

Comparative and combined effects of seralutinib and nintedanib suggest synergistic anti-fibrotic and anti-inflammatory activity in IPF patient-derived lung models

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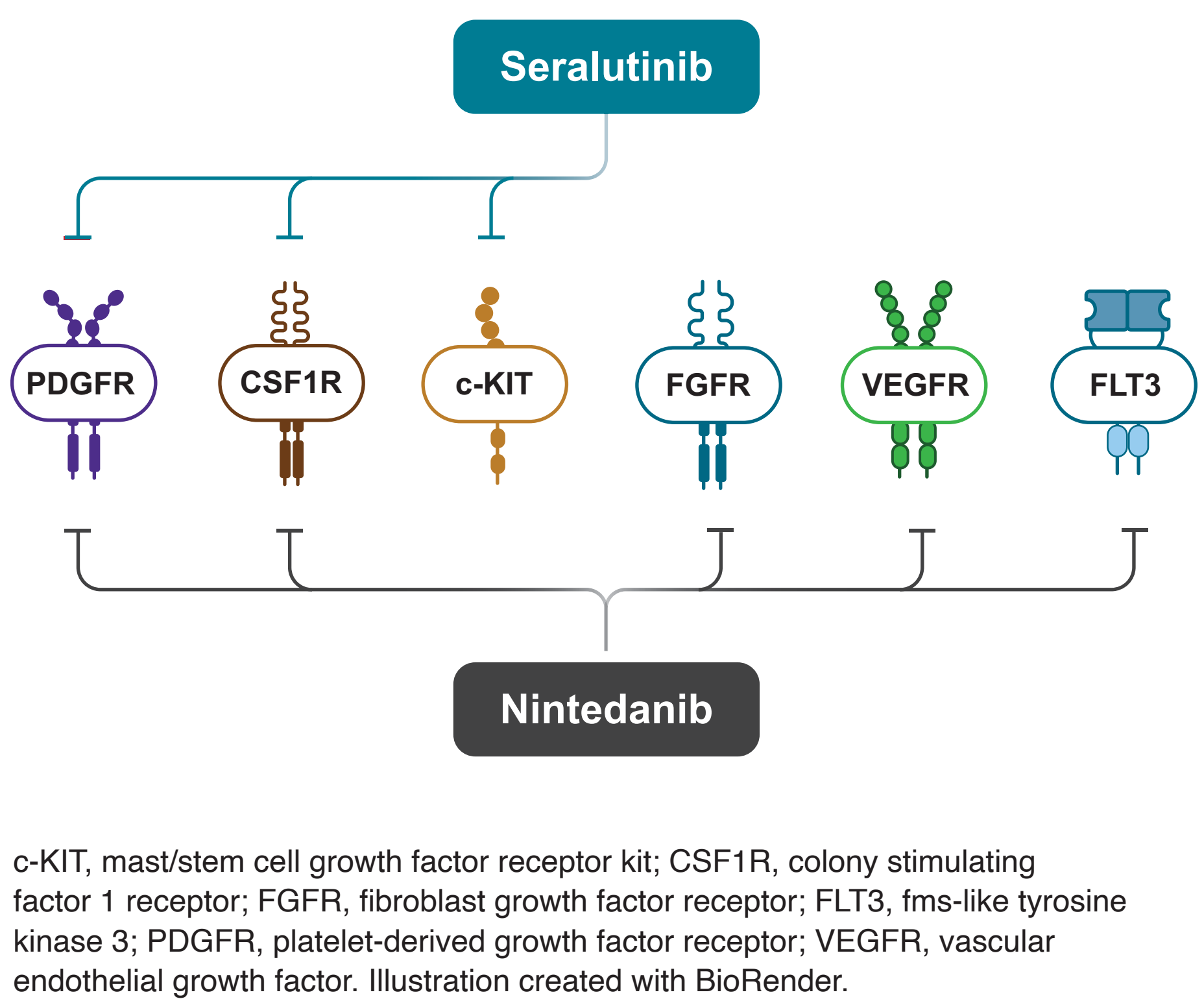


