Characterizing the Antifibrotic Activity of Bexotegrast on Distinct Fibroblast Populations in PCLS from Multiple ILD Subtypes

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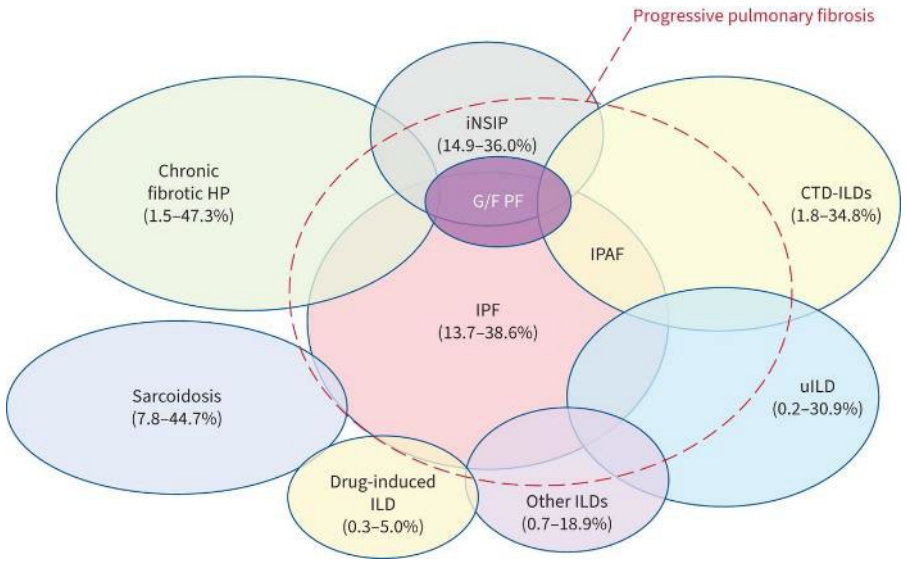
Disclosures

Pliant Therapeutics

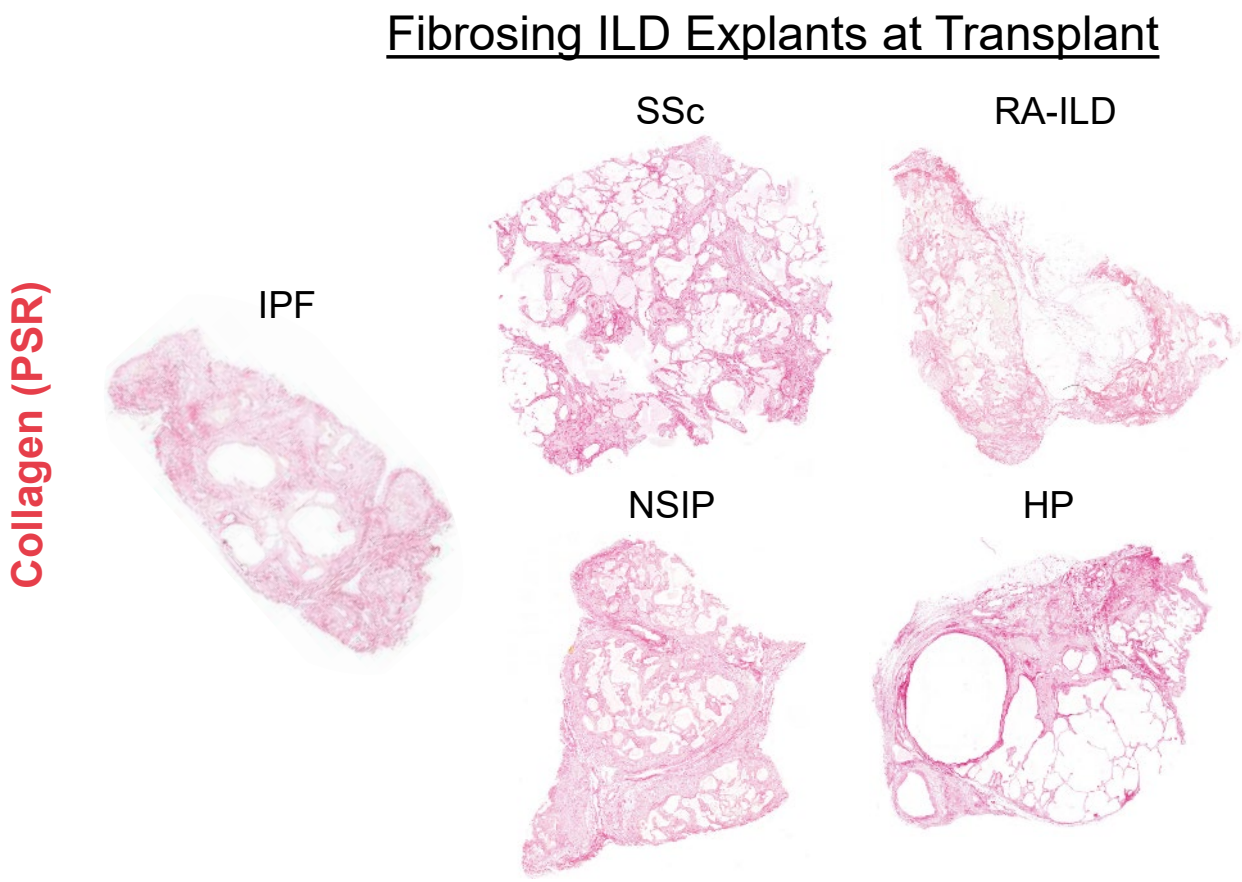
- Employee and shareholder

Progressive Pulmonary Fibrosis

- PPF is interstitial lung disease (ILD) with radiological signs of fibrosis and progression over time (Rajan, et al. 2023)

