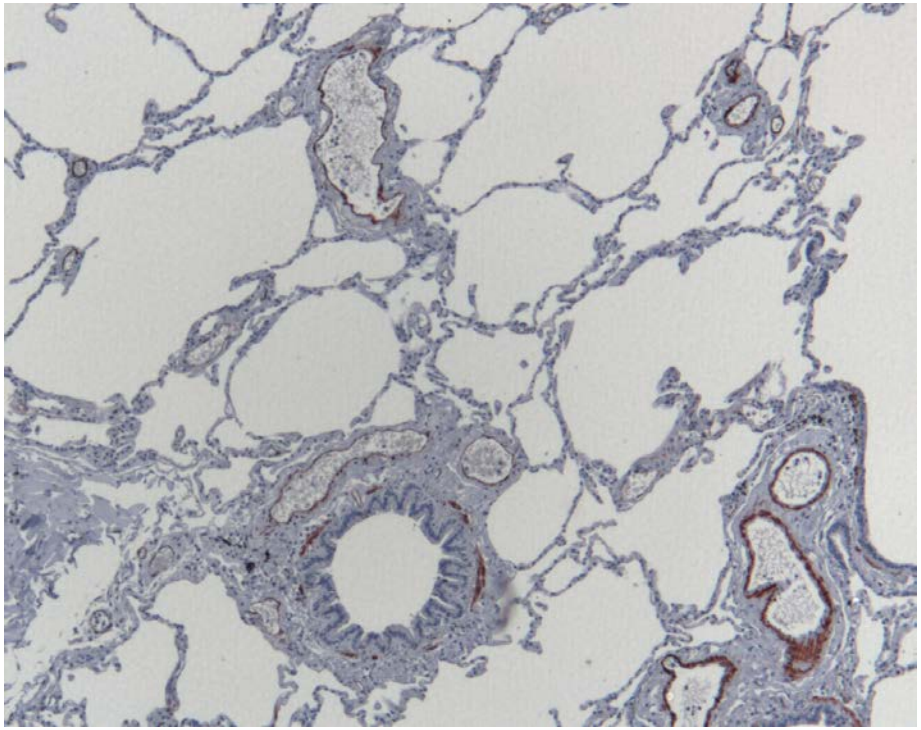
Air space percentage quantification and airway resistance correlation





What about fibroblast phenotypes?

Idiopathic Pulmonary Fibrosis (IPF)



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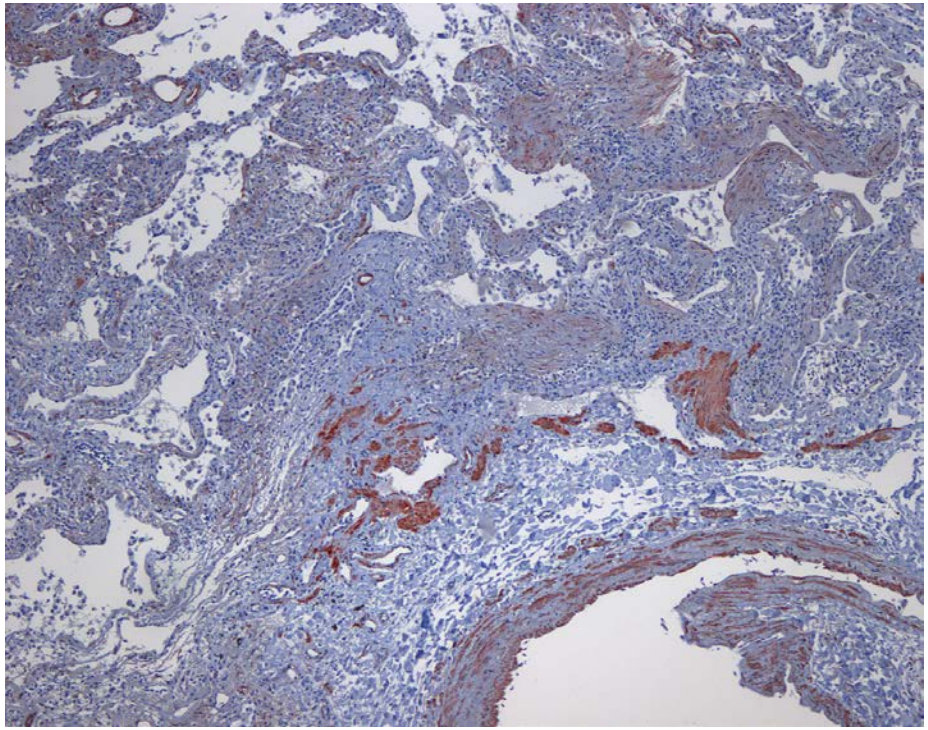