Presented at:
ERS Congress 2026
5–9 September
Barcelona, Spain

BACKGROUND

- Fibrosis, inflammation and proliferation drive pulmonary vascular remodeling and fibrosis in pulmonary hypertension (PH) and interstitial lung disease (ILD)¹
- Seralutinib is an investigational inhaled tyrosine kinase inhibitor that targets PDGFR α/β , CSF1R, and c-KIT^{2,3} (**Figure 1**)
- Nintedanib, approved for multiple subtypes of fibrosing ILD, targets overlapping and distinct kinases
- In the phase 2 TORREY study (NCT04456998) and open-label extension in patients with Group 1 PH, seralutinib decreased circulating fibrotic biomarkers, including pro-collagen $\alpha 1(I)$ ^{4,5}
- We evaluated the anti-fibrotic and anti-inflammatory effects of seralutinib and nintedanib alone and in combination in idiopathic pulmonary fibrosis (IPF) patient-derived precision-cut lung slices (PCLS) and human lung fibroblasts (HLF)

Figure 1. Overview of kinases inhibited by seralutinib and nintedanib

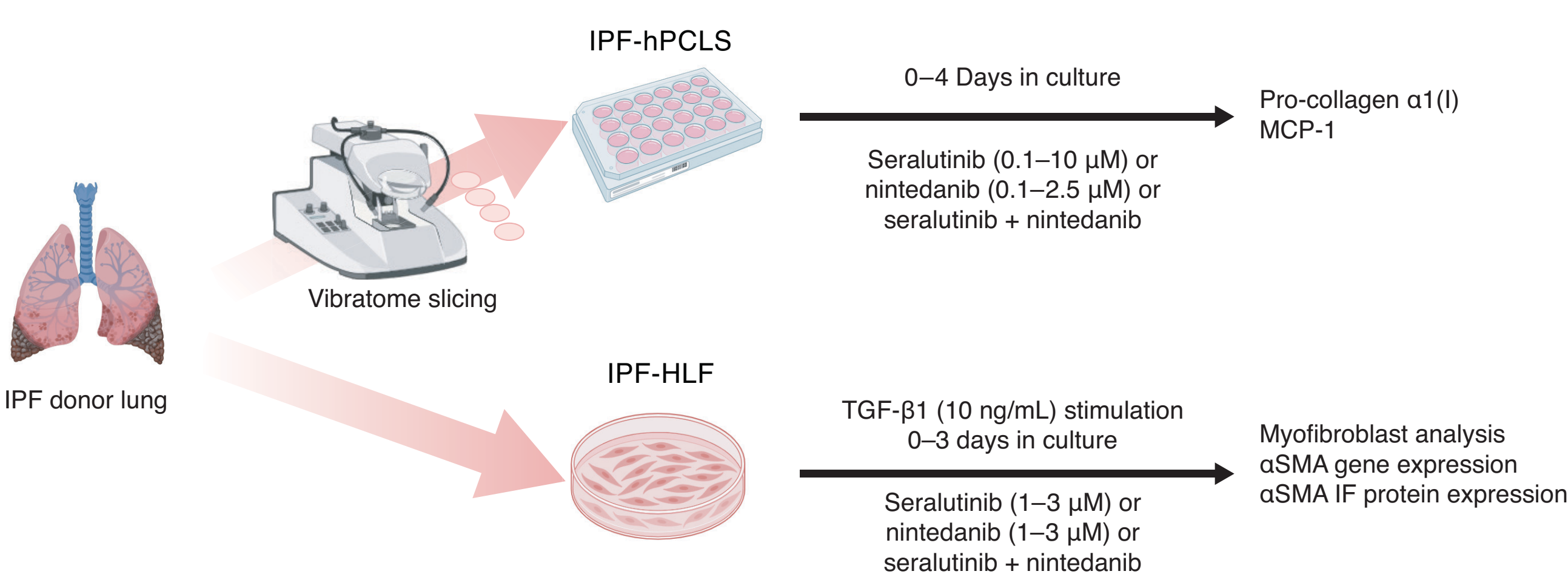


METHODS

Effect of seralutinib on release of pro-fibrotic markers from IPF human (h) PCLS cultures

- PCLS from three IPF donors were cultured and treated for 4 days with vehicle, seralutinib, or nintedanib⁶ or a combination of both (**Figure 2**)
- Supernatants were collected at 96 h and pro-fibrotic markers evaluated using ELISA or MSD kits