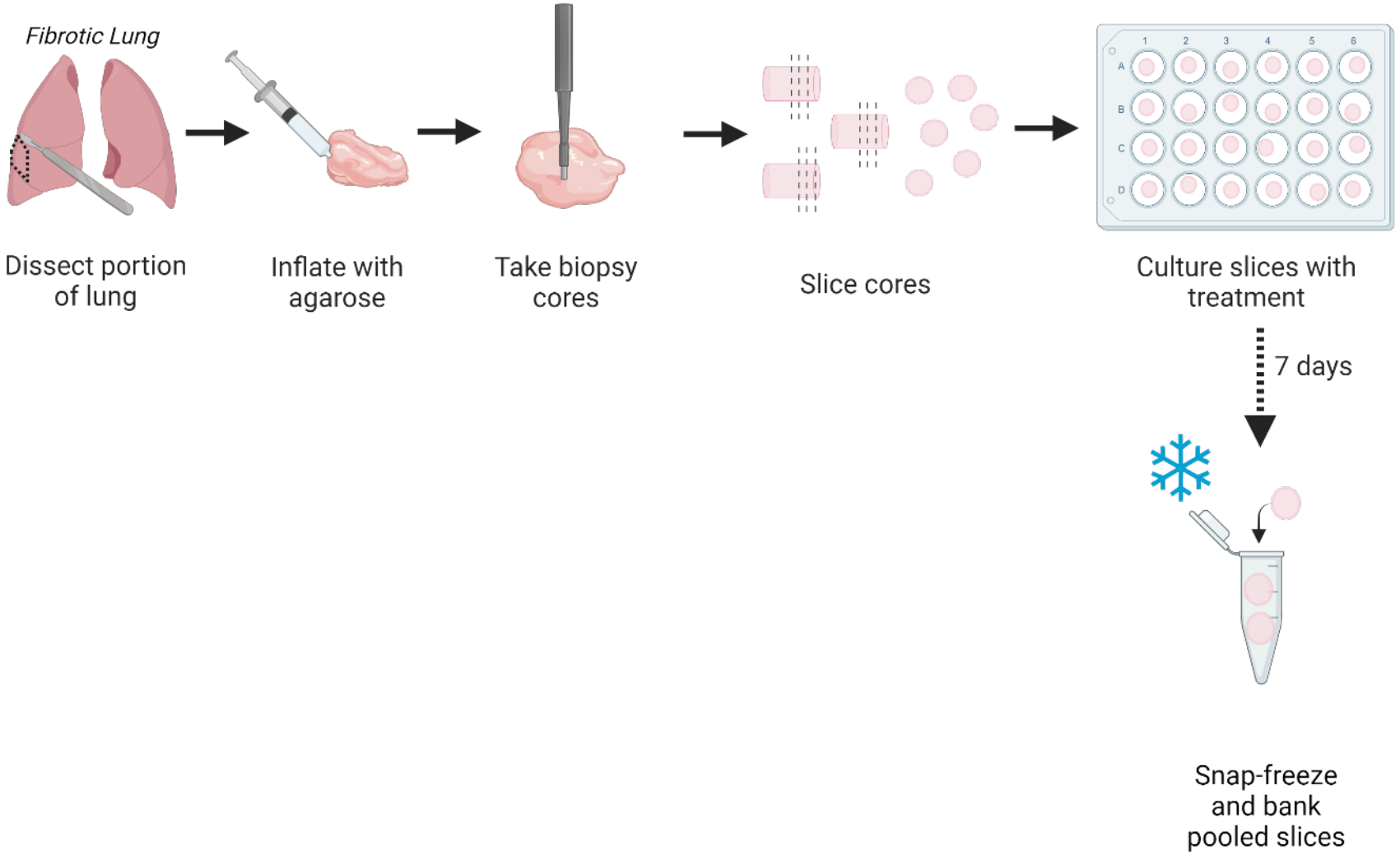


Rajan, et al. 2023



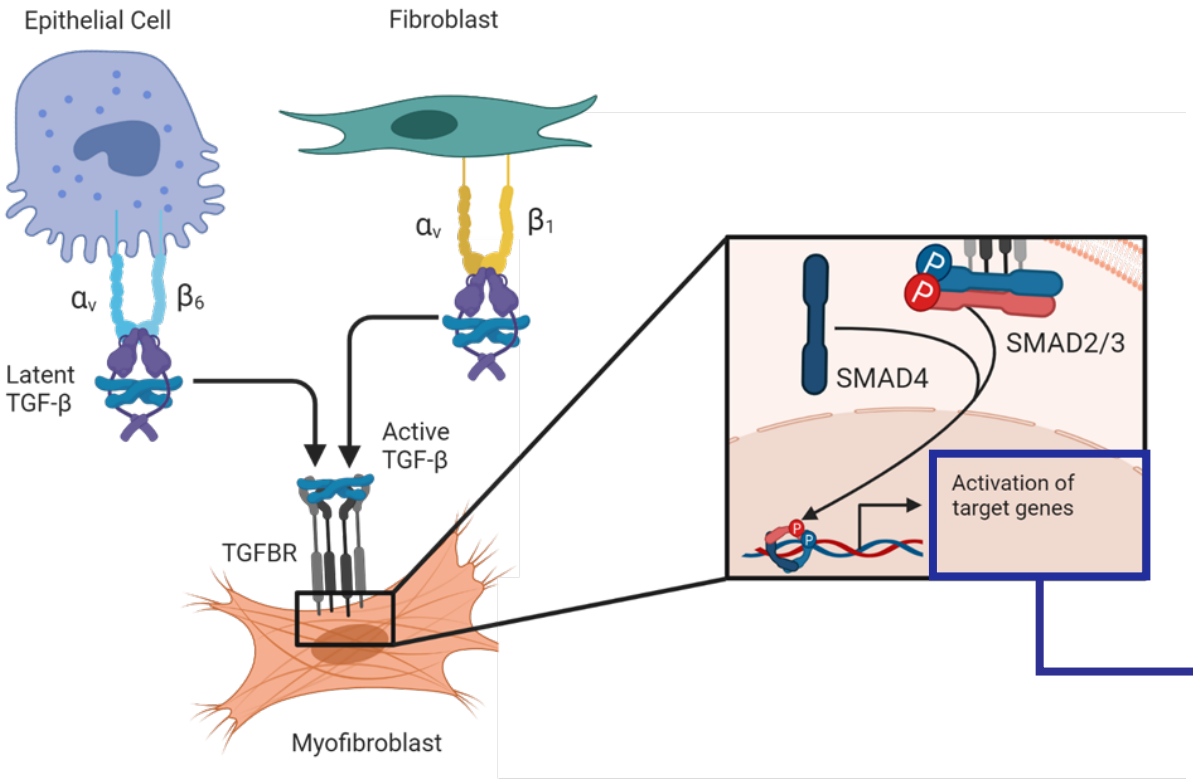
Transcriptomic Analysis of Precision-Cut Lung Slices: A Novel Approach to Investigate Drug MOA in Fibrotic Lung Explants

PCLS



$\alpha_V\beta_6/\alpha_V\beta_1$ Integrins Drive TGF-β Activation in Lung Fibrosis

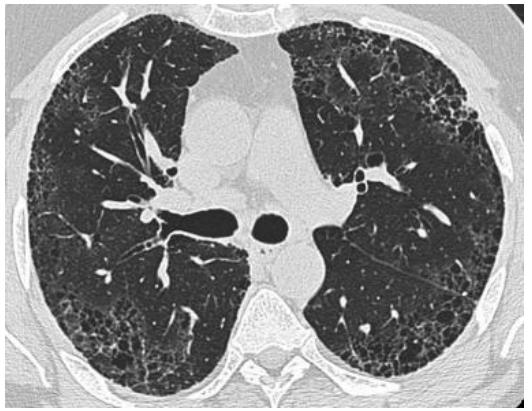
$\alpha_V\beta_6/\alpha_V\beta_1$ integrins promote fibrosis by activating TGF-β



- TGF-β is a central mediator of fibrosis
- $\alpha_V\beta_6/\alpha_V\beta_1$ integrins activate latent TGF-β in fibrotic tissue
- Systemic TGF-β blockade carries toxicity risks

