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Seralutinib Targets Fibrotic Pathways in IPF: Evidence From Single-cell Transcriptomics

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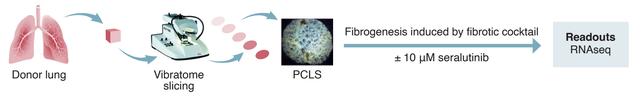
BACKGROUND

- Seralutinib is an inhaled receptor tyrosine kinase inhibitor that targets PDGFRα/β, CSF1R, and c-KIT, and is under development for pulmonary hypertension (PH), including pulmonary arterial hypertension (PAH) and PH associated with interstitial lung disease (ILD)[1,2]
- In the phase 2 TORREY trial in PAH (NCT04456998), seralutinib decreased pulmonary vascular resistance and reduced circulating proteins associated with extracellular matrix remodeling[3,4]
- To further investigate its antifibrotic potential, we identified seralutinib-associated signatures from a human (h) precision-cut lung slice (PCLS) fibrosis model and the TORREY study, and mapped them to scRNAseq profiles from idiopathic pulmonary fibrosis (IPF) patient lungs

METHODS

Seralutinib signature generation

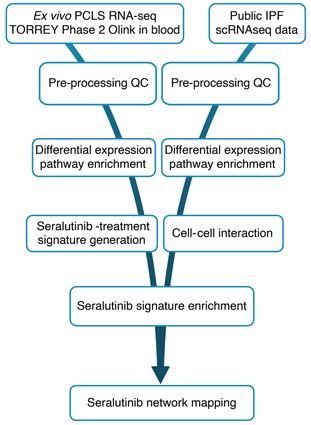
- **Gene signatures** were identified from RNAseq analysis of *ex vivo* PCLS cultures stimulated with pro-fibrotic cocktail and treated with 10 µM seralutinib or vehicle



- **Proteomic signatures** were determined from TORREY PAH patients treated for 24 weeks with 90 mg BID seralutinib or placebo, Olink Explore 3072 assay[4]

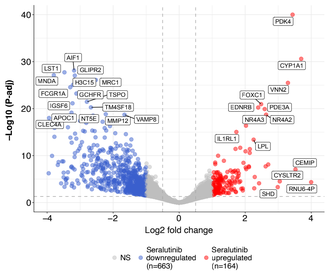
Single-cell transcriptomics and data integration:

- 7 publicly available scRNAseq datasets of IPF (n=80) and control (n=58) lungs (486,114 cells) were used to map seralutinib-associated proteins and gene signatures to IPF lung populations.[5-9] scRNAseq datasets were processed individually in R using Seurat v4. An integrated lung epithelial single-cell dataset was constructed from GSE135893, GSE136831, GSE128033 and GSE156310. Epithelial cell types were extracted, re-normalized, scaled and integrated
- Differentially expressed genes were computed using the FindMarkers function separately for each dataset. Combined p-values were generated using the minimump function (Tippett's method) from metap R package and adjusted using the BH correction
- Gene set enrichment analysis was performed with PIANO for seralutinib PCLS signatures and Reactome pathways across IPF single-cell populations
- Cell-cell interactions predicted with Omnipath (commercial license, curation effort ≥4 publications)

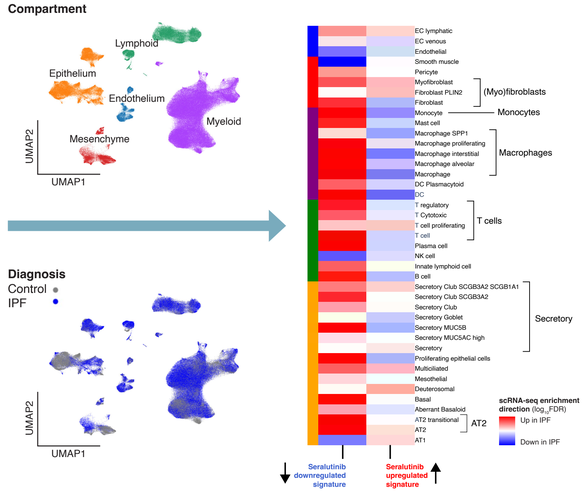


RESULTS

Seralutinib hPCLS gene signatures are enriched in single-cell lung populations of IPF patients