Figure 2. IPF-hPCLS and HLF experimental setup



Effect of seralutinib on fibroblast-to-myofibroblast transition in IPF-HLFs

- IPF-HLF were pre-treated with seralutinib, nintedanib, or combination of both and stimulated with 10 ng/mL TGF- β for 3 days (**Figure 2**)
- Alpha-smooth muscle actin (α SMA) gene expression levels were determined by quantitative PCR and protein expression was assessed by immunofluorescent (IF) staining

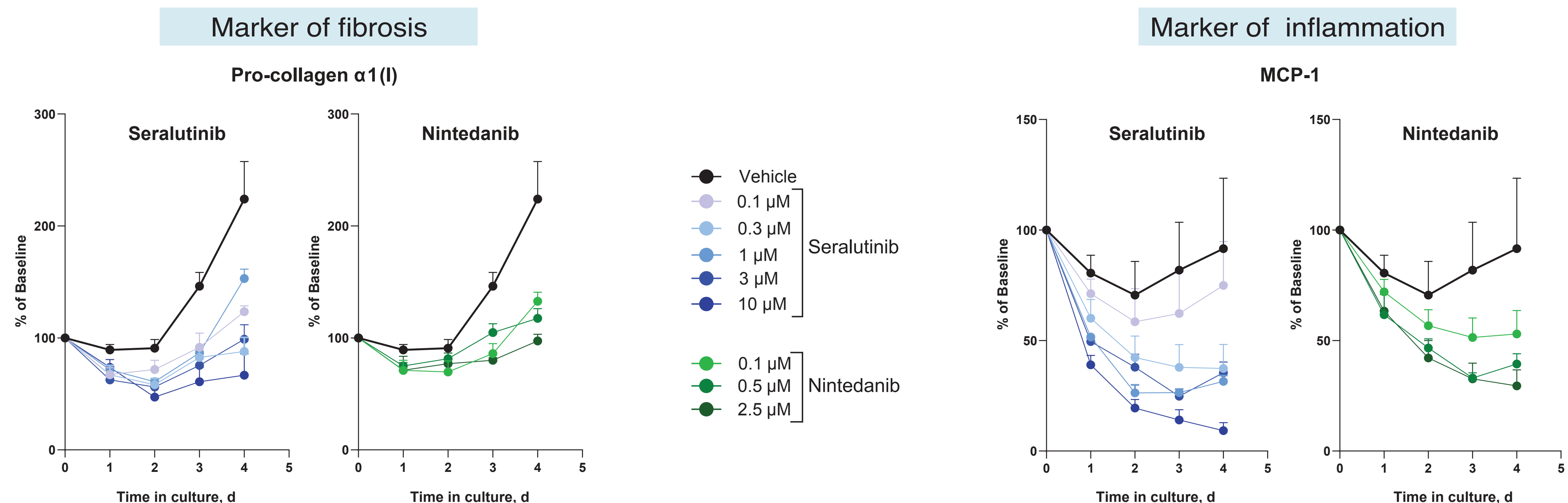
Table 1. hPCLS donor demographics

Donor	Age, y	Sex	Smoking history	FVC, % predicted	Key clinical context
TOR 1.1	63	Male	Former smoker	44.0%	Advanced IPF explant tissue
TOR 1.3	65	Male	Never smoker	35.3%	Advanced IPF; on nintedanib/immunosuppression
TOR 1.4	57	Male	Never smoker	33.6%	Advanced IPF with PH; on nintedanib/immunosuppression

These donor tissues reflect severe, clinically advanced IPF, supporting the relevance of the PCLS model for testing anti-fibrotic and anti-inflammatory activity in human fibrotic lung tissue. FVC, forced vital capacity; (h)PCLS, (human) precision-cut lung slice; IPF, idiopathic pulmonary fibrosis; PH, pulmonary hypertension.