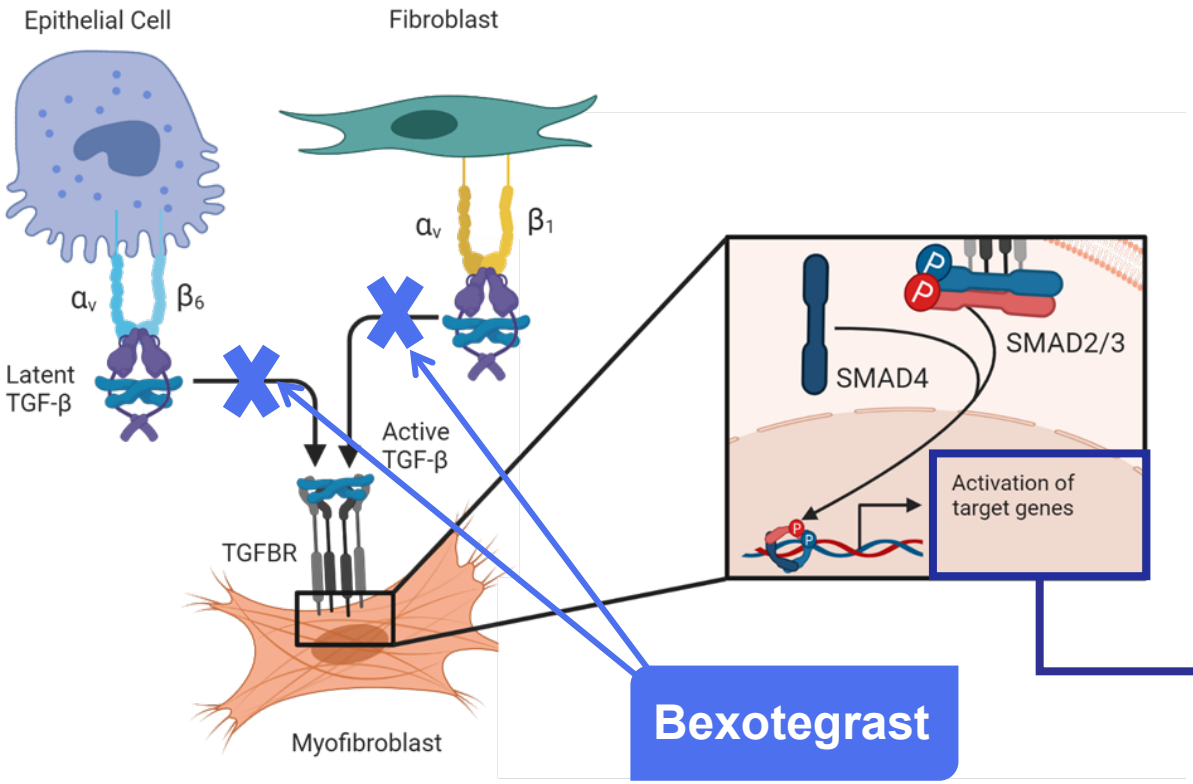
COL1A1
COL3A1
TIMP1
CCN2
ENPP2
…

FIBROSIS



Bexotegrast Reduces TGF-β Signaling and Downstream Profibrotic Pathways through Inhibition of Integrins $\alpha_V\beta_6/\alpha_V\beta_1$

$\alpha_V\beta_6/\alpha_V\beta_1$ integrins promote fibrosis by activating TGF-β

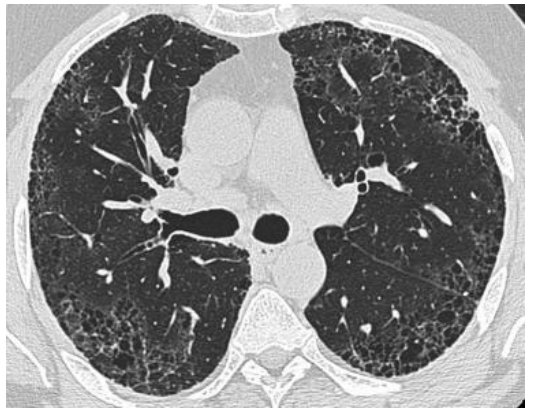


- TGF-β is a central mediator of fibrosis
- $\alpha_V\beta_6/\alpha_V\beta_1$ integrins activate latent TGF-β in fibrotic tissue
- Systemic TGF-β blockade carries toxicity risks

Localized TGF-β inhibition in the fibrotic lung may provide a novel approach to treat pulmonary fibrosis, without affecting TGF-β signaling systemically

