CIRCULATING ITGB6 LEVELS ARE ELEVATED IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS AND REDUCED FOLLOWING LUNG TRANSPLANT

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ABSTRACT

Background

The activation of latent TGF-β by integrin $\alpha_v\beta_6$ is a well-known driver of fibrogenesis in idiopathic pulmonary fibrosis (IPF). Circulating levels of integrin beta-6 (ITGB6), the beta subunit of the integrin heterodimer $\alpha_v\beta_6$, were recently shown to be predictive of progression in patients with interstitial lung disease (Bowman, W.S. et al. Lancet Respir Med 2022; 10(6):593-602). In addition, we recently observed significantly reduced levels of circulating ITGB6 in patients with IPF receiving bexotegrast, a dual inhibitor of integrins $\alpha_v\beta_6$ and $\alpha_v\beta_1$ currently being evaluated in Phase 2 clinical trials for IPF (Lancaster, L. et al. ATS Int Conf May 2023). However, little is known about how ITGB6 concentrations in patients with IPF differ from those in healthy subjects.

Methods

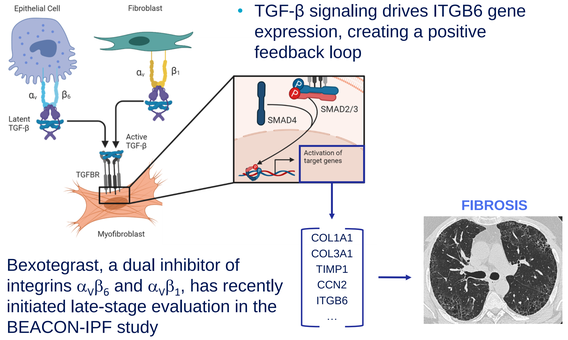
Here we directly compared serum concentrations of ITGB6 (and additional proteins) in patients with IPF to healthy subjects by proximity extension assay (Olink 384 Explore Inflammation panel). ITGB6 and other protein concentrations before and 3-12 months following lung transplant were also compared in a subset of patients.

Results

Serum ITGB6 levels were significantly elevated by approximately 2.5-fold in patients with IPF compared to healthy controls ($p < 0.0001$; Fig 1A). Furthermore, serum ITGB6 concentrations were significantly reduced by an average of 36% in patients with IPF following lung transplant ($p < 0.05$; Fig1B). Relative quantitation of additional proteins identified >100 as significantly elevated or reduced in patients with IPF compared to healthy subjects (FDR < 0.05) and assessed their change in concentration post-transplant.

BACKGROUND

Integrins $\alpha_v\beta_6$ and $\alpha_v\beta_1$ promote pulmonary fibrosis through the activation of latent TGF-β resulting in new collagen synthesis



- TGF-β signaling drives ITGB6 gene expression, creating a positive feedback loop
- Bexotegrast, a dual inhibitor of integrins $\alpha_v\beta_6$ and $\alpha_v\beta_1$, has recently initiated late-stage evaluation in the BEACON-IPF study

- Elevated plasma ITGB6 levels have previously been shown to associate with disease progression in large cohorts of patients with IPF and non-IPF interstitial lung disease (ILD)[1,2]
- A 12-week Phase 2a clinical trial evaluating the safety and efficacy of bexotegrast, a dual inhibitor of integrins $\alpha_v\beta_6$ and $\alpha_v\beta_1$, in patients with IPF, showed a significant reduction in both FVC decline (Fig 1A) and circulating ITGB6 levels (Fig 1B) in participants treated with bexotegrast vs placebo[3].

Figure 1: LS Mean change from baseline in FVC and Plasma ITGB6 Levels in Patients with IPF

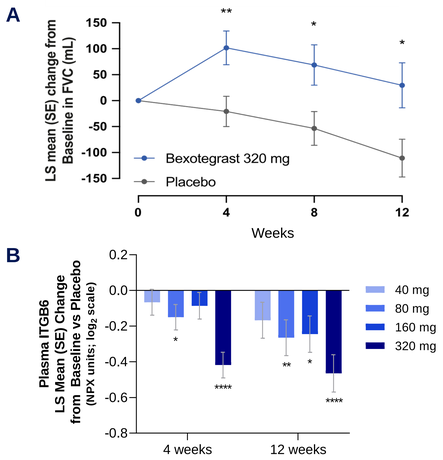


Figure 1: 12-week interim results from INTEGRIS-IPF (A Randomized, Double-blind, Dose-ranging, Placebo Controlled Phase 2a Evaluation of the Safety, Tolerability and Pharmacokinetics of PLN-74809 in Participants With Idiopathic Pulmonary Fibrosis)[3]. A) Change in FVC from Baseline through Week 12 in participants receiving 320 mg bexotegrast compared with placebo. FVC change from Baseline analyzed in efficacy mITT population using an MMRM. B) Change from Baseline to Week 12 for exploratory endpoint plasma ITGB6 analyzed in the pharmacodynamic analysis population using an MMRM.
*p<0.05 vs. placebo; **p<0.01 vs. placebo; ****p<0.0001 vs. placebo; FVC, forced vital capacity; ITGB6, integrin beta-6; LS, least squares; mITT, modified intent-to-treat; MMRM, mixed model for repeated measures; NPX, Normalized Protein eXpression; SE, standard error

STUDY AIMS

1. **Determine the relative difference in circulating ITGB6 levels between patients with IPF and healthy subjects**
2. **Assess the impact of lung transplant on circulating ITGB6 levels in patients with IPF**
3. **Explore the effect of lung transplant on additional circulating proteins dysregulated in patients with IPF compared with healthy controls**

