BEXOTEGRAST IS ANTIFIBROTIC IN PRECISION-CUT LUNG SLICES PREPARED FROM FIBROTIC INTERSTITIAL LUNG DISEASE EXPLANTS

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BACKGROUND AND RATIONALE

Idiopathic pulmonary fibrosis (IPF) is the prototypical progressive fibrosing interstitial lung disease (ILDs); however, progressive fibrosis can also be observed in other ILDs. Interstitial lung disease (ILD) with radiological signs of fibrosis and progression over time is referred to as progressive pulmonary fibrosis (PPF) and includes a range of underlying diagnoses.[1]

TGF-β is a master regulator of fibrotic disease, including pulmonary fibrosis. Integrins $\alpha_v\beta_6$ and $\alpha_v\beta_1$ promote pulmonary fibrosis through the activation of latent TGF-β, a key driver of fibrosis, which leads to myofibroblast activation and deposition of fibrotic scar (Figure 1).

Bexotegrast (PLN-74809) is an oral, once daily, dual-selective $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrin inhibitor currently in late-stage evaluation for the treatment of IPF (BEACON-IPF; NCT06097260).[2,3] Pre-clinical evaluation of bexotegrast in precision-cut lung slices (PCLS) from IPF patient explants demonstrated decreased profibrogenic gene expression.[4] In addition to IPF, integrin β_6 expression is elevated in epithelial cells across multiple fibrotic ILDs (Figure 2).[5]

Therefore, in this study, we evaluated the antifibrotic activity of bexotegrast in PCLS generated from explants taken from patients with progressive fibrosing ILDs other than IPF.

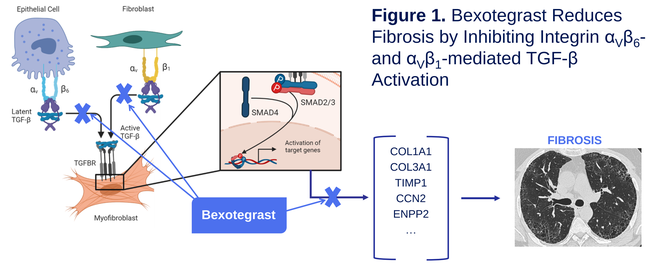


Figure 1. Bexotegrast Reduces Fibrosis by Inhibiting Integrin $\alpha_V\beta_6$- and $\alpha_V\beta_1$-mediated TGF-β Activation

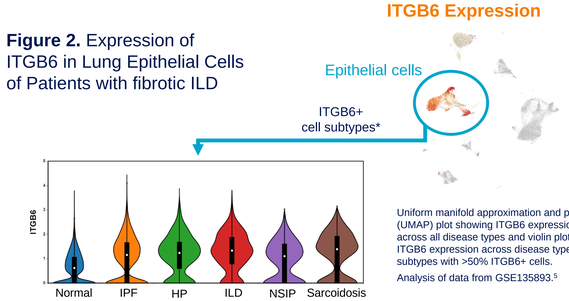


Figure 2. Expression of ITGB6 in Lung Epithelial Cells of Patients with fibrotic ILD

Uniform manifold approximation and projection (UMAP) plot showing ITGB6 expression in all cells across all disease types and violin plot comparing ITGB6 expression across disease types in cell subtypes with >50% ITGB6+ cells.

Analysis of data from GSE135893.[5]

STUDY DESIGN AND METHODS

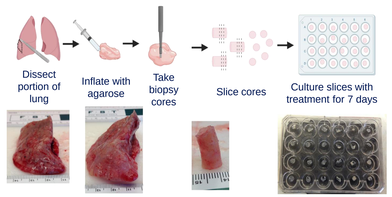
Characterization of Fibrotic ILD Explants

Lung explants taken at the time of transplant from patients with fibrotic ILD were assessed for fibrosis by picrosirius red staining and for expression of $\alpha_v\beta_6$ by immunohistochemistry.

Precision-cut Lung Slices

Precision-cut lung slices (PCLS) were generated from fibrotic lung explants and cultured for 7 days in the presence of bexotegrast, TGF-β1 type I receptor inhibitor (ALK5i; R-268712), or vehicle. Treated PCLS were then analyzed for changes in profibrogenic gene expression using a NanoString custom fibrosis panel (Figure 3).

