ATS 2021 Welcome

Sotatercept Analog RAP-011 Reduces Right Ventricular Hypertrophy and Alleviates Pulmonary Hypertension in a ZSF1 Rat Model of Heart Failure with Preserved Ejection Fraction

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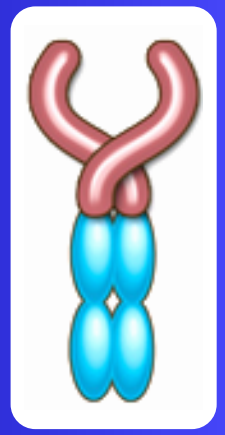
Disclosure to Learners

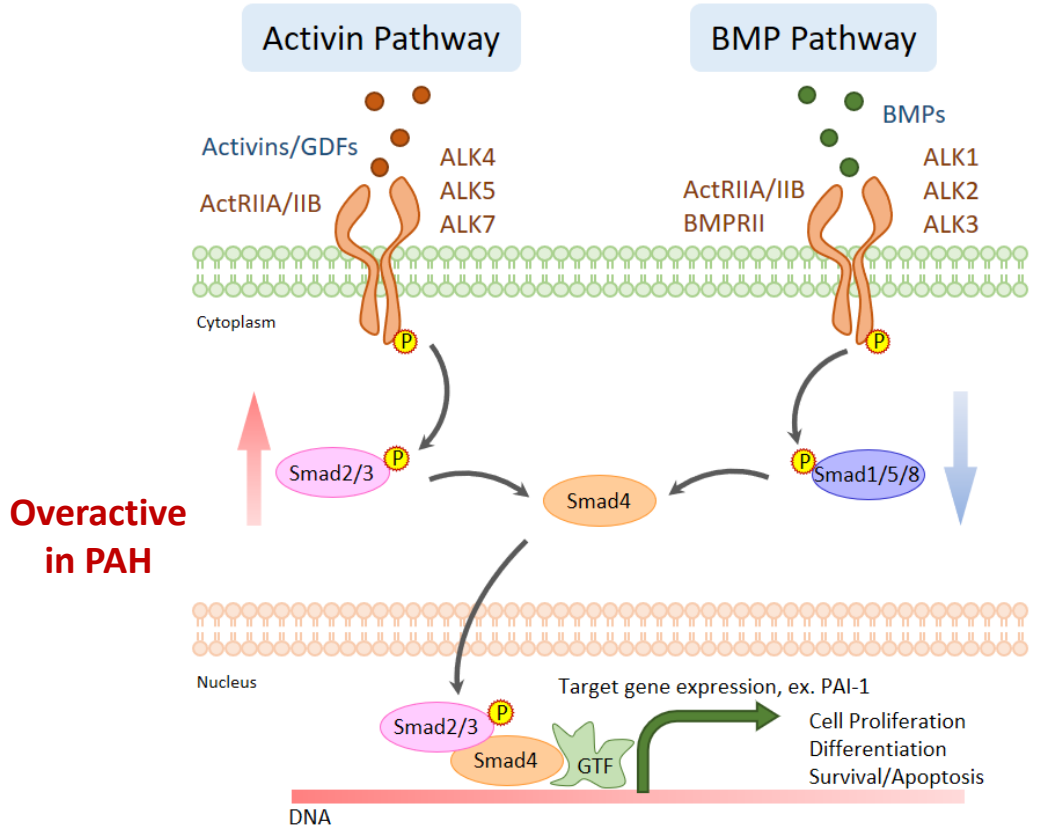
- **Financial relationships with relevant companies within the past 24 months:**
  - *Acceleron Pharma, Senior Scientist*.

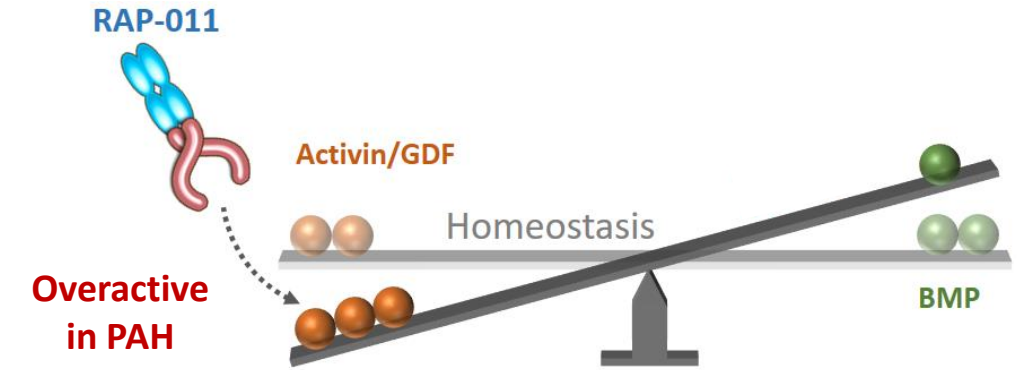
Sotatercept Analog RAP-011 (ActRIIA-Fc)