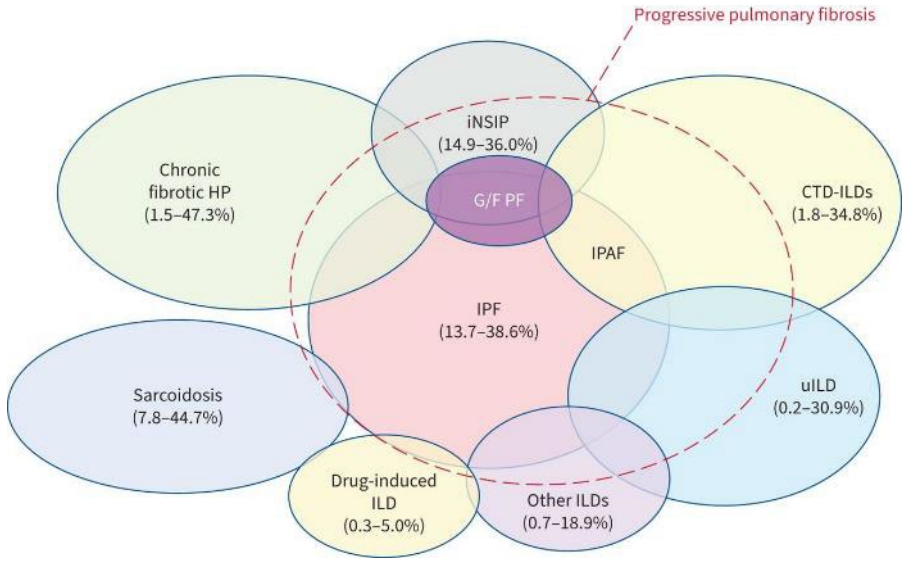
COL1A1
COL3A1
TIMP1
CCN2
ENPP2
…

FIBROSIS

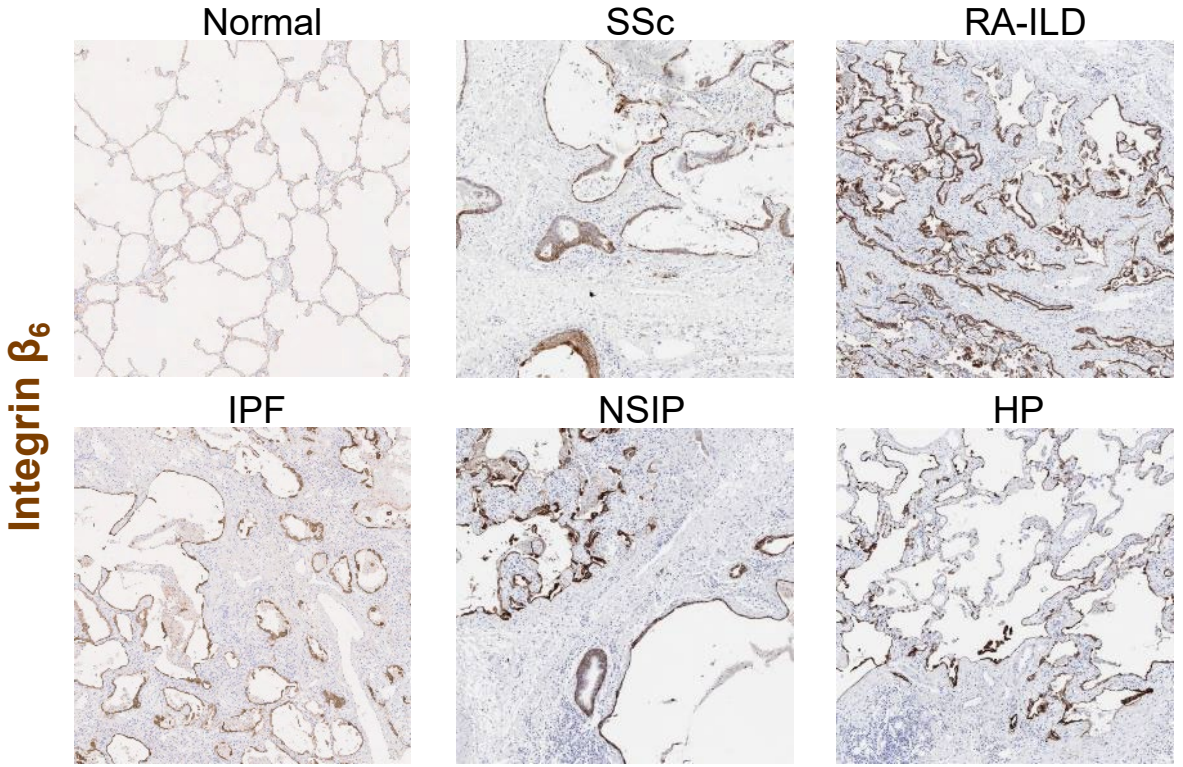


Integrin $\alpha_v\beta_6$ Expression Is Elevated in Fibrotic ILD Explants

