PRECLINICAL MODELS SUPPORT THE SYNERGISTIC POTENTIAL OF SERALUTINIB AND SOTATERCEPT IN TREATING PULMONARY ARTERIAL HYPERTENSION (PAH)

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Ravikumar Sitapara[1], Eduardo Garcia[1], Robin Osterhout[1], Zhaoqing Ding[1], Lawrence S. Zisman[1], Thao Duong-Verlé[1], Robert F. Roscigno[1], Richard Aranda[1], Marc Humbert[2,3], Ly Tu[2,3], Christophe Guignabert[2,3], Jean-Marie Bruey[1]

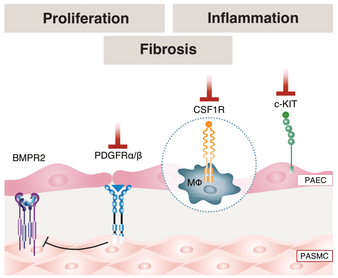
[1]Gossamer Bio, Inc., San Diego, CA, USA; [2]Université Paris-Saclay, Hypertension Pulmonaire: Physiopathology and Innovation Thérapeutique, HPPIT, Faculté de Médecine, Le Kremlin-Bicêtre, France; [3]INSERM UMR_S 999, HPPIT, Le Kremlin-Bicêtre, France

BACKGROUND

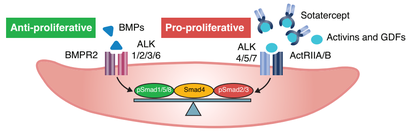
- PAH is a progressive disease characterized by pathogenic remodeling of the pulmonary vasculature, driven by proliferation, intimal fibrosis, and inflammation
- Seralutinib and sotatercept target different pathways associated with vascular remodeling
- Crosstalk between platelet-derived growth factor receptor (PDGFR) and transforming growth factor beta (TGF-ß) superfamily signaling suggests these therapies may have complementary reverse remodeling mechanisms of action
- To test this hypothesis, this study examines the combination of seralutinib and ACTRIIA-Fc (sotatercept analog) in preclinical models

ActRII, activin type II receptor; ALK, activin receptor-like kinase; BMP, bone morphogenetic protein; BMPR, bone morphogenetic protein receptor; c-KIT, mast/stem cell growth factor receptor kit; CSF1R, colony stimulating factor 1 receptor; GDF, growth differentiation factor; MΦ, macrophage; PAEC, pulmonary artery endothelial cell; PASMC, pulmonary artery smooth muscle cell; PDGFR, platelet-derived growth factor receptor.

Seralutinib
targets pathways that contribute to



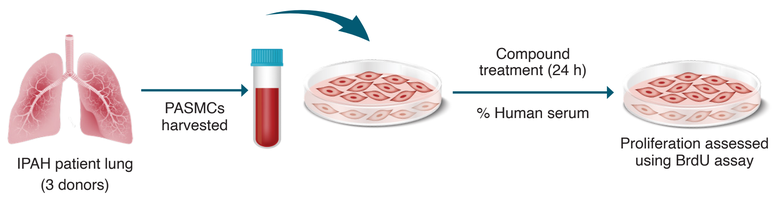
Sotatercept
restores balance between pro- and anti-proliferative pathways



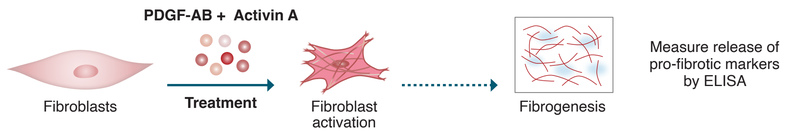
Sotatercept illustration adapted from: Humbert M, et al. *N Engl J Med*. 2021;384:1204-1215.

METHODS

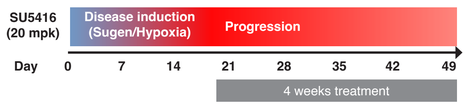
In vitro proliferation assay in idiopathic PAH (IPAH) patient-derived pulmonary artery smooth muscle cells (PASMCs):



In vitro fibrogenesis assay in human lung fibroblasts and human cardiac fibroblasts:



In vivo Sugen hypoxia (SuHx) rat model of PAH:



Group	N
Healthy control	5
SuHx Vehicle control (Inhalation, sc IgG)	7
SuHx Seralutinib (Inhalation)	7
SuHx ACTRIIA-Fc (sc)	7
SuHx Seralutinib + ACTRIIA-Fc	7

Dose, frequency, and route

- Seralutinib: **15 mg/kg**; BID passive inhalation
- ACTRIIA-Fc: **5 mg/kg**; 2x per week sc injection

Dry-powder formulation delivered by nose-only passive inhalation

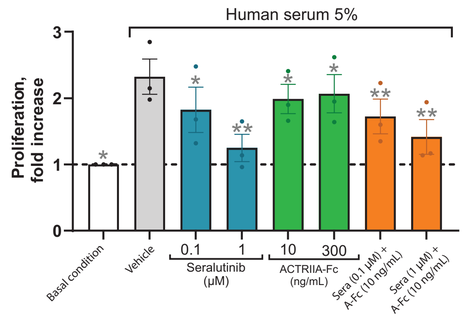
Readouts

Hemodynamics | Echocardiography | RV hypertrophy | Histomorphometry

BID, twice daily; BrdU, bromodeoxyuridine; ELISA, enzyme-linked immunosorbent assay; IgG, immunoglobulin G; IPAH, idiopathic pulmonary arterial hypertension; PASMC, pulmonary artery smooth muscle cell; PDGF, platelet-derived growth factor; RV, right ventricular; sc, subcutaneous; SuHx, Sugen hypoxia.

RESULTS

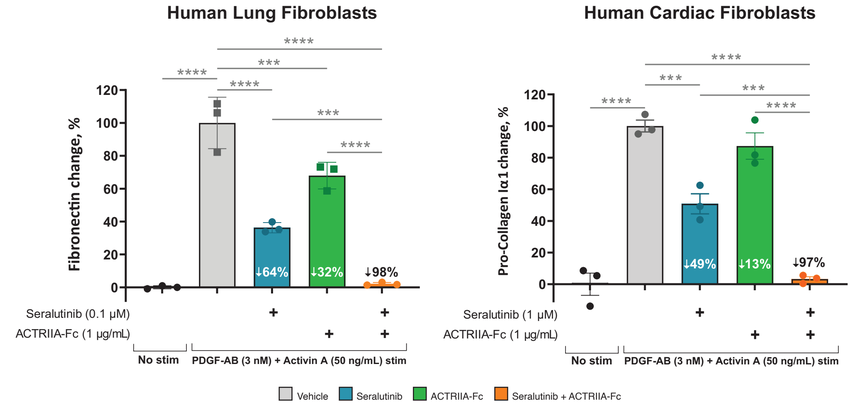
Seralutinib is more potent than ACTRIIA-Fc in inhibiting proliferation of IPAH patient-derived PASMCs



- Seralutinib shows a dose-dependent effect on serum-induced proliferation
- ACTRIIA-Fc has a modest anti-proliferative effect on serum-induced proliferation

Data are represented as fold change in proliferation from basal condition. Bar graphs represent mean ± SEM (n=3). One-way ANOVA followed by Fisher's LSD test. * $p < 0.05$ and ** $p < 0.01$ versus vehicle control. A-Fc, ACTRIIA-Fc; ANOVA, analysis of variance; LSD, least significant difference; SEM, standard error of the mean; sera, seralutinib.

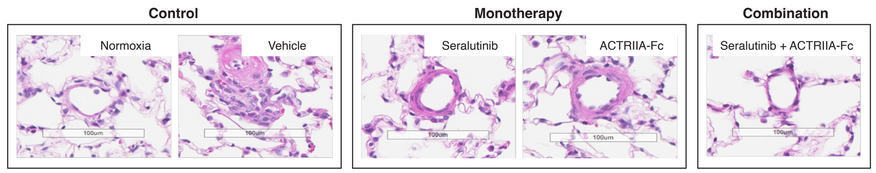
Combination treatment led to synergistic reduction of pro-fibrotic markers in an *in vitro* fibrogenesis assay



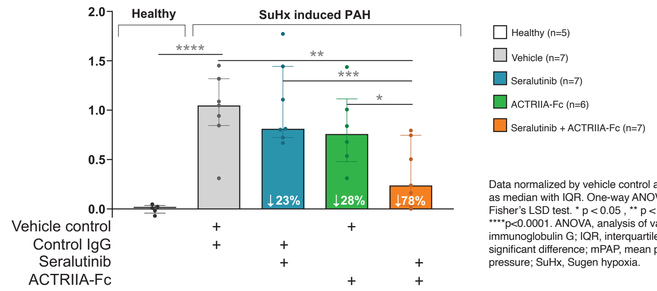
Data are represented as percent change in pro-collagen Iα1 or fibronectin, where unstimulated control = 0% and vehicle stimulation control =100%. Bar graphs represent mean ± SEM (n=3). One-way ANOVA followed by Fisher's LSD test. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$. ANOVA, analysis of variance; LSD, least significant difference; PDGF, platelet-derived growth factor; SEM, standard error of the mean; stim, stimulation.

Combination of seralutinib and ACTRIIA-Fc shows synergistic effect in improving pulmonary hemodynamics and right ventricular (RV) function (*in vivo* SuHx PAH model)

Combination shows more significant pulmonary vascular reverse remodeling (representative images):

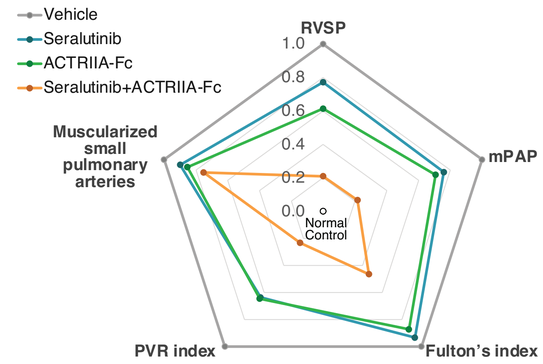


Combination shows synergistic improvement in mPAP:



Data normalized by vehicle control and expressed as median with IQR. One-way ANOVA followed by Fisher's LSD test. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, ****$p<0.0001$. ANOVA, analysis of variance; IgG, immunoglobulin G; IQR, interquartile range; LSD, least significant difference; mPAP, mean pulmonary artery pressure; SuHx, Sugen hypoxia.

Multiparameter comparison graph highlights the synergistic efficacy of combination therapy:



Radar plot representing the change in RVSP, mPAP, RV hypertrophy (Fulton's index), PVR index, and muscularized small pulmonary arteries for each treatment group. Data represented are calculated by normalizing the median of each treatment with vehicle and normal controls. Parameter value = (Value - value of normal) / (value of vehicle - value of normal). mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; RVSP, right ventricular systolic pressure.

CONCLUSIONS

- Combination of seralutinib and the sotatercept analog significantly reduced muscularization of small pulmonary vessels, and synergistically improved pulmonary hemodynamics and RV hypertrophy
- Combination led to synergistic reduction of pro-fibrotic markers *in vitro*
- Results highlight the complementary reverse remodeling mechanisms of action of seralutinib and sotatercept, supporting the clinical potential of combination therapy
- The phase 2 open-label extension (NCT04816604) and phase 3 PROSERA studies (NCT05934526) allow for protocol-specified use of sotatercept with seralutinib

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