Activin and GDF ligand trap

- Homodimeric fusion protein
- Extracellular domain of human ActRIIA linked to murine IgG2a Fc domain
- Proposed to act by rebalancing activin and BMP signaling







Yung LM, Yang P, Joshi S et al. Sci Transl Med 2020

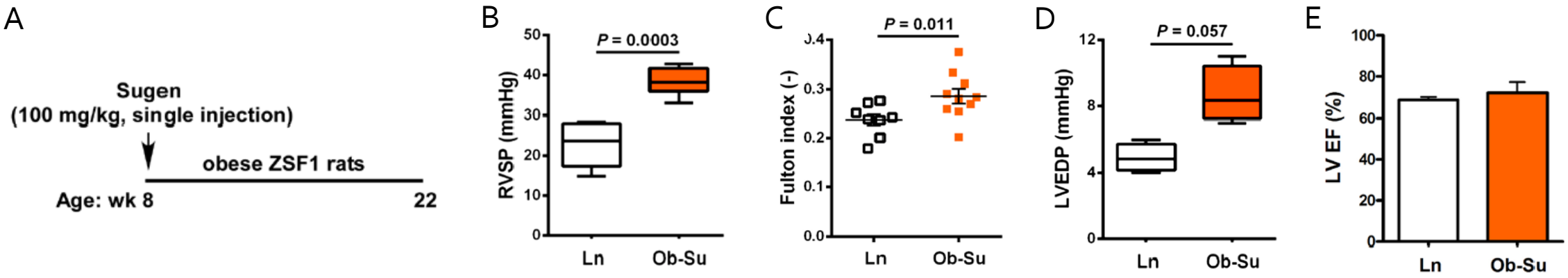
Background

Group 2 Pulmonary Hypertension (PH-HFpEF)

- Group 2 PH is a post-capillary hypertension secondary to **left heart disease.**
- Heart failure with diastolic dysfunction is more commonly referred to as **heart failure with preserved ejection fraction (HFpEF)**, and is the most common cause of Group 2 PH.

Rat Model of PH-HFpEF (Lai et al., Circulation 2016)

- A **"two-hit" model** with multiple features of metabolic syndrome due to **(1)** double leptin receptor defect (obese ZSF1 rat) and **(2)** VEGF receptor blockade with the small-molecule inhibitor SU5416.