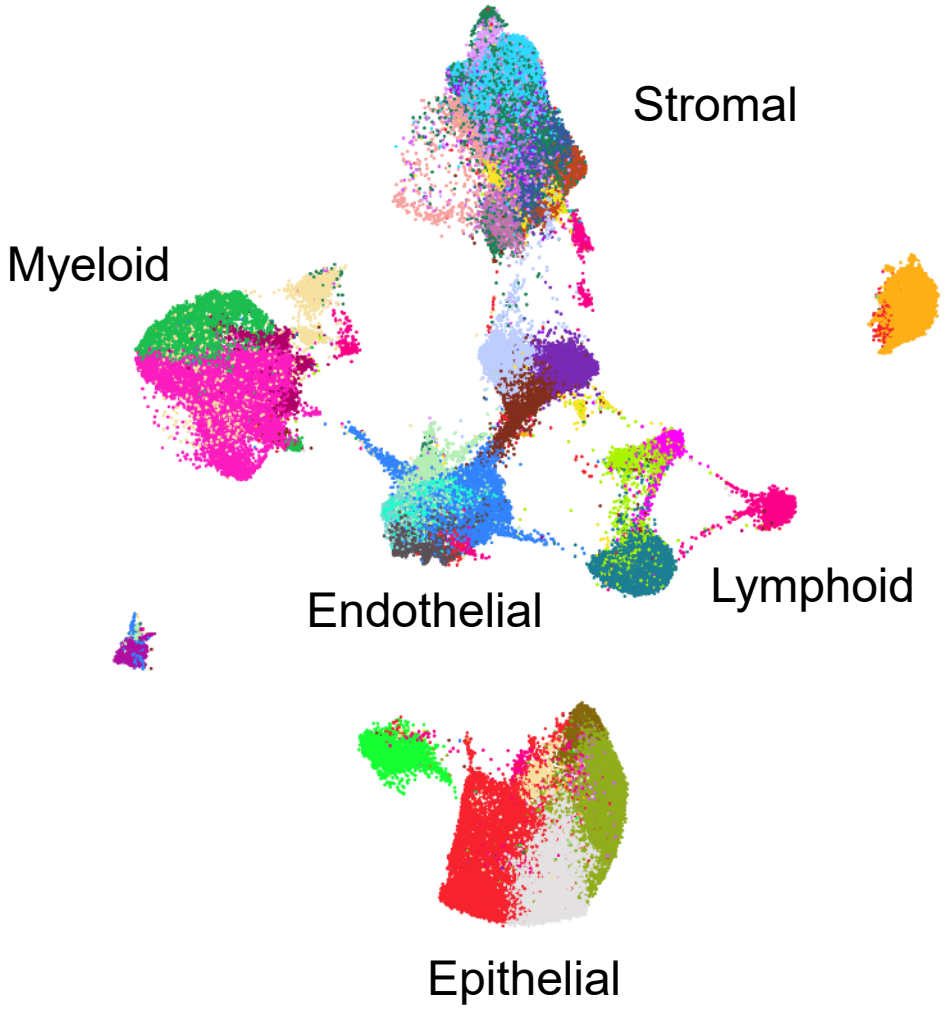
- PPF is interstitial lung disease (ILD) with radiological signs of fibrosis and progression over time (Rajan, et al. 2023)
- Integrin β_6 (ITGB6) expression is elevated in IPF and in PPF



