CHEST

Seralutinib Exhibits Anti-fibrotic Effects in Human Models of Pulmonary Fibrosis: An Emerging Option for Group 1 and 3 Pulmonary Hypertension?

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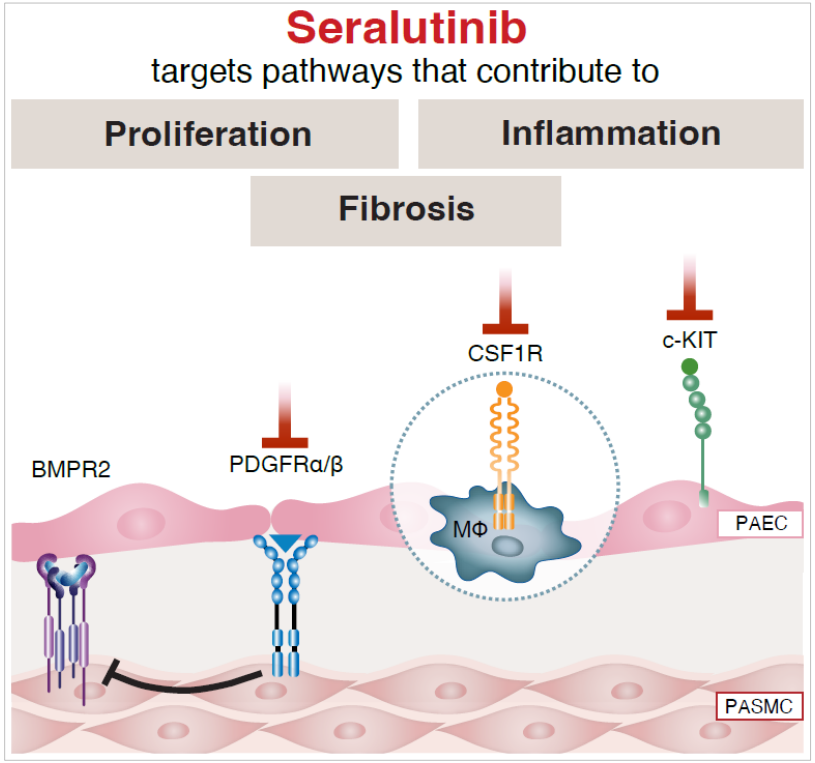
Background

- Seralutinib is a potent, inhaled, PDGFRα/β, CSF1R and c-KIT kinase inhibitor, targeting pathways driving vascular remodeling in pulmonary arterial hypertension (PAH)
- The phase 2 TORREY study of seralutinib in adults with WHO Group I PH met its primary endpoint of reduction in pulmonary vascular resistance (PVR) at 24 weeks[1]
- In an exploratory analysis of TORREY, seralutinib decreased circulating fibrotic biomarkers, including collagen Iα1, suggestive of an anti-fibrotic effect
- Fibrosis is one of the underlying processes contributing to pulmonary vascular and lung tissue remodeling and stiffening in WHO Groups 1 and 3 PH

