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Seralutinib decreases endotrophin (PRO-C6) production, a mediator of fibrosis and inflammation, in an *in vitro* model of pulmonary fibrosis

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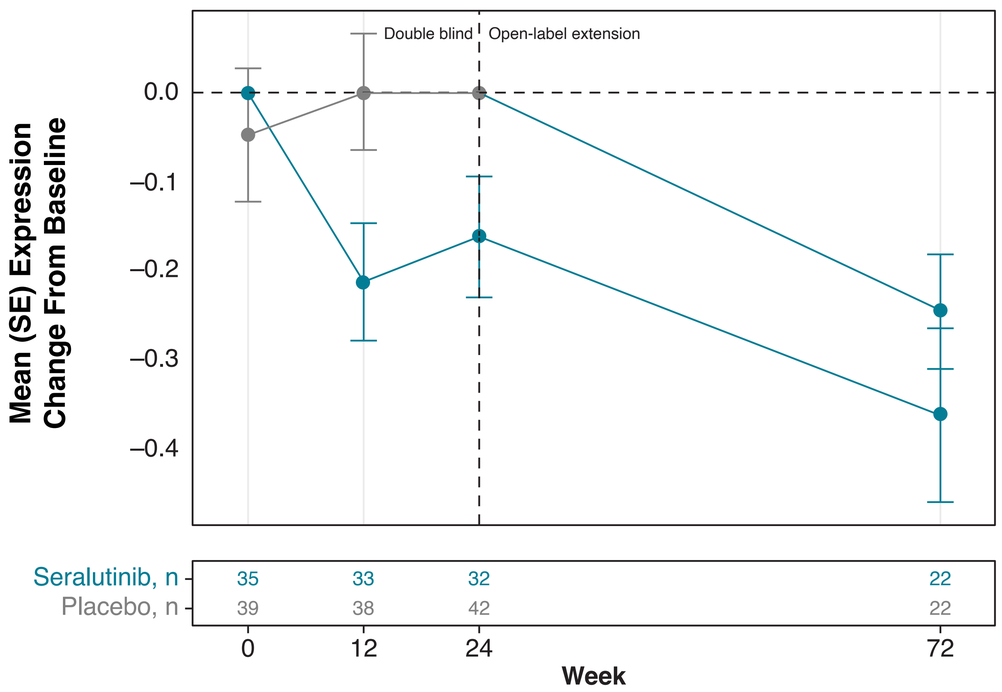
BACKGROUND

- Extracellular matrix (ECM) remodeling and fibroblast activation contribute toward pulmonary vascular remodeling in group 1 and 3 pulmonary hypertension (PH)[1,2]
- Seralutinib, an inhaled PDGFR, CSF1R, and c-KIT tyrosine kinase inhibitor, improved pulmonary vascular resistance and decreased circulating ECM biomarkers, including COL6A3, in patients with PAH in the TORREY study (NCT04456998; **Figure 1**), and fibrogenic factors in *in vitro* models of fibrosis[3-7]
- ECM component collagen type VI α3 chain (COL6A3) is produced by activated fibroblasts and, under pro-fibrotic conditions, is proteolytically cleaved to release the bioactive matrikine, endotrophin (PRO-C6)[8-10]
- PRO-C6 is a marker and mediator of fibrosis and inflammation in interstitial lung diseases with underlying fibrosis,[9,11] highlighting its potential as a surrogate biomarker of pulmonary fibrosis in PH associated with interstitial lung disease (ILD)
- The goal of this study is to demonstrate seralutinib's direct effect on the production of PRO-C6 in an *in vitro* model of human pulmonary fibrosis

Figure 1. In the TORREY and open-label extension studies, circulating COL6A3 was reduced with seralutinib treatment in PAH patients

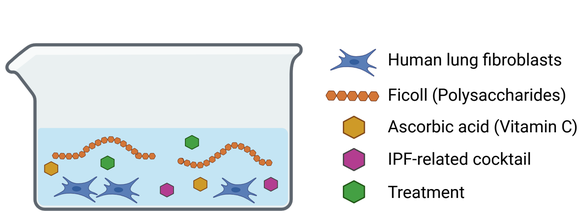


SE, standard error.

METHODS

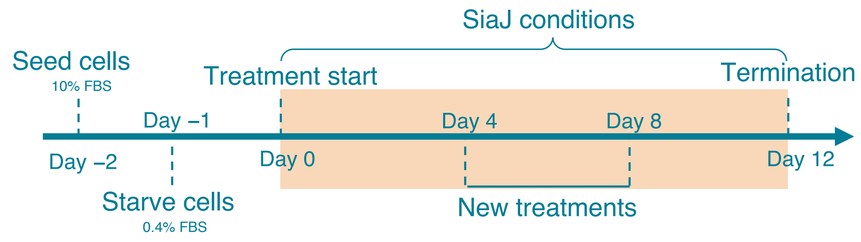
Human lung fibroblast (HLF) Scar-in-a-Jar model

- Following the Scar-in-a-Jar model[12] healthy HLFs (NHLF) were stimulated with a fibrotic cocktail (FC) for 12 days
- Supernatants were collected on days 8 and 12 to quantify the C-terminal fragment of COL6A3, using the Nordic PRO-C6™ assay
- FC, seralutinib (0.1-3 µM), and treatment controls (nintedanib; 0.03-1 µM) were administered on days 0, 4, and 8



IPF-related fibrotic cocktail (FC)