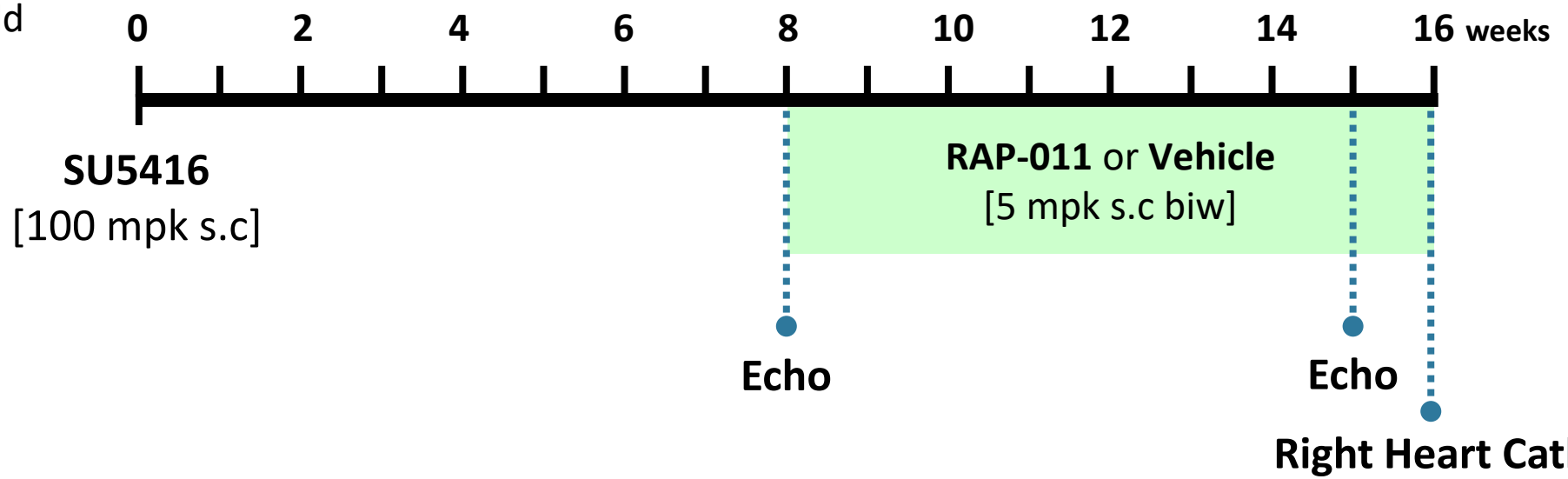
Aim and Approach

Aim

To determine whether treatment with **RAP-011** confers therapeutic benefits in experimental **Group 2 PH** (PH-HFpEF)