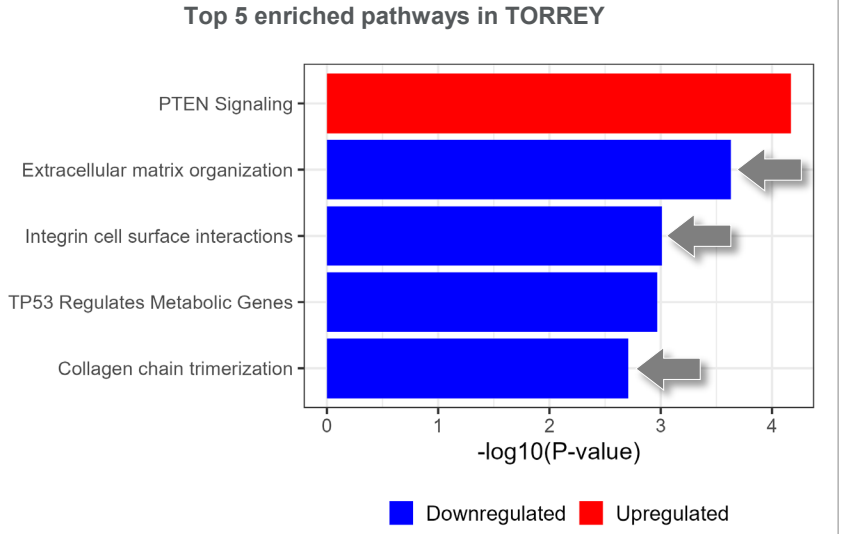


Blunt arrows indicate inhibition.
BMPR2, bone morphogenetic protein receptor type 2; c-KIT, mast/stem cell growth factor receptor kit; CSF1R, colony stimulating factor 1 receptor; MΦ, macrophage; OLE, open-label extension; ; PAEC, pulmonary artery endothelial cell; PASMC, pulmonary artery smooth muscle cell; P(A)H, pulmonary (arterial) hypertension; PDGFR, platelet-derived growth factor receptor; PVR, pulmonary vascular resistance.

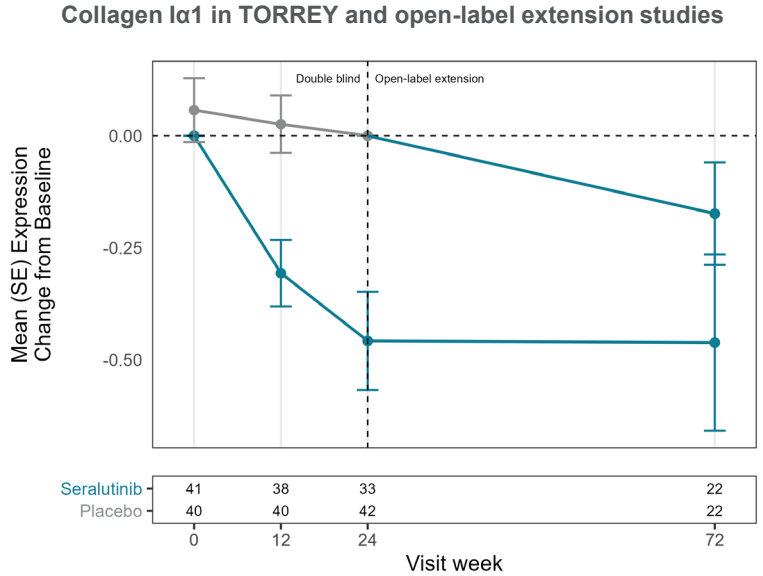
1 Frantz RP, et al. *Lancet Respir Med* 2024;12(7):523-534.
TORREY: NCT04456998, OLE: NCT04816604

Seralutinib treatment decreased fibrosis-related circulating proteins in the TORREY phase 2 study in WHO Group 1 PH

- Seralutinib decreased circulating proteins and pathways relevant to extracellular matrix remodeling and fibrosis (arrows)
- Changes were maintained over 72 weeks of treatment in the open-label extension