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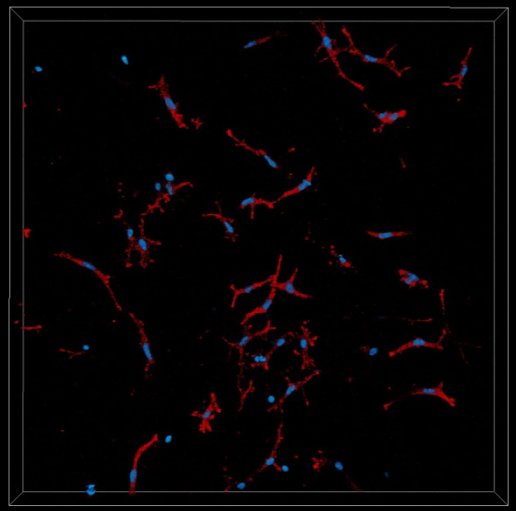
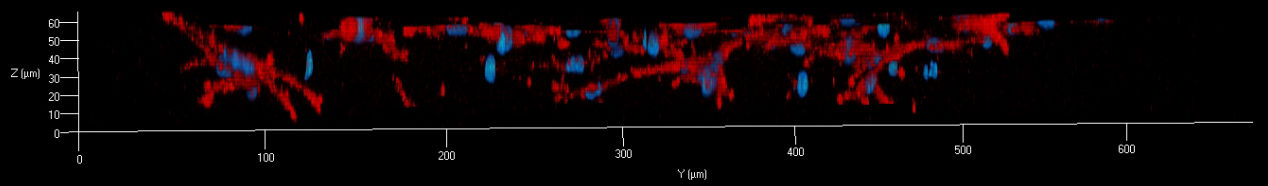
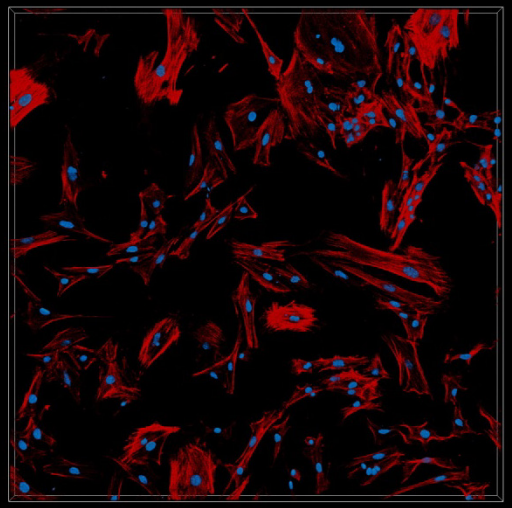
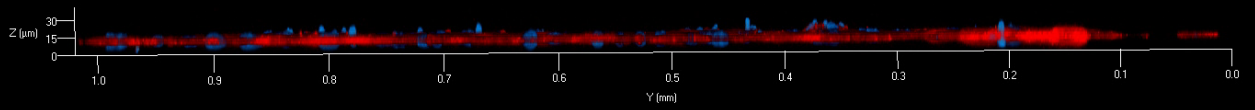
cells in gel