Rajan, et al. 2023



snRNA-seq of Non-IPF Fibrotic PCLS Identified Target Cell Populations

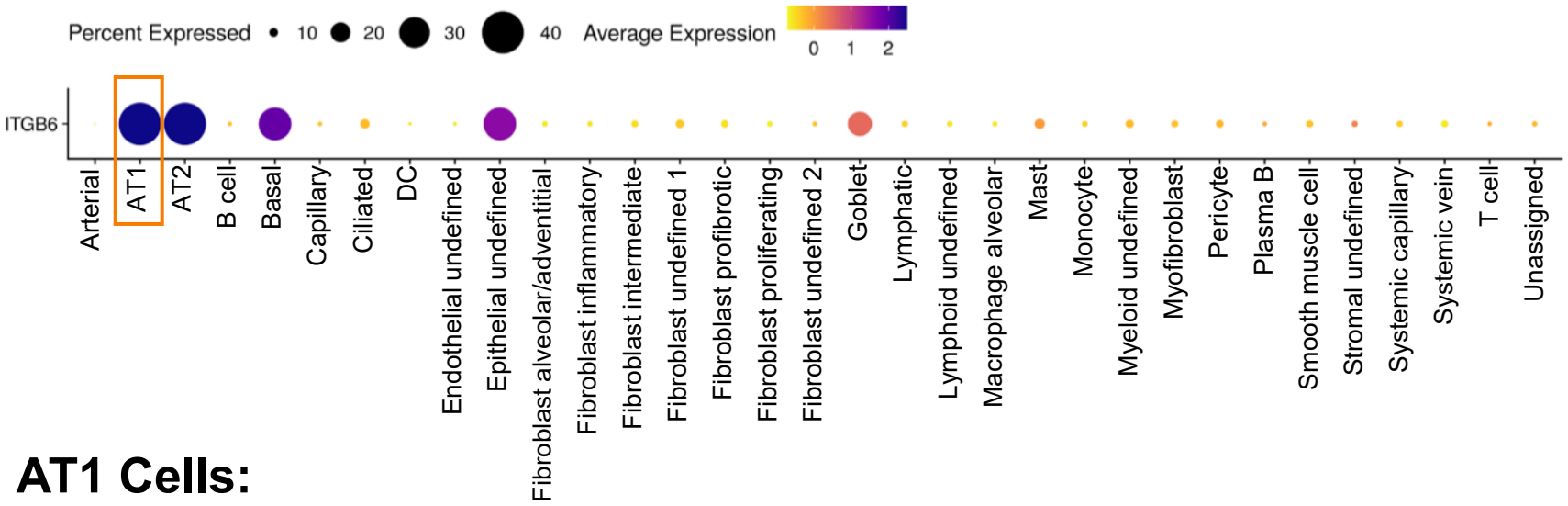


- 3 Non-IPF fibrotic ILD donors
  - 2 RA-ILD, 1 HP
- PCLS treated for 7 days with bexotegrast
- >150,000 nuclei isolated
- Annotations based on published fibrotic lung single cell RNAseq datasets

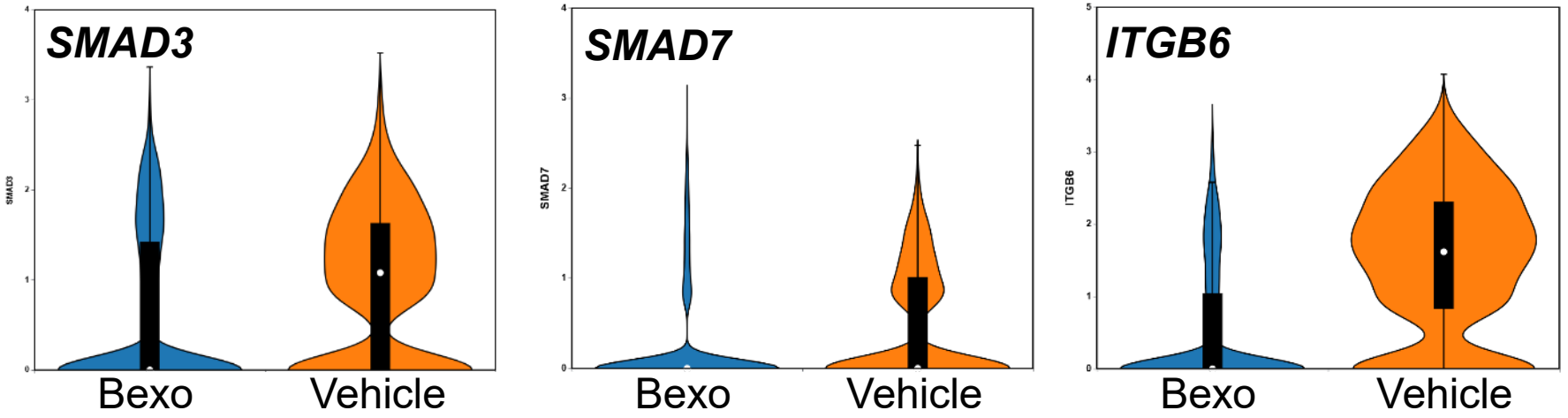
- Arterial
- AT1
- AT2
- B cell
- Basal
- Capillary
- Ciliated
- DC
- Endothelial undefined
- Epithelial undefined
- Fibroblast alveolar/adventitial
- Fibroblast inflammatory
- Fibroblast intermediate
- Fibroblast undefined 1
- Fibroblast profibrotic
- Fibroblast proliferating
- Fibroblast undefined 2
- Goblet
- Lymphatic
- Lymphoid undefined
- Macrophage alveolar
- Mast
- Monocyte
- Myeloid undefined
- Myofibroblast
- Pericyte
- Plasma B
- Smooth muscle cell
- Stromal undefined
- Systemic capillary
- Systemic vein
- T cell
- Unassigned