METHODS

- Serum collected from patients with IPF (n=17) and healthy subjects (n=15) was analyzed via Olink Explore 384 Inflammation protein panel
- For a subset of patients with IPF (n=8), serum collected ≤ 2 months prior to lung transplant was compared to additional samples collected 3-12 months post-transplant

Table 1: Participant sample information

Subject Group	n	Age (mean ± stdev)	Gender	% pred FVC (mean ± stdev)
Healthy (BioIVT)	15	54.5 ± 8.4	8 M, 7 F	n/a
IPF (Stanford)	17	67.4 ± 8.5	14 M, 3F	53.6 ± 19.6

IPF patient % predicted FVC data collected pre-transplant; FVC, forced vital capacity;
IPF, idiopathic pulmonary fibrosis; n/a, not available

RESULTS

- Relative quantitation of serum ITGB6 levels showed significantly elevated levels (approximately 2.5-fold higher) in patients with IPF in comparison to healthy subjects (Fig 2A)
- Serum ITGB6 levels were significantly reduced in patients with IPF following transplant (Fig 2B)

Figure 2: Comparison of serum ITGB6 levels between healthy subjects and patients with IPF (pre- and post-lung transplant)

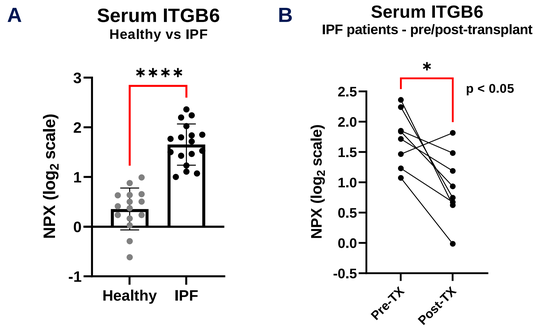


Figure 2: (A) Serum concentration of ITGB6 in patients with IPF and healthy subjects measured in NPX units (arbitrary units for relative quantitation in log2 scale). (B) Serum concentration of ITGB6 in subset of patients with IPF compared pre- and 3-12 months post-lung transplant. Note that single participant with elevated post-transplant serum ITGB6 levels was analyzed pre/post a second lung transplant (previously received unilateral lung transplant followed by grade II rejection)
*p<0.05 vs. placebo; ****p<0.0001 vs. placebo; IPF, idiopathic pulmonary fibrosis; ITGB6, integrin beta-6; NPX, Normalized Protein eXpression; Tx, transplant

- Relative quantitation of additional proteins detected by the Olink panel identified >100 as significantly elevated or reduced by ≥ log2 fold change of 0.5 in patients with IPF compared to healthy subjects (FDR < 0.05; Fig 3)

Figure 3: Comparison of relative serum protein concentrations between patients with IPF and healthy subjects

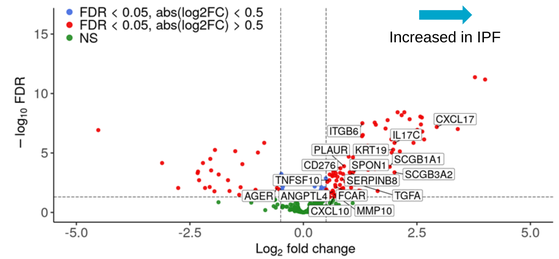


Figure 3: Volcano plot of relative serum concentrations of 307 proteins compared between healthy subjects and patients with IPF. Vertical dashed lines indicate cutoff for absolute log2 fold change of 0.5. Horizontal dashed line indicates cutoff for FDR < 0.05.
FC, fold change; FDR, false discovery rate; IPF, idiopathic pulmonary fibrosis; NS, not significant

- A subset of those proteins found to be significantly increased or decreased in patients with IPF were also found to change following transplant (Table 2)

Protein ID	Log2 FC reduction Post-TX vs Pre-TX (FDR < 0.1)
SCGB3A2	-2.32
PDLIM7	-1.86
MPIG6B	-1.78
SKAP2	-1.64
MANF	-1.52
EGF	-1.46
DBNL	-1.38
BANK1	-1.29
CXCL17	-1.25
CASP2	-1.17
LAMP3	-1.16
CLIP2	-1.06
CRKL	-1.03
DPP10	-1.02
STX8	-0.87
MMP10	-0.85
ITGB6	-0.79
ANGPTL2	-0.77
CD6	-0.72
NCF2	-0.72
HGF	-0.70
CXCL12	-0.68
GZMA	-0.66
DAG1	-0.59

Table 2: Comparison of relative serum protein levels in patients with IPF pre- and post-transplant

Protein ID	Log2 FC increase Post-TX vs Pre-TX (FDR < 0.1)
PROK1	1.26
AGER	1.04
CD276	0.96
LGALS4	0.93
CDSN	0.89
ANGPTL4	0.84
GAL	0.74
LILRB4	0.74
AGRP	0.68
B4GALT1	0.64
CLSTN2	0.60
SCG3	0.59

Serum proteins significantly increased or decreased in patients with IPF vs healthy controls were compared pre/post-transplant
FDR, false discovery rate; FC, fold change; IPF, idiopathic pulmonary fibrosis;

CONCLUSIONS

- **Circulating ITGB6 levels, previously shown to predict disease progression in patients with ILD, are significantly elevated in patients with IPF and reduced following lung transplant**
- **Further analysis of circulating ITGB6 in clinical trials may help to better characterize its utility as an early biomarker of response to anti-fibrotic therapy**

References: 1. Bowman, W.S. et al. Lancet Respir Med 2022; 10(6):593-602, 2. Oldham, J. et al. AJRCCM 2023;207:A6533, 3. Lancaster LH, et al. AJRCCM 2023;207:A2777

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Disclosures: MD, EB, PK, RA, and ST are employees and shareholders of Pliant Therapeutics