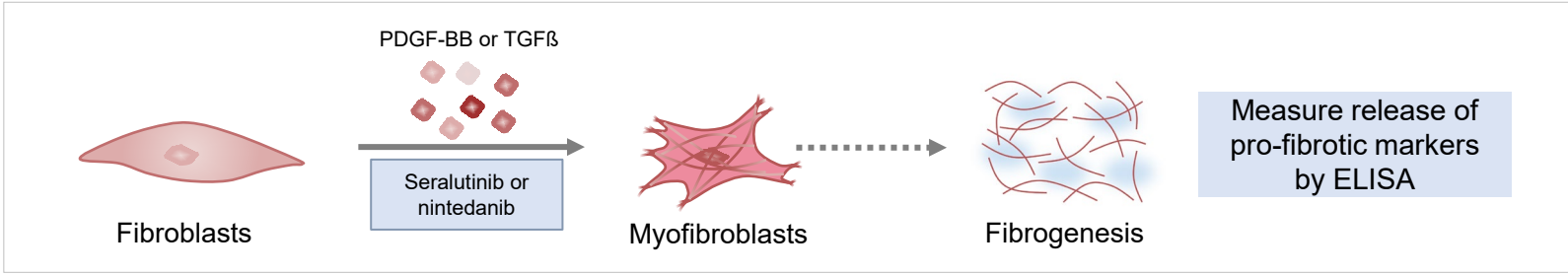


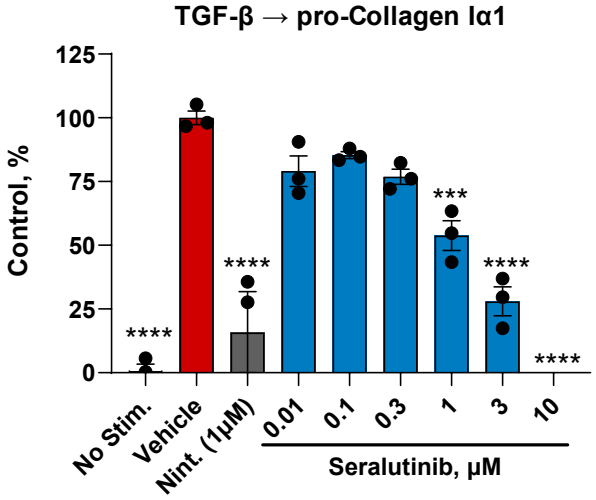
Arrows indicate enriched pathways relevant to fibrosis. Pathway directionality derived from QIAGEN IPA z-scores. Ghofrani HA, et al. *Am J Respir Crit Care Med.* 2024;209:A7383.

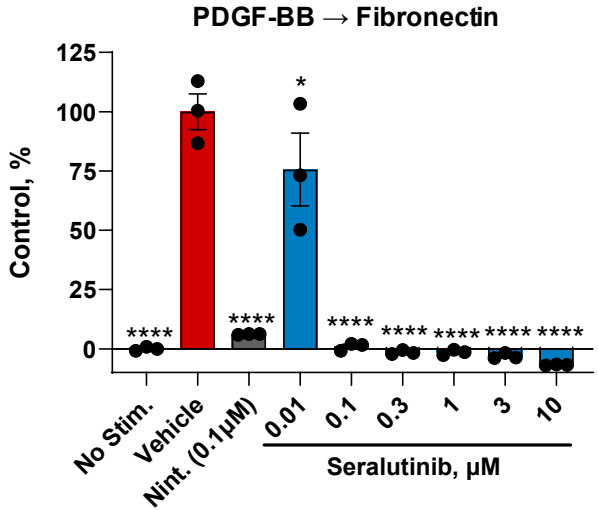


Circulating COL1A1 measured using Olink Explore assay.
Open-label extension results presented at ERS 2024 (Abstract number: OA1872)

Seralutinib decreased release of pro-collagen Iα1 and fibronectin from human lung fibroblasts in Scar-in-a-jar fibrogenesis assay







Nint, Nintedanib; Stim, stimulation. Data are presented as mean ± SEM (N=3). Statistical analysis performed using one-way ANOVA with Dunnett's multiple comparison test. *p<0.05, ***p<0.001, and ****p<0.0001 vs. vehicle.

Seralutinib decreased release of profibrotic proteins in human precision-cut lung slices (PCLS) fibrogenesis assay