Bexotegrast Reduced Markers of TGF-β Signaling in AT1 Cells

ITGB6



AT1 Cells:



- ITGB6 is expressed most highly in AT1, AT2, and basal cells
- In AT1 cells, bexotegrast significantly reduced genes related to TGF-β signaling
- Decreased *ITGB6* expression is consistent with reductions in TGF-β signaling and the reduced circulating ITGB6 observed in INTEGRIS-IPF[1]

1. Lancaster et al., AJRCCM 2024

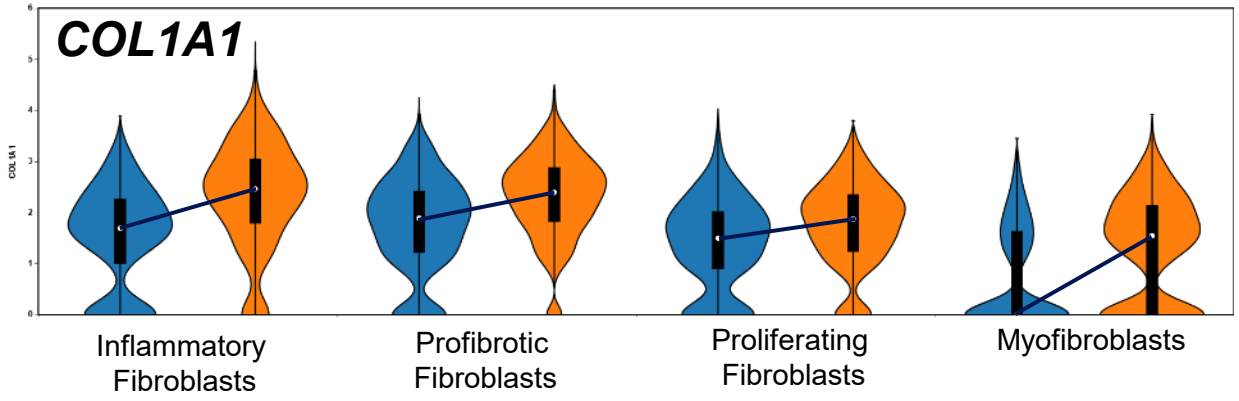
Bexo = bexotegrast

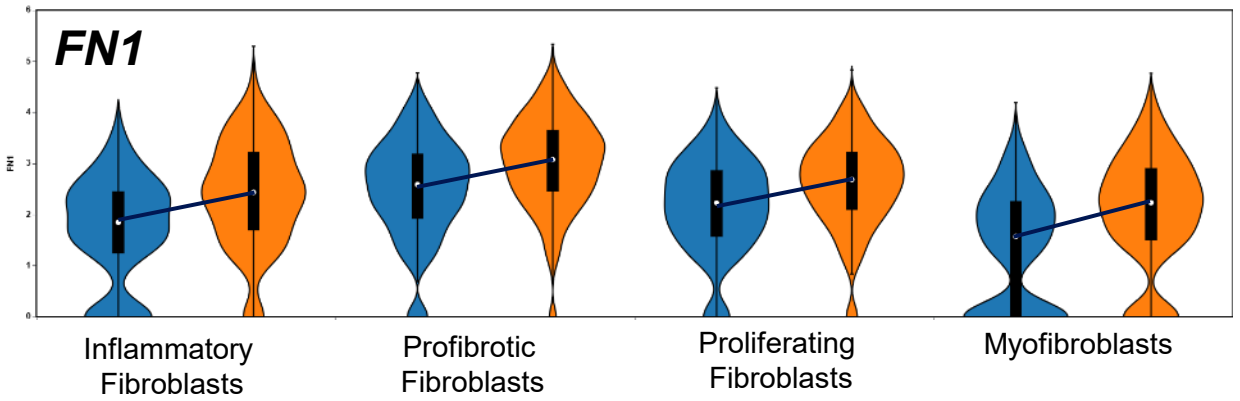
Bexotegrast Significantly Reduced Fibrogenic Gene Expression in Multiple Fibroblast Populations

- Across all stromal cells, bexotegrast significantly reduced the expression of genes related to extracellular matrix and collagen
- Fibrogenic genes (e.g. *COL1A1* and *FN1*) were significantly reduced across multiple fibroblast subtypes

Top Downregulated BP GO Terms in Stromal Cells

ID	Description	Adj. p value
GO:0030198	extracellular matrix organization	2E-23
GO:0043062	extracellular structure organization	2E-23
GO:0045229	external encapsulating structure organization	2E-23
GO:0030199	collagen fibril organization	5.5E-11
GO:0085029	extracellular matrix assembly	3.5E-08