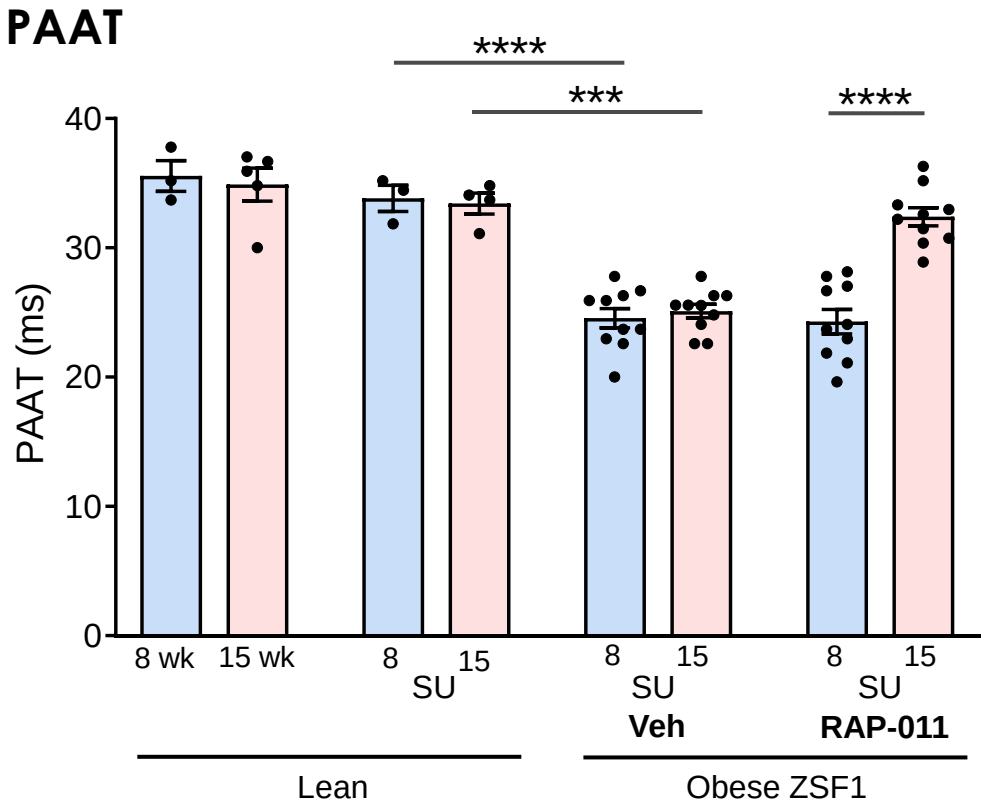
Approach

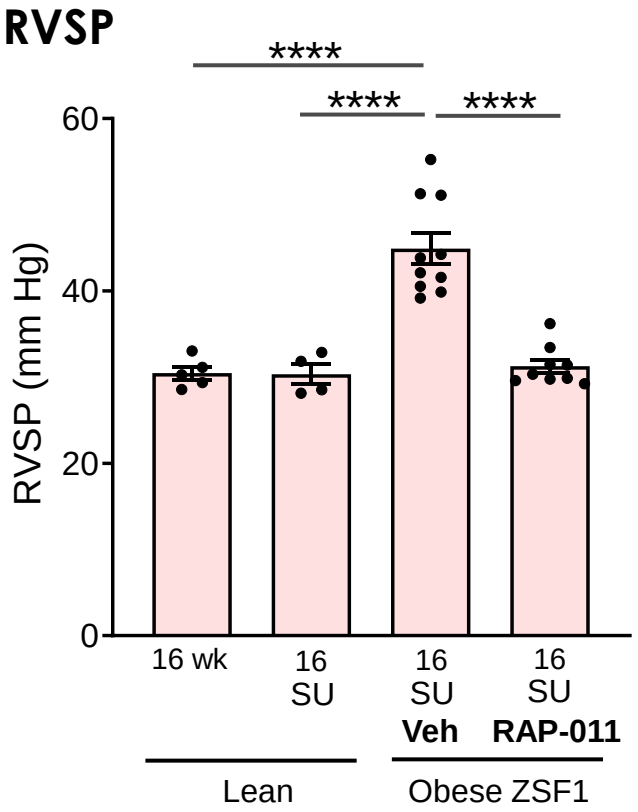
Obese ZSF1 Rat
8 weeks old



Results: RAP-011 Normalized Cardiopulmonary Function

Therapeutic treatment with RAP-011 normalized pulmonary artery acceleration time (**PAAT**) and right ventricular systolic pressure (**RVSP**) in the rat model of Group 2 PH (PH-HFpEF) ($P < 0.0001$).



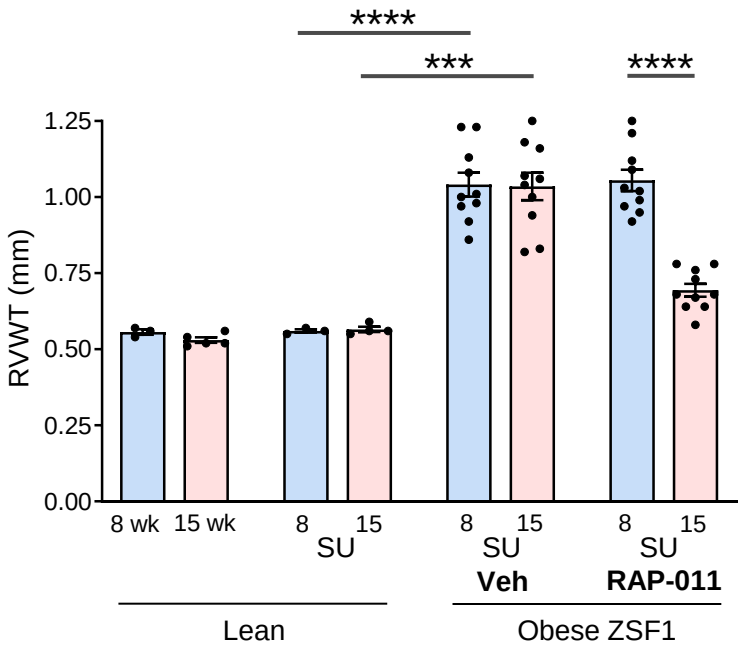


SU, SU5416

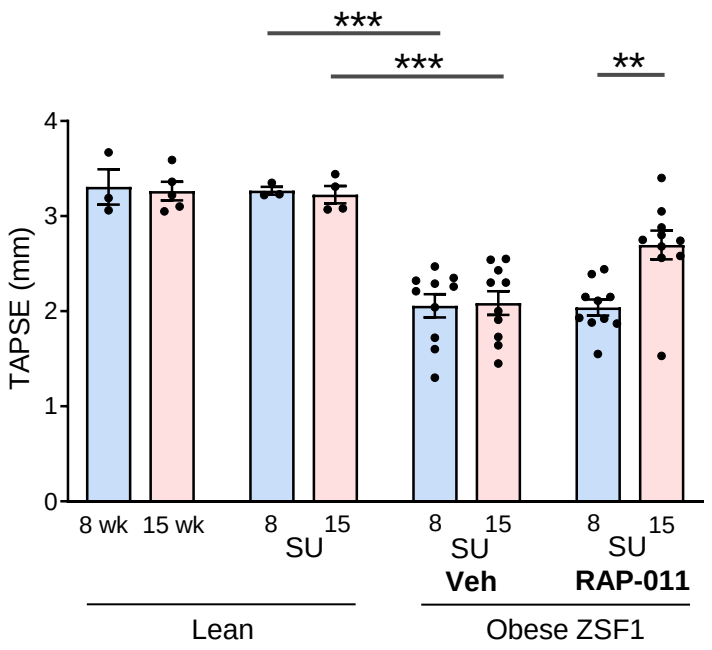
Results: RAP-011 Normalized Right Ventricular Structure and Function

Therapeutic treatment with RAP-011 normalized right ventricle wall thickness (**RVWT**), tricuspid annular plane systolic excursion (**TAPSE**), and the Fulton Index [**RV(LV+S)**] in a rat model of Group 2 PH (PH-HFpEF).

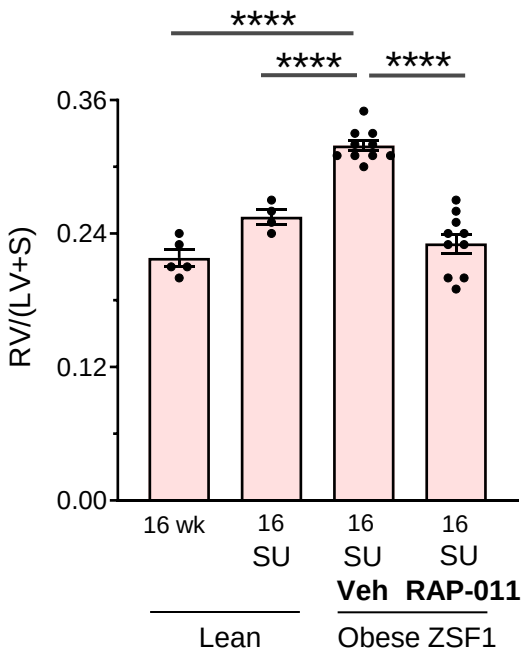
RVWT



TAPSE

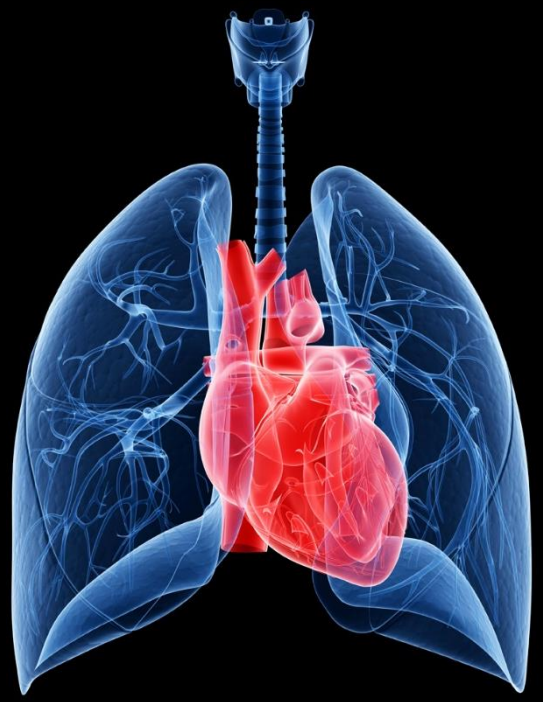


Fulton index



SU, SU5416

Conclusions



- Therapeutic treatment with the rodent sotatercept analog RAP-011 reduces PH and restores right ventricular structure and function in a rat model of Group 2 PH (PH-HFpEF).
- These results implicate activins and GDF ligands in the etiology of experimental PH-HFpEF.
- Our findings support clinical evaluation of sotatercept in patients with Group 2 PH.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sotatercept for the Treatment of Pulmonary Arterial Hypertension

Marc Humbert, M.D., Ph.D., Vallerie McLaughlin, M.D., J. Simon R. Gibbs, M.D., Mardi Gomberg-Maitland, M.D., Marius M. Hoeper, M.D., Ioana R. Preston, M.D., Rogerio Souza, M.D., Ph.D., Aaron Waxman, M.D., Ph.D., Pilar Escribano Subias, M.D., Ph.D., Jeremy Feldman, M.D., Gisela Meyer, M.D., David Montani, M.D., Ph.D., et al., for the PULSAR Trial Investigators*

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