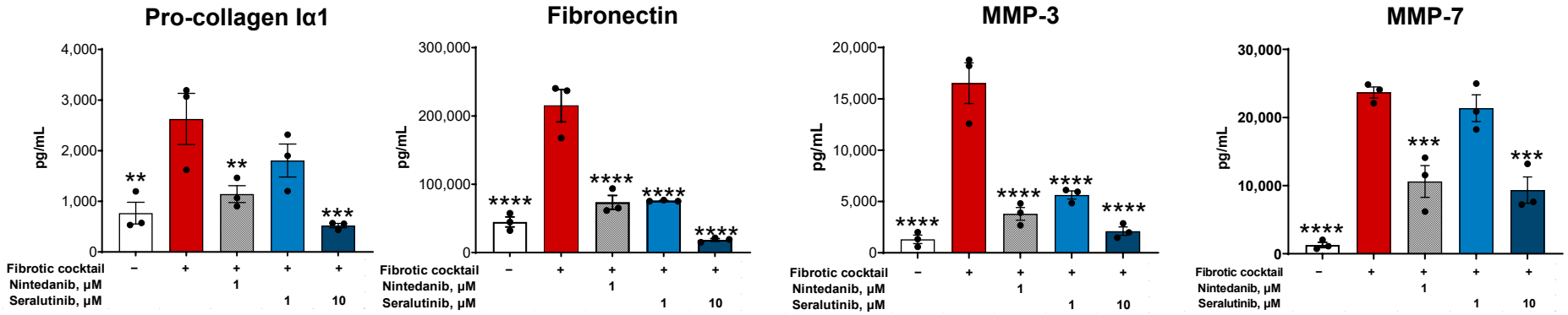
Donor lung | Vibratome slicing | PCLS

Fibrogenesis induced by fibrotic cocktail

Seralutinib or Nintedanib

Readouts

1. Release profibrotic markers (by Luminex multiplex assay)
2. Pathway changes in PCLS (by RNAseq)



Data presented as mean ± SEM (N=3). Statistical analysis performed using one-way ANOVA with Dunnett's multiple comparison test. **p<0.01, ***p<0.001 and ****p<0.0001 vs. vehicle.

- Seralutinib also inhibits MCP-1, Serpin E1, and TIMP-1 in the hPCLS fibrogenesis assay

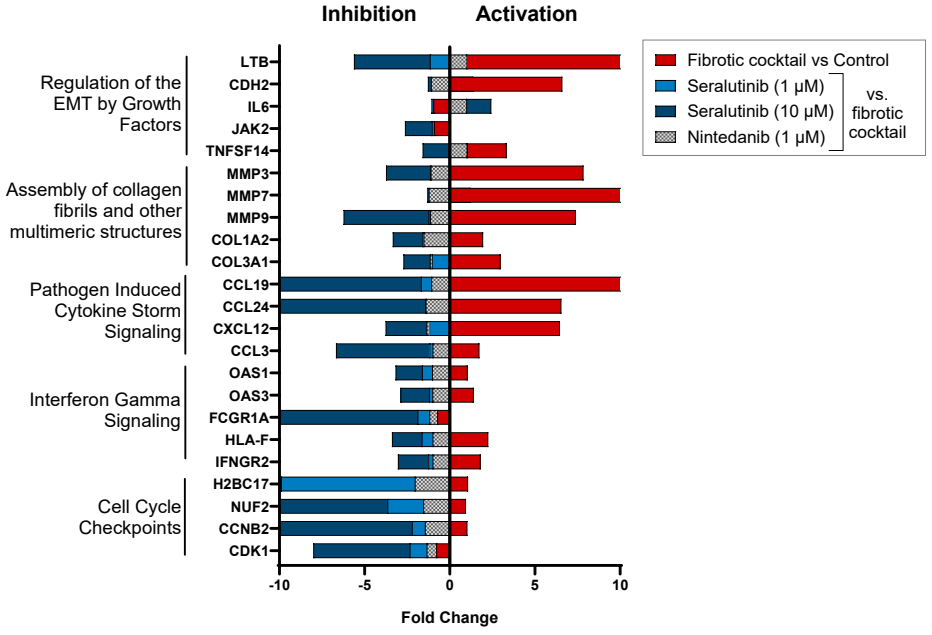
Seralutinib reversed fibrosis-related pathways in human PCLS fibrogenesis assay

- Fibrotic cocktail induces pro-inflammatory pathways and EMT

Hallmark Pathway	Fibrotic cocktail vs untreated		Seralutinib 10μM 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 Dn	-1.92	0.001	1.09	0.516

GSEA Analysis of top 10 MSigDB hallmark pathways enriched by fibrotic cocktail vs. untreated control. NES, normalized enrichment score (red: increasing, blue: decreasing); P-adj, BH-adjusted p-values.

- Selected genes reversed by treatment with seralutinib



Fold changes >10 are plotted as 10

Conclusions

- Seralutinib decreased release of pro-collagen Iα1 and fibronectin from human lung fibroblasts in Scar-in-a-jar fibrogenesis assay
- Seralutinib reversed fibrotic cocktail-induced induction of pro-collagen Iα1, fibronectin, MMP-3 and MMP-7 proteins, and pro-fibrotic genes and pathways in hPCLS cultures fibrogenesis assay
- Collectively, these data along with TORREY circulating fibrotic biomarker data support further investigation of seralutinib as a potential inhaled treatment option for WHO Group 1 and Group 3 PH