Novel therapies that reverse remodeled pulmonary arteries, improve pulmonary hemodynamics and restore right ventricular (RV) structure and function would be beneficial in pulmonary arterial hypertension (PAH). Ablation activin/BMP signaling plays a prominent role in pulmonary vascular remodeling. Sotatercept (ActRIIA-Fc) is a recombinant homodimeric fusion protein consisting of the extracellular domain of human ActRIIA linked to immunoglobulin (Ig) G1 Fc domain. Sotatercept is a selective ligand trap for activin/CGDs and does not bind to TGFβ. It is currently being evaluated in phase 2 clinical trials in PAH (PULSAR and SPECTRA).

**Introduction**

Mechanistically, ActRIIA-Fc does this in part by reversing pulmonary vascular remodeling.

**Hypothesis**

ActRIIA-Fc exerts its disease-modifying effects by reducing Smad2/3 overactivation, thereby rebalancing activin/BMP signaling and reversing pulmonary vascular remodeling. Mechanistically, ActRIIA-Fc does this in part by inhibiting activin/CGD-induced proliferation of endothelial and smooth muscle cells.

**Methods**

1. ActRIIA-Fc attenuates elevated levels of activin and Smad2/3 activation in the lungs and RV of SU/Hx/Nx PAH rat.

2. ActRIIA-Fc reduces muscularization of pulmonary arteries, reverses vascular remodeling, decreases pSmad2/3 and PAI-1 expression in the lungs of SU/Hx/Nx PAH rat.

3. ActRIIA-Fc restores endothelial function in SU/Hx/Nx PAH rat lungs.


5. ActRIIA-Fc decreases right ventricular systolic pressure, total pulmonary resistance index, RV hypertrophy and improves RV function in SU/Hx/Nx PAH rat.

6. ActRIIA-Fc improves right ventricular geometry.

**Results**

- **Lung**
  - ActRIIA-Fc attenuates elevated levels of activin and Smad2/3 activation in the lungs and RV of SU/Hx/Nx PAH rat.
  - ActRIIA-Fc reduces muscularization of pulmonary arteries, reverses vascular remodeling, decreases pSmad2/3 and PAI-1 expression in the lungs of SU/Hx/Nx PAH rat.
  - ActRIIA-Fc restores endothelial function in SU/Hx/Nx PAH rat lungs.

- **RV**
  - ActRIIA-Fc improves right ventricular geometry.

**Conclusion**

ActRIIA-Fc reverses pulmonary vascular remodeling, improves pulmonary hemodynamics and improves RV function by reducing Smad2/3 overactivation and rebalancing activin/BMP signaling in pulmonary arteries and RV. These changes could potentially translate to distinct clinical benefit over currently available therapies for PAH.

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