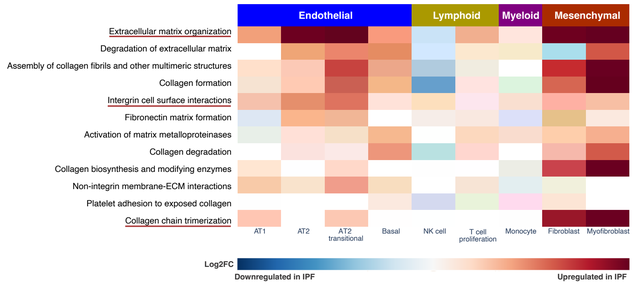
Hallmark Pathway	Fibrotic cocktail vs untreated		Seralutinib 10 µM vs fibrotic cocktail	
	NES	p-adj	NES	p-adj
Epithelial Mesenchymal Transition	2.62	<0.001	−1.52	0.026
Tnfa Signaling via Nfkb	2.34	<0.001	1.41	0.028
Inflammatory Response	2.24	<0.001	−1.46	0.062
Interferon Gamma Response	2.02	<0.001	−2.06	<0.001
Coagulation	2.02	0.001	−1.6	0.031
Kras Signaling Up	1.96	<0.001	−1.47	0.049
Allograft Rejection	1.82	0.005	−1.94	<0.001
Hypoxia	1.76	0.006	−1.13	0.487
Complement	1.75	0.01	−1.78	<0.001
Kras Signaling On	−1.92	0.001	1.09	0.516



- In fibrotic cocktail-induced hPCLS cultures, seralutinib countered fibrotic gene expression by downregulating ECM, EMT and epithelial repair[10]
- Gene set enrichment analysis of seralutinib signatures was performed across 7 IPF single-cell datasets
- Seralutinib signatures are significantly enriched in IPF fibroblasts, AT2, secretory cells and macrophages

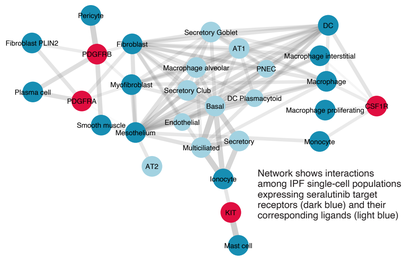
ECM-related pathways decreased by seralutinib in PAH patients were upregulated in IPF myofibroblasts, fibroblasts, AT2 and endothelial cells

- In IPF vs control scRNAseq data, mesenchymal and epithelial cell populations were enriched in dysregulated ECM-, so collagen-, fibronectin- and integrin-related pathways
- 3 out of the top 5 pathways that had been downregulated by seralutinib in TORREY are upregulated in IPF in key cell types (highlighted in red)

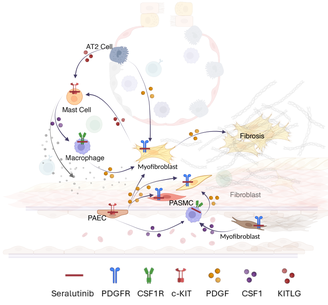


Cell populations expressing seralutinib targets show substantial interactions with IPF disease-relevant cell populations

Seralutinib targets expressed in IPF cell populations (scRNA-seq) → **Cell-cell interactions inferred from curated receptor-ligand interactions** → **Seralutinib targets digital cell-cell interaction network in IPF**



Network shows interactions among IPF single-cell populations expressing seralutinib target receptors (dark blue) and their corresponding ligands (light blue)



- Seralutinib receptors are expressed primarily in mast cells, smooth muscle, macrophages, monocytes and fibroblasts
- In IPF, these cell populations closely interact with each other, and also with AT1, AT2, endothelial and secretory cells, based on a predicted receptor-ligand interaction network, suggesting that seralutinib effect may propagate to these cells. This is consistent with previous vascular-endothelial effects observed in PAH models and patients[1,11]

CONCLUSIONS

- Seralutinib modulated fibrotic pathways as demonstrated in PCLS cultures at gene level and in circulating proteins in PAH patients
- Seralutinib signatures are elevated in disease-relevant cell populations in IPF, suggesting a potential to have broad multi-cellular impact on fibrosis
- Cell populations expressing seralutinib targets show substantial interactions with various lung cell types relevant to IPF
- Together, these results support the development of seralutinib as a novel inhaled therapy for fibrotic lung diseases

References: **1** Galkin A, et al. *Eur Respir J.* 2022;60(6):2102356. **2** Pullamsetti SS, et al. *Int J Mol Sci.* 2023;24(16):12653. **3** Frantz RP, et al. *Lancet Respir Med.* 2024;12(7):523-534. **4** Ghofrani HA, et al. *Am J Respir Crit Care Med.* 2024;209:A7383. **5** Adams TS, et al. *Sci Adv.* 2020;6(28):eaba1983 (GSE136831). **6** Habermann AC, et al. *Sci Adv.* 2020;6(28):eaba1972 (GSE135893). **7** Yao C, et al. *Am J Respir Crit Care Med.* 2021;203(6):707-717 (GSE146981). **8** Valenzi E, et al. *Front Immunol.* 2021;12:595811 (GSE156310). **9** Jaeger B, et al. *Nat Commun.* 2022;13(1):5637 (GSE141939). **10** Sitapara R, et al. *Chest.* 2024;166(4 suppl):A5844-A5846. **11** Osterhout R, et al. *Eur Respir J.* 2024;64(suppl 68):OA1872.

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