cells on top of gel





1. TGFβ1 and EGF enhance the invasion capacity of CCL206 fibroblasts

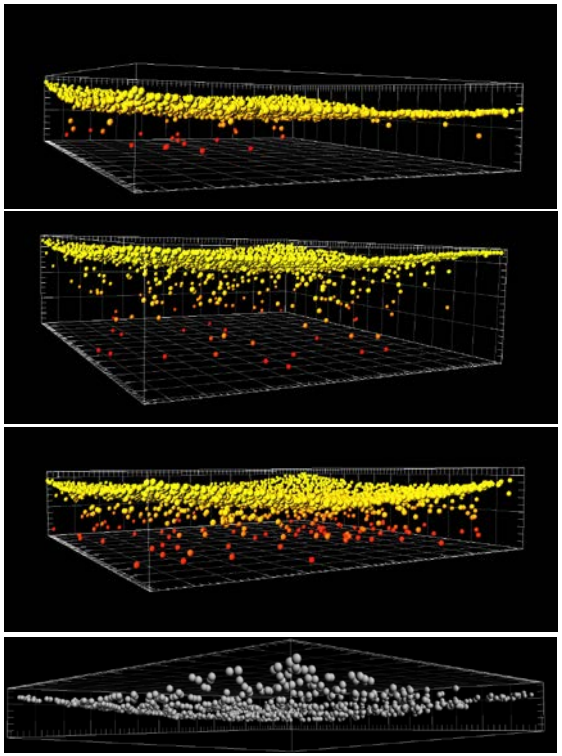
1h — Prepare collagen matrices (3.2mg/ml)
Seed cells (1% FCS)

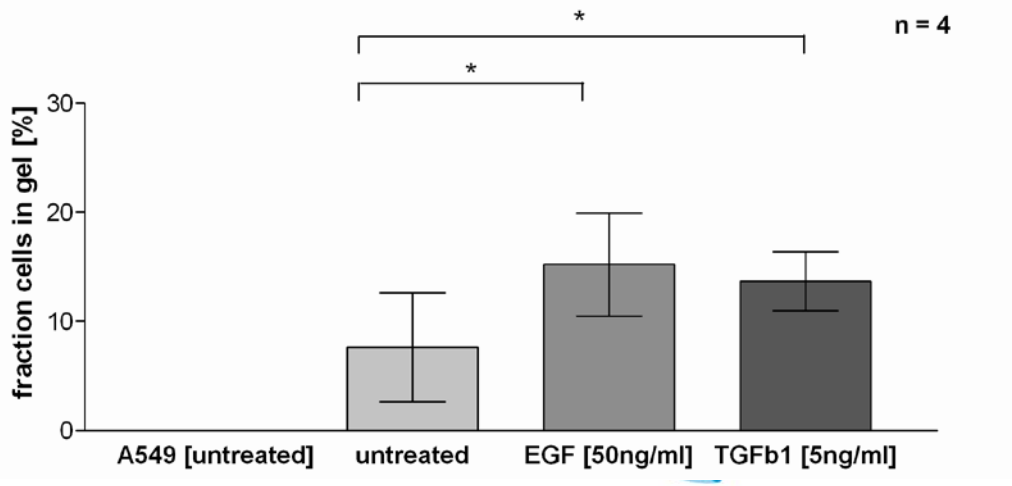
24h — Treatment (TGFβ1, EGF) (1% FCS)

