ATS 2021 Welcome

Sotatercept Analog RAP-011 Alleviates Cardiopulmonary Remodeling and Inflammation in a Model of Heritable PAH Arising from *Bmpr2* Haploinsufficiency

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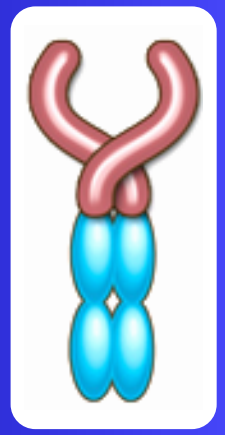
Disclosure to Learners

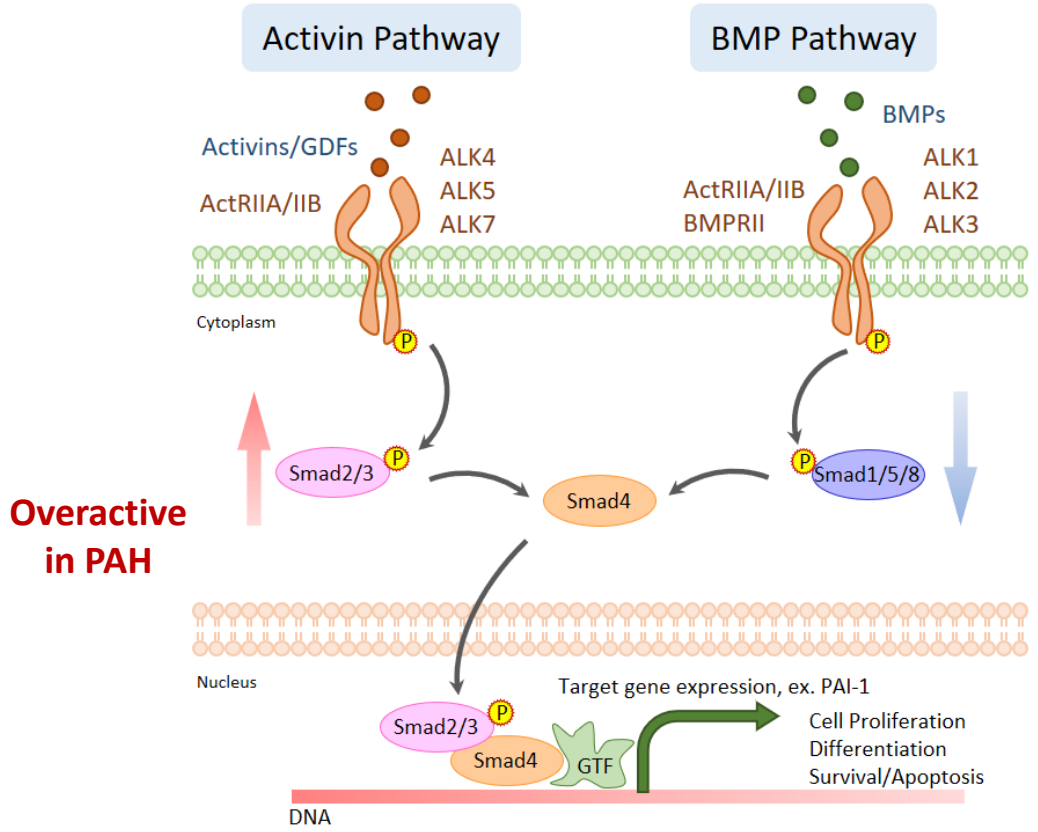
- **Financial relationships with relevant companies within the past 24 months:**
  - *Acceleron Pharma, Senior Scientist*.

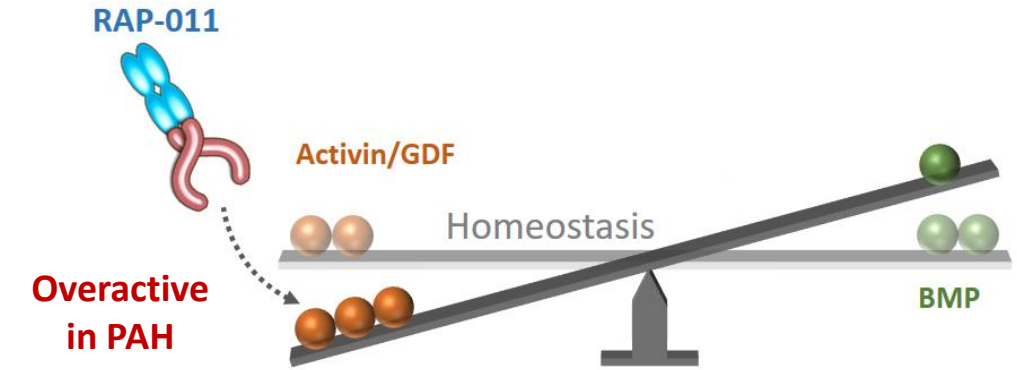
Sotatercept Analog RAP-011 (ActRIIA-Fc)

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

Aim and Approach

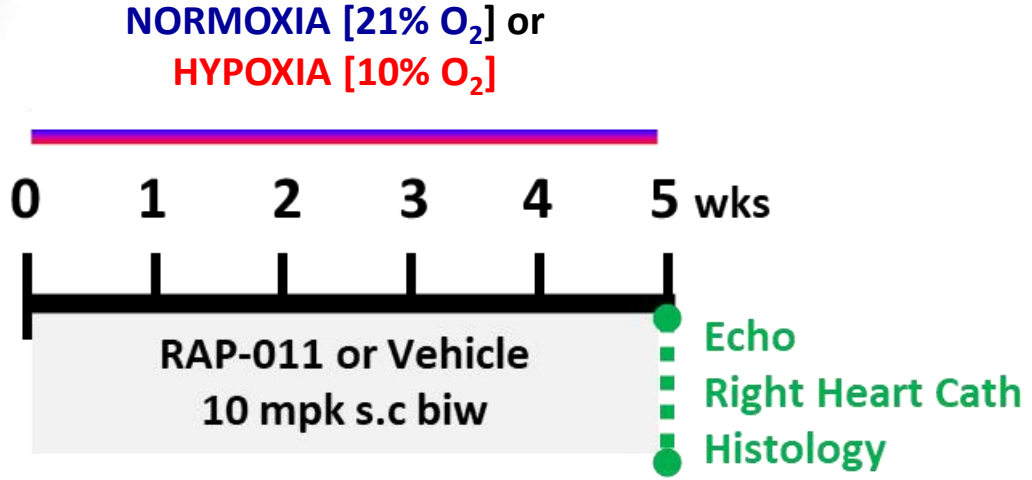
Aim

To determine whether RAP-011 suppresses cardiopulmonary remodeling and macrophage infiltration in a genetic model of heritable PAH arising from *Bmpr2* haploinsufficiency.

Approach

Bmpr2 $^{+/R899X}$

(Age: ~4 months)



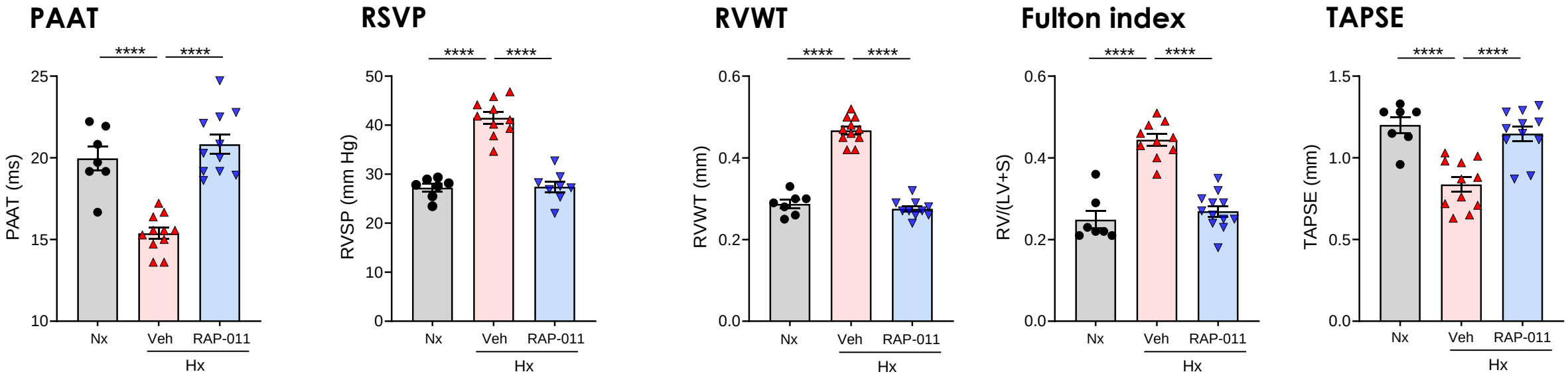
Results: RAP-011 Alleviated Cardiopulmonary Remodeling

PAAT & RVSP

- RAP-011 normalized pulmonary artery acceleration time (**PAAT**) and RV systolic pressure (**RVSP**) in *Bmpr2*$^{+/R899X}$ mice exposed to hypoxia (P < 0.0001)

RVWT, Fulton Index & TAPSE

- RAP-011 normalized RV wall thickness (**RVWT**), Fulton index [**RV/(LV+S)**], and tricuspid annular plane systolic excursion (**TAPSE**) in *Bmpr2*$^{+/R899X}$ mice exposed to hypoxia (P < 0.0001)

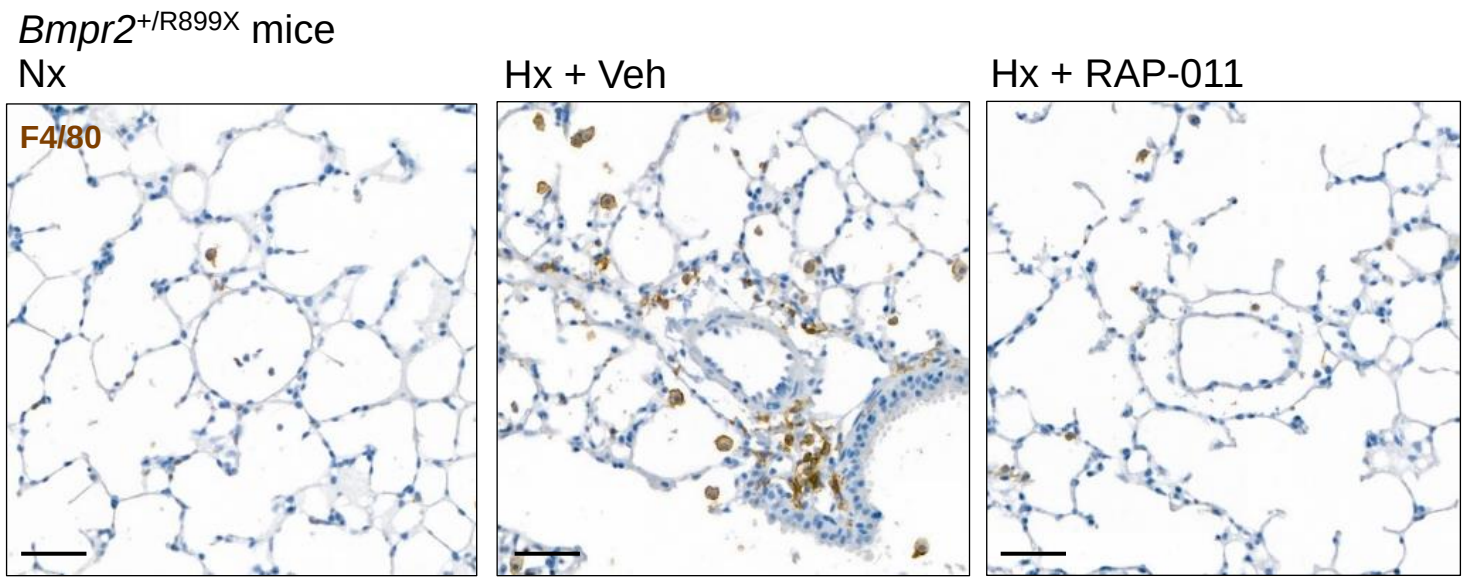