TGF-β	IL-8	MCP-1
IL-1β	IL-33	TSLP
TNF-α	IL-13	IL-14

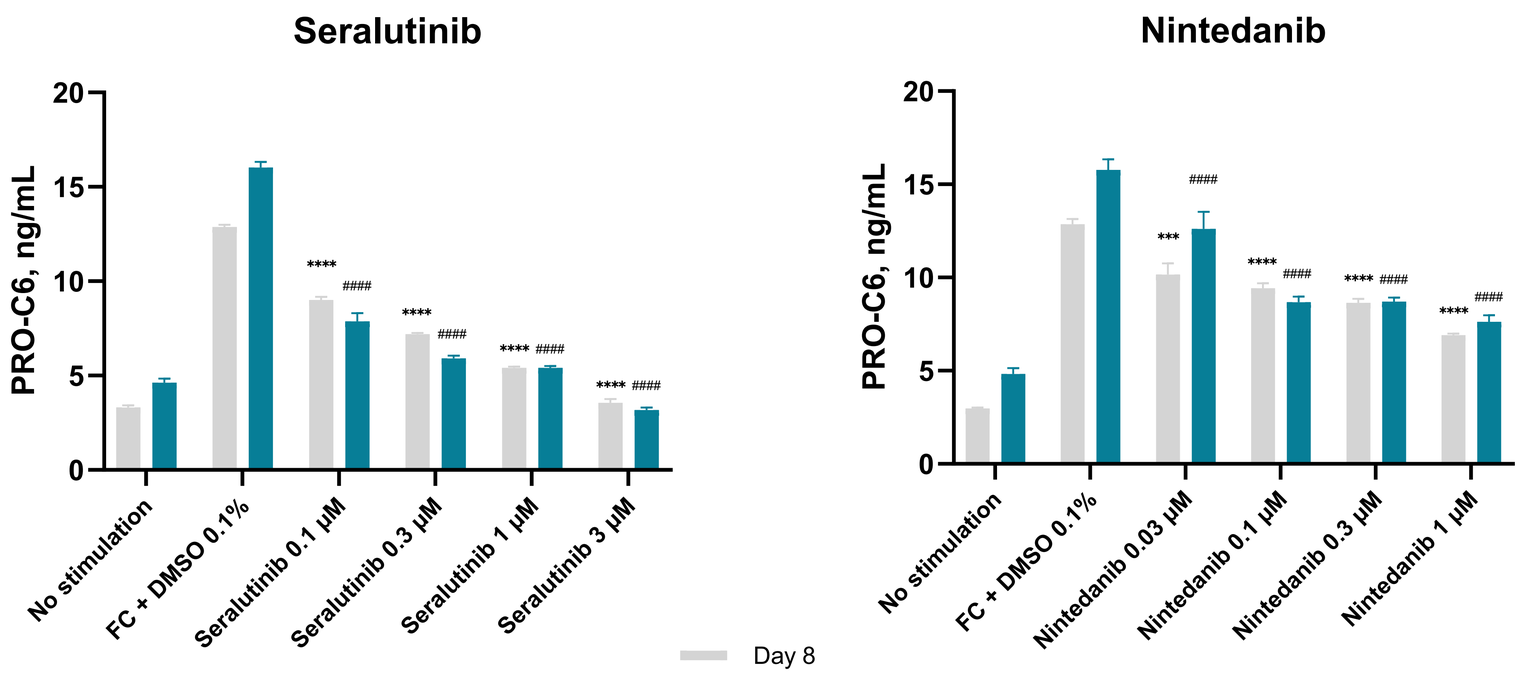


FBS, fetal bovine serum; IL, interleukin; IPF, idiopathic pulmonary fibrosis; MCP-1, monocyte chemoattractant protein 1; SiaJ, Scar-in-a-Jar; TGF, transforming growth factor; TNF, tumor necrosis factor; TSLP, thymic stromal lymphopoietin.

RESULTS

- Stimulating NHLFs with the FC increased PRO-C6 levels (2.3-fold) at day 8 and day 12 compared to unstimulated cells
- Seralutinib treatment compared to vehicle treatment (FC+DMSO 0.1%) reduced PRO-C6 levels by 1.3× (0.1 µM) to 3.2× (1 µM) at both day 8 and day 12
- Nintedanib treatment compared to vehicle treatment (FC+DMSO 0.1%) reduced PRO-C6 levels by 1.5× (0.1 µM) to 2.0× (1 µM) at both day 8 and day 12

Figure 2. Seralutinib inhibited the production of endotrophin (PRO-C6) in healthy human lung fibroblasts stimulated with a fibrotic cocktail



NHLF were stimulated with fibrotic cocktail and treated with either seralutinib (0.1 µM, 0.3 µM, 1 µM, or 3 µM) or nintedanib (0.03 µM, 0.1 µM, 0.3 µM, or 1 µM). PRO-C6 was measured in the supernatant at day 8 and day 12 post treatment and fibrotic cocktail stimulation. Data are expressed as mean ± SEM (n=4). Statistics was performed using two-way ANOVA followed by Dunnett's multiple comparisons test. *** p<0.001, **** p<0.0001, test group vs. vehicle treatment on day 8, #### p<0.0001, test group vs. vehicle treatment group on day 12. NHLF, healthy human lung fibroblast; SEM, standard error of the mean.

CONCLUSIONS

- Consistent with clinical TORREY biomarker data and preclinical models of pulmonary fibrosis, seralutinib demonstrated significant suppression of PRO-C6 production by HLFs, reinforcing its potential to target pulmonary fibrosis in PH-ILD
- These data encourage the continued investigation of PRO-C6 as a surrogate biomarker of pulmonary fibrosis and its role in the pathophysiology of PH-ILD in the phase 3 SERANATA study (NCT07181382) of seralutinib for the treatment of PH-ILD

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