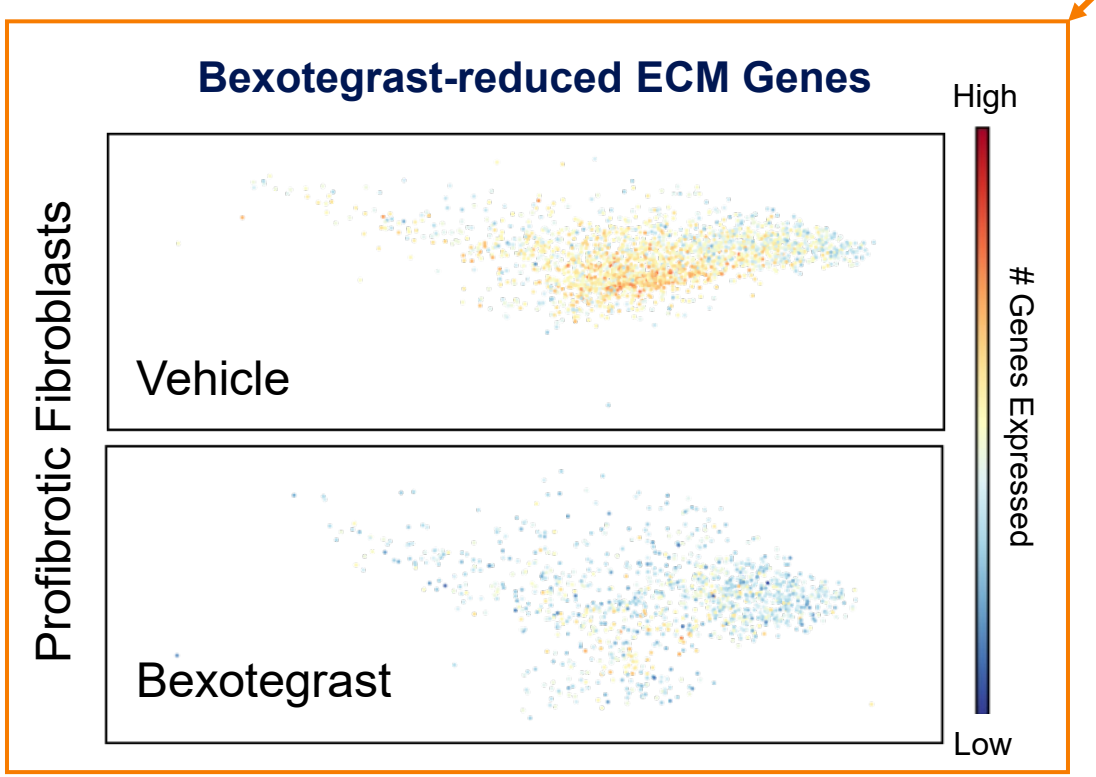




Bexotegrast **Vehicle**

Bexotegrast Significantly Reduced Fibrogenic Gene Expression in Profibrotic Fibroblasts

- *CTHRC1*^{Hi}/*COL1A1*^{Hi} population of profibrotic fibroblasts were identified
- Bexotegrast significantly reduced genes related to extracellular matrix



Top Downregulated BP GO Terms in Profibrotic Fibroblasts

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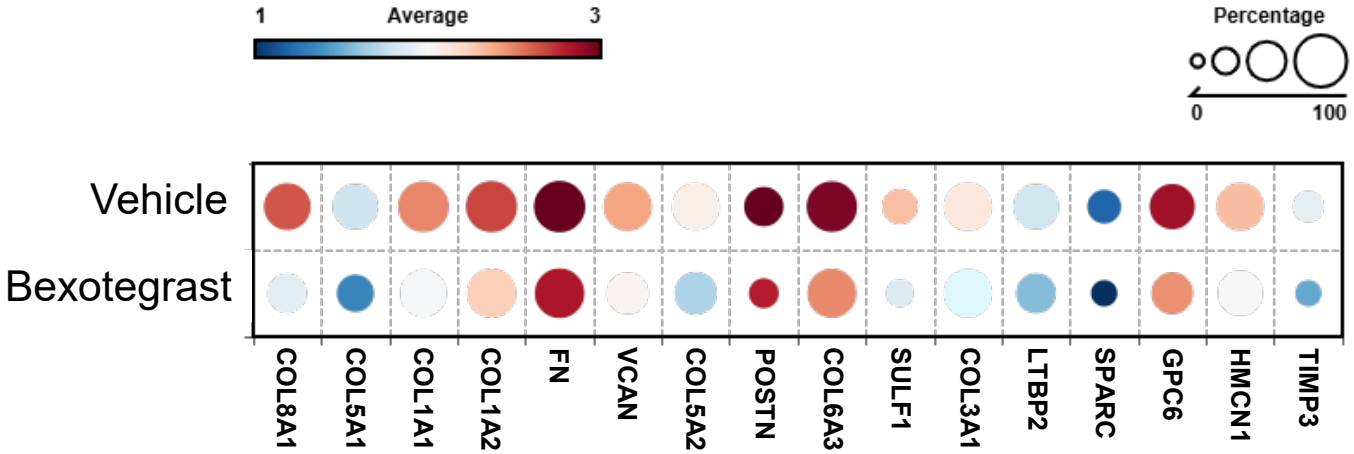
GO:0030198	extracellular matrix organization	1.1E-13
GO:0043062	extracellular structure organization	1.1E-13
GO:0045229	external encapsulating structure organization	1.1E-13
GO:0030199	collagen fibril organization	8.94E-07
GO:0030111	regulation of Wnt signaling pathway	0.000113



Summary and Conclusions

- snRNA-seq of PCLS can be used to evaluate the effects of novel therapeutics on specific cell populations within fibrosing ILD explants
- Integrin $\alpha_V\beta_6$ expression is increased in lungs of patients with multiple fibrotic ILD subtypes
- Bexotegrast, a dual $\alpha_V\beta_6/\alpha_V\beta_1$ inhibitor, reduced expression of genes related to TGF-β signaling and fibrogenesis in AT1 cells and multiple fibroblast subpopulations
- These data are consistent with our observations in IPF explants and support further investigation of the antifibrotic activity of bexotegrast in PPF

Thank You!

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