72h invasion

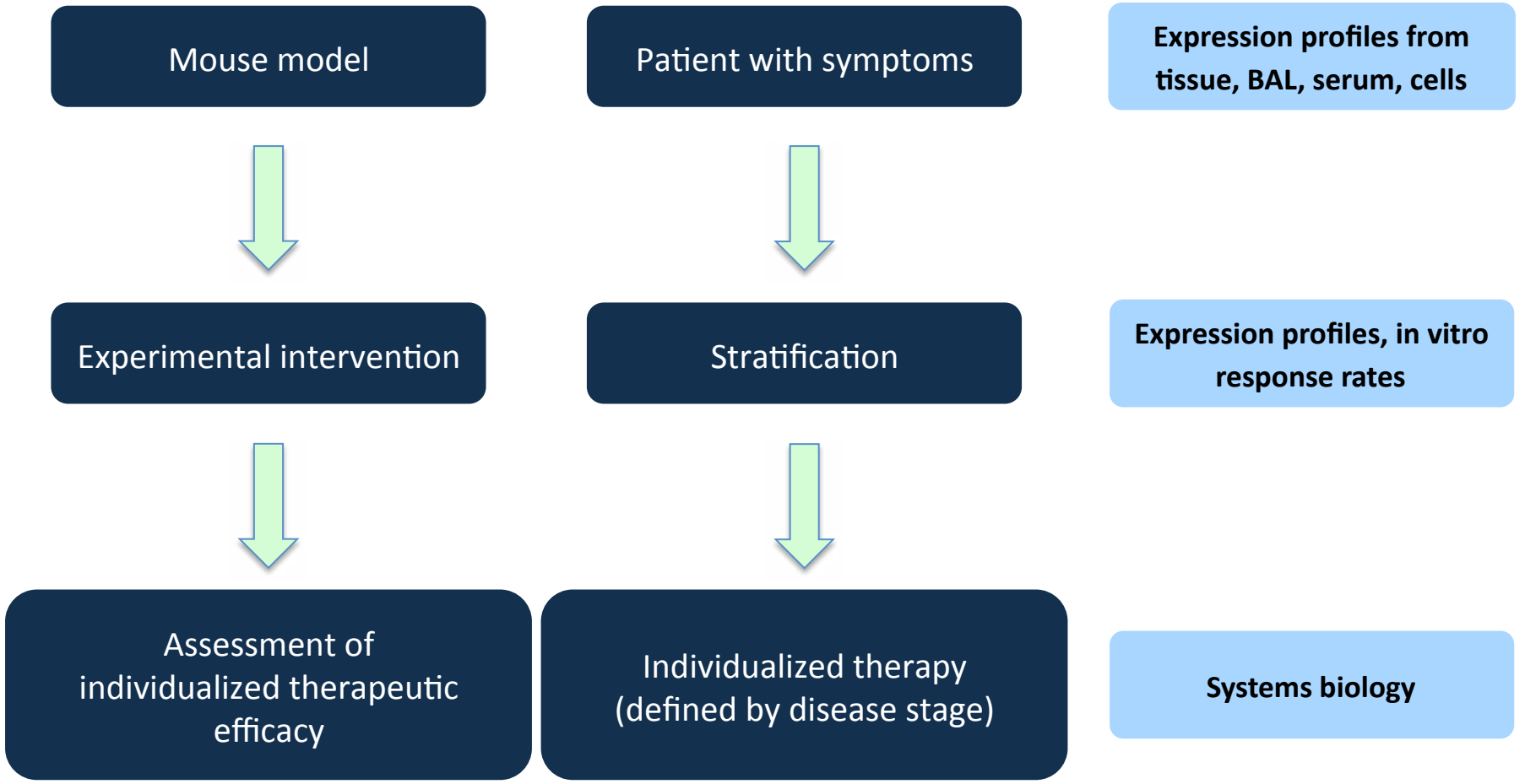
96h — Fix cells + DAPI staining

LSM confocal microscopy, analysis IMARIS

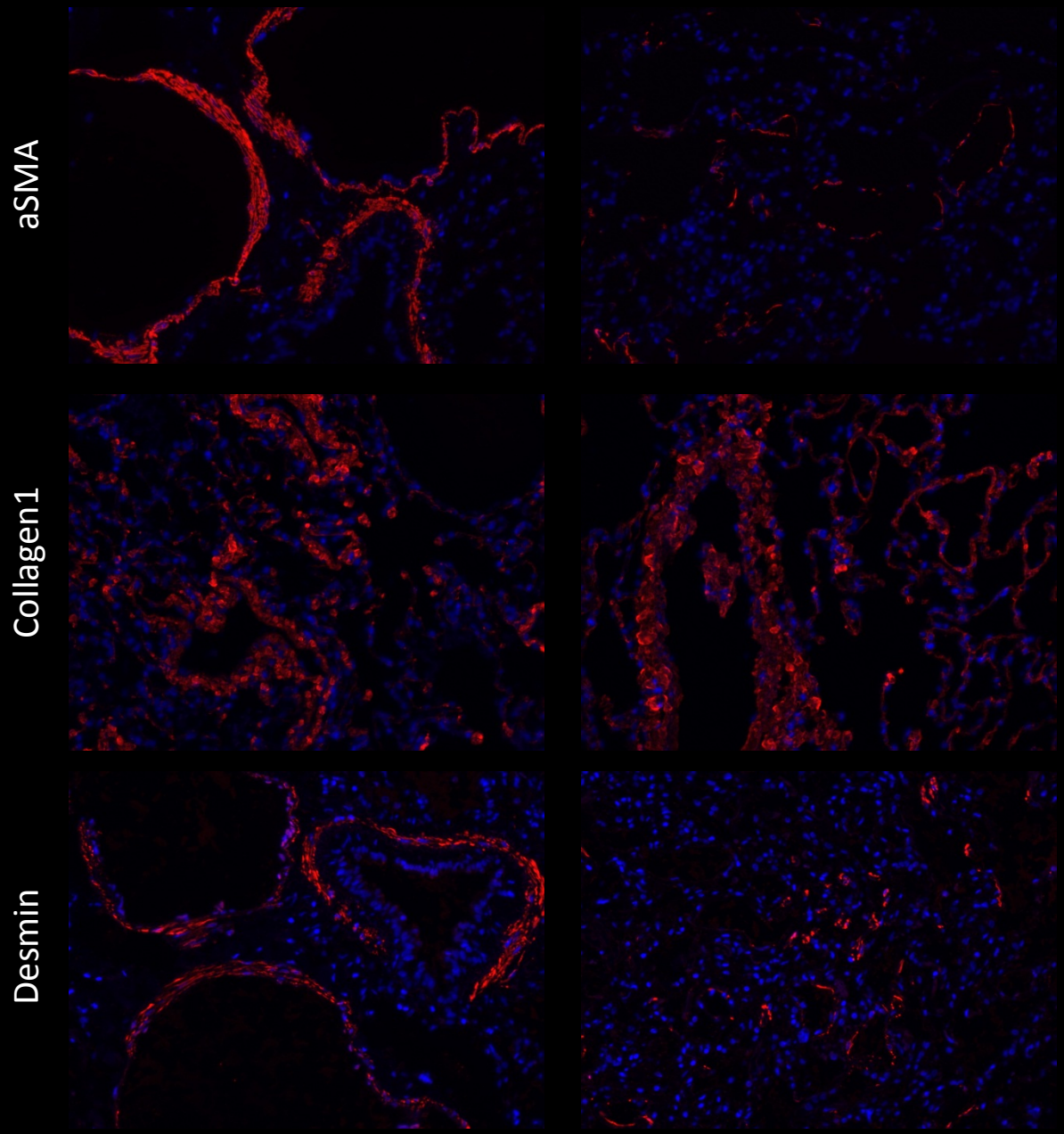




Parallel universes



Donor



Acknowledgments

Thanks to the **Eickelberg Lab**

- Dr. Nikica Miše
- **Bettina Oehrle**
- Juliane Bartmann
- **Dr. Johannes Schwarz**
- **Dr. Gerald Burgstaller**
- Dr. Olga Bermudez
- Dr. Miriam Ayturan
- **Isis Fernandez**
- **Dr. Katharina Heinzelmann**
- Ann-Christin Beitel
- **Daniela Dietel**
- Constanze Heise
- Elisabeth Hennen
- **Katharina Lippl**
- Markus Utzt
- Alexander Schütte

With this,

Thank you for your attention