Figure 3. Flowchart of PCLS Generation and Culture

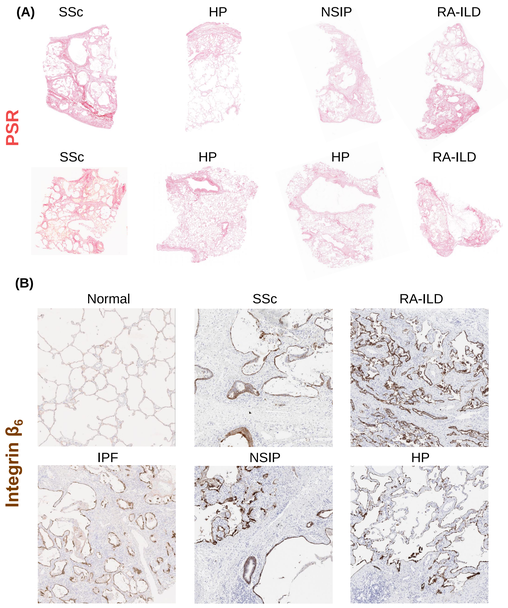


CONCLUSIONS

- Integrin $\alpha_v\beta_6$ expression is increased in lungs of patients with fibrotic ILD
- Bexotegrast (dual $\alpha_v\beta_6/\alpha_v\beta_1$ inhibitor) treatment decreased profibrogenic gene expression in PCLS generated from diverse ILD lung explants, including SSc, RA-ILD, HP, and NSIP
- Antifibrotic activity was similar in fibrotic PCLS from IPF and non-IPF explants.
- These data support further investigation into the antifibrotic activity of bexotegrast in ILD-associated PPF
- Late-stage evaluation of bexotegrast will further explore the efficacy and safety in participants with IPF (BEACON-IPF; NCT06097260)

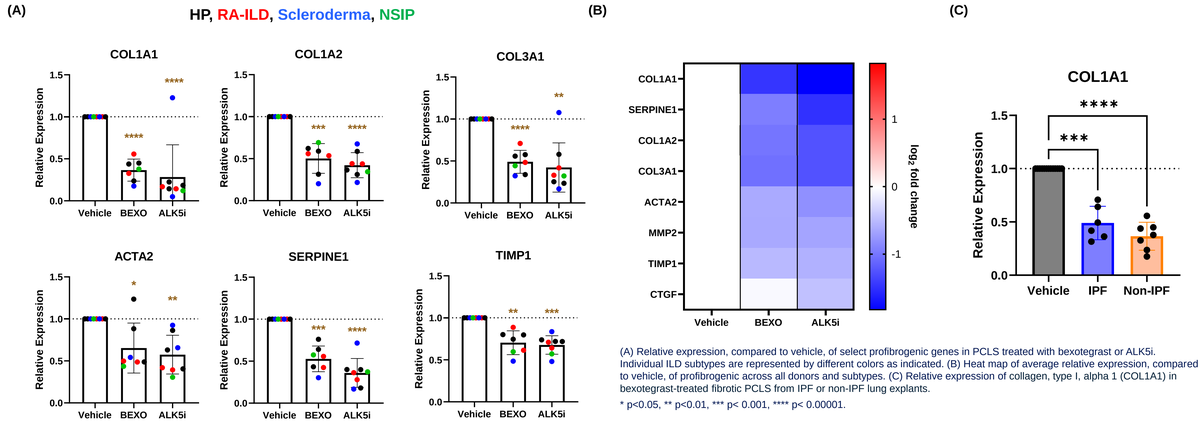
RESULTS

Figure 4. ILD Explants Have Fibrosis and Increased $\alpha_V\beta_6$ Expression



Staining for (A) collagen via picrosirus red (PSR) and (B) integrin β6 (brown) in fibrotic ILD explants.

Figure 5. Bexotegrast Significantly Reduced Profibrogenic Gene Expression in Fibrotic PCLS Regardless of Etiology



(A) Relative expression, compared to vehicle, of select profibrogenic genes in PCLS treated with bexotegrast or ALK5i. Individual ILD subtypes are represented by different colors as indicated. (B) Heat map of average relative expression, compared to vehicle, of profibrogenic across all donors and subtypes. (C) Relative expression of collagen, type I, alpha 1 (COL1A1) in bexotegrast-treated fibrotic PCLS from IPF or non-IPF lung explants.

* p<0.05, ** p<0.01, *** p< 0.001, **** p< 0.00001.

- Lung explants collected at the time of transplant from patients with scleroderma (SSc), rheumatoid arthritis-interstitial lung disease (RA-ILD), hypersensitivity pneumonitis (HP) and nonspecific interstitial pneumonia (NSIP) showed evidence of fibrosis and increased expression of integrin $\alpha_V\beta_6$ compared to control lung tissue (Figure 4).
- Treatment of fibrotic PCLS with bexotegrast significantly reduced collagen gene expression (*COL1A1*, -63%, p<0.0001; *COL1A2*, -50%, p<0.001), as well as markers of TGF-b-signaling (*SERPINE1*, -44%, p<0.001) and pathologic fibroblasts (*CTHRC1*, -48%, p<0.01) (Figure 5A, B).
- Bexotegrast treatment of PCLS from IPF and non-IPF lung explants resulted in similar inhibition of *COL1A1* gene expression by ~50% (Figure 5C).

References: 1. Rajan et al. Eur Respir J (2023). 2. Lancaster et al. AJRCCM (2024). 3.ERS Presentations OA2861, OA1058, PA4260. 4. Decaris et al. Respir Res (2021). 5. Habermann et al. Sci Adv (2020).

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