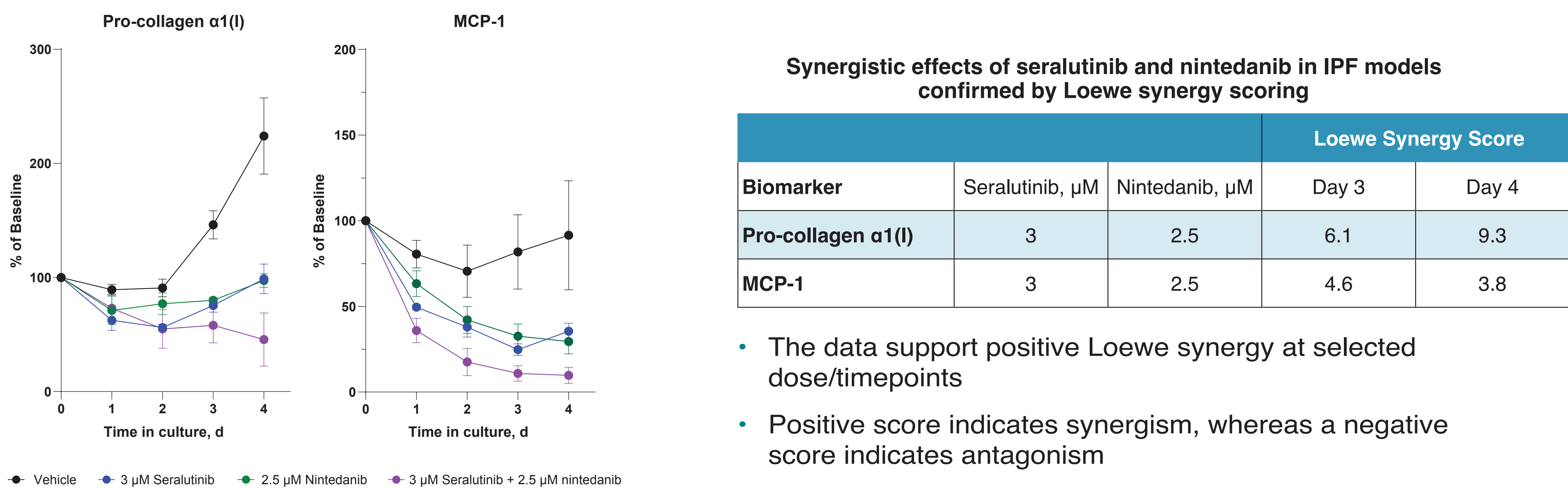
RESULTS

Figure 3. Seralutinib shows equipotent effect vs nintedanib in inhibition of release of pro-fibrotic proteins in three independent IPF-hPCLS donors



Levels of pro-collagen $\alpha 1(I)$ and MCP-1 in IPF-PCLS culture media, expressed as % of vehicle baseline (black), following single-agent dose response with seralutinib (0.1–10 μ M) or nintedanib (0.1–2.5 μ M). Data are from n=3 donors (n=5–6 culture media samples per donor) per condition and time point, and are presented as mean $\pm$ SEM.

Figure 4. Combination of seralutinib and nintedanib potentiates inhibitory effects on pro-fibrotic protein secretion in IPF-PCLS



Levels of pro-collagen $\alpha 1(I)$ and MCP-1 in IPF-PCLS culture media, expressed as % of vehicle baseline, following treatment with vehicle (black), seralutinib 3 μ M (blue), nintedanib 2.5 μ M (green), or the combination of both (purple). Data are from n=3 donors (n=5–6 culture media samples per donor) per condition and time point, and are presented as mean $\pm$ SEM. The Loewe synergy scoring analysis is shown on the right.

SUMMARY

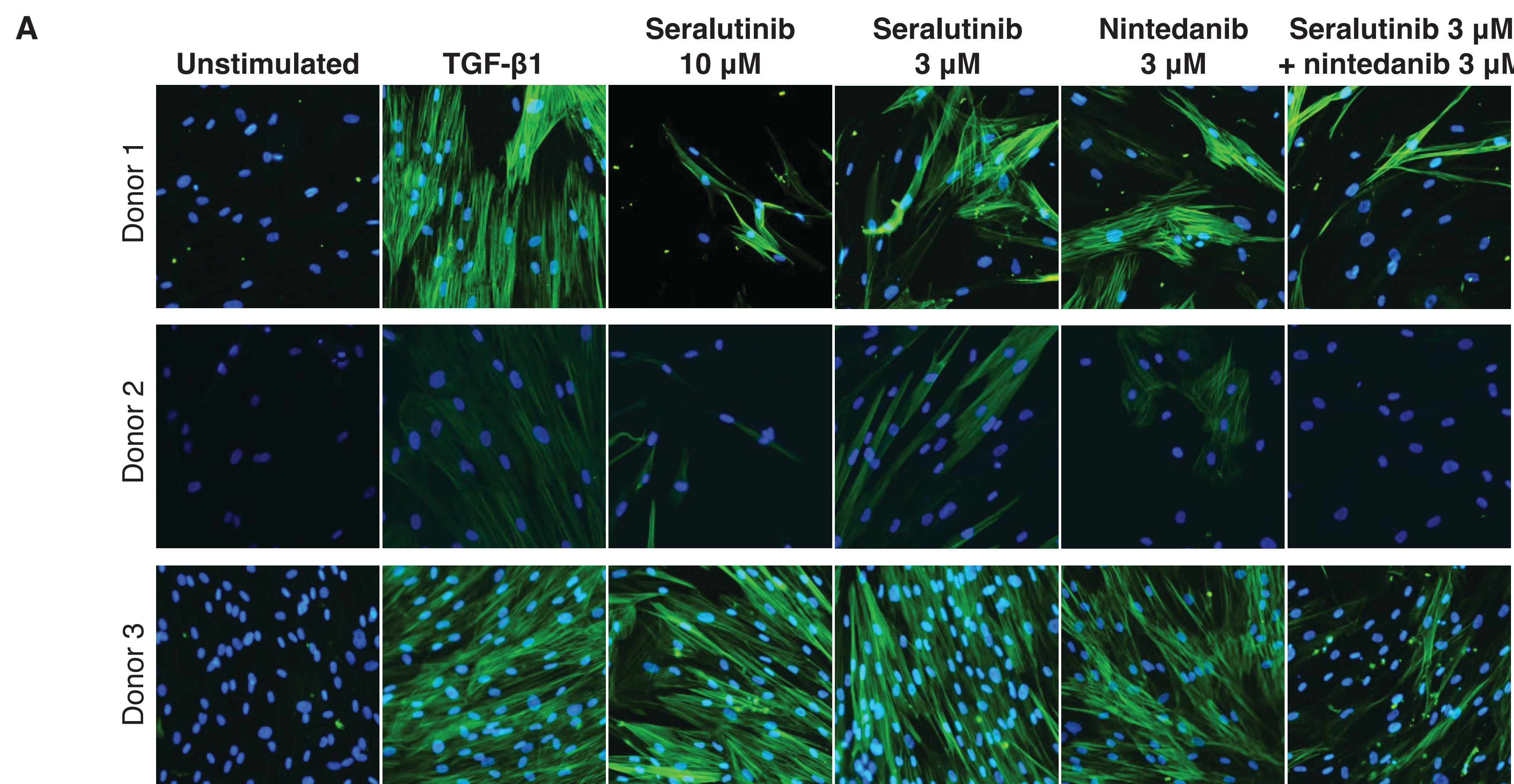
In IPF PCLS:

- Seralutinib and nintedanib suppressed pro-fibrotic protein pro-collagen $\alpha 1(I)$ to a similar extent
- Seralutinib suppressed pro-inflammatory protein MCP-1 to a greater extent than nintedanib
- Combined inhibition produced synergistic effects on these markers at selected dose/timepoints

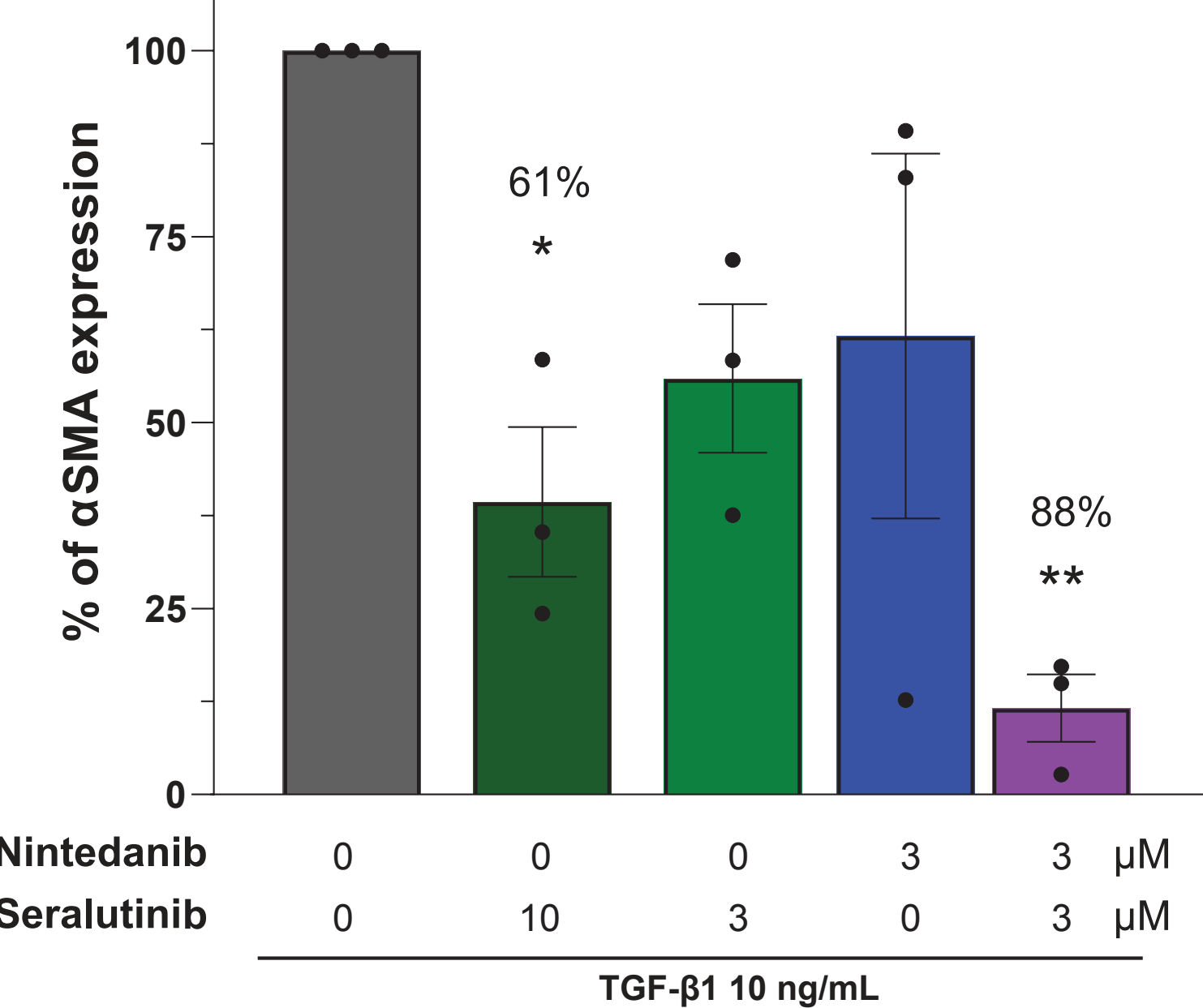
In IPF patient-derived fibroblasts:

- Combined seralutinib and nintedanib decreased fibroblast-to-myofibroblast transition, consistent with reduced activation of key effector cells responsible for fibrotic remodeling
- The collective preclinical and translational evidence supports further evaluation of seralutinib–nintedanib combination therapy in fibrotic lung diseases, including IPF and PH-ILD
- Interpretation is limited by the short duration of the experiments and the small number of donor samples evaluated

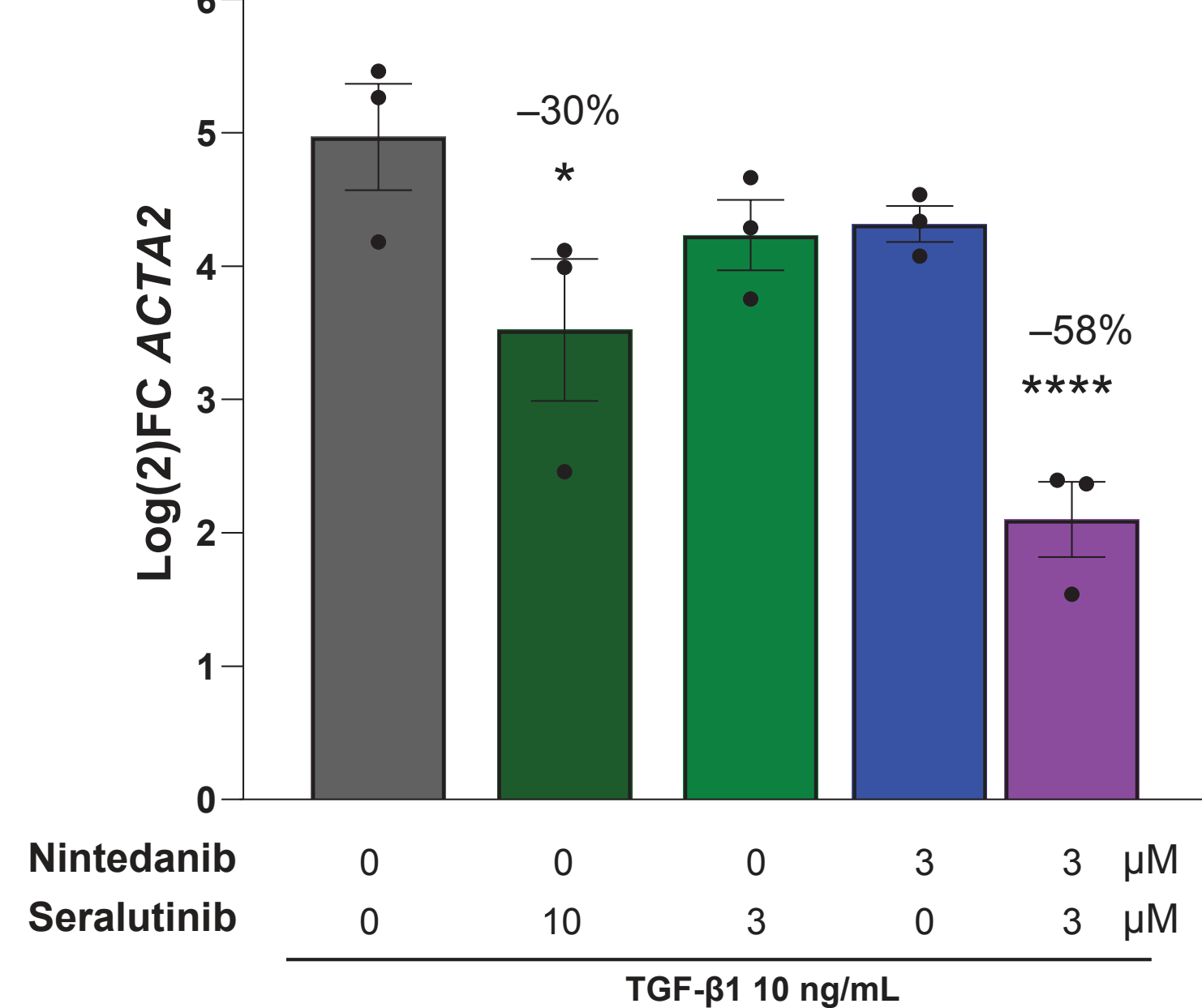
Figure 5. Seralutinib inhibited TGF- β -induced α SMA in IPF-HLFs



B



C



A Immunofluorescent imaging and **B** quantification of α SMA levels. Seralutinib reduced amount of TGF- β -induced α SMA expressed at clinically relevant doses in IPF-HLF cells. **C** Change in gene expression levels of *ACTA2* in IPF-HLF cells. Gene upregulated due to TGF- β stimulation and dose-dependent inhibition by seralutinib.

Data are expressed as mean $\pm$ SEM (N=3 donors). Statistical analysis was performed using one-way ANOVA Dunnett's multiple comparisons test. *p<0.05, **p<0.01, ***p<0.001 versus TGF- β 1-treated cells.

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Disclosures: Ayodeji Adegunsoye received research grants from the Pulmonary Fibrosis Foundation, the American College of Chest Physicians, and the National Institutes of Health for the conduct of studies in pulmonary fibrosis; provided consultancy services to Abbvie, Baxter, Brainomix, Gossamer Bio USA, Inc., Inogen, InsMed, Medscape, patientMpower, PureTech, United Therapeutics, Roche, and Boehringer Ingelheim; and served on a pulmonary fibrosis educational forum for Boehringer Ingelheim

Research supported by: Chiesi Farmaceutici S.p.A. and Gossamer Bio USA, Inc.



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