A Selective TGFβ Ligand Trap Attenuates Pulmonary Arterial Hypertension

Yung LM¹, Nikolic I¹, Paskin-Flerlage SD¹, Pearsall RS², Kumar R², Yu PB¹

¹Division of Cardiology, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, U.S.A.
²Acceleron Pharma, Inc., Cambridge, MA, U.S.A.

Purpose: We aim to test the impact of TGFBRII-Fc, a selective TGFβ1/3 ligand trap, upon experimental PAH and pulmonary vascular remodeling.

Background: Transforming Growth Factor-β (TGFβ) ligands serve as critical regulators of development and tissue homeostasis, signaling via type I and type II serine-threonine kinase receptors to regulate broad transcriptional programs. Excessive TGFβ-mediated signaling is implicated in the pathogenesis of pulmonary arterial hypertension (PAH), based in part on the ability of broad inhibitors of TGFβ/Activin/GDF/Nodal receptors ALK4/5/7 to attenuate experimental PAH. While these inhibitors are effective and promising, their clinical application is limited by cardiovascular and systemic toxicity. Also, these broad inhibition strategies do not delineate the specific contribution of TGFβ vs. a multitude of other ligands. We tested the impact of TGFBRII-Fc, a selective TGFβ1/3 ligand trap, upon experimental PAH and pulmonary vascular remodeling.

Methods: Signaling studies utilized cultured human pulmonary artery smooth muscle cells. PAH was studied in monocrotaline-treated Sprague-Dawley rats, SUGEN/hypoxia-treated Sprague-Dawley rats and SUGEN/hypoxia-treated C57BL/6 mice. PAH, cardiac function, remodeling, and valve structure were assessed by ultrasound, invasive hemodynamic measurements, and histomorphometry.

Results: TGFBRII-Fc is an inhibitor of TGFβ1 and TGFβ3 but not TGFβ2 signaling. In vivo, treatment with TGFBRII-Fc attenuated SMAD2 phosphorylation, normalized expression of PAI-1, and mitigated PAH and pulmonary vascular remodeling in monocrotaline-treated rats, SUGEN/hypoxia-treated rats and SUGEN/hypoxia-treated mice. Administration of TGFBRII-Fc to monocrotaline-treated rats with established PAH improved right ventricular systolic pressures, right ventricular function, and survival. Importantly, no cardiac structural or valvular abnormalities were observed following treatment with TGFBRII-Fc.

Conclusions: Our findings directly implicate TGFβ1/3 in the pathogenesis of PAH while demonstrating the efficacy and tolerability of selective TGFβ ligand blockade for improving hemodynamics, remodeling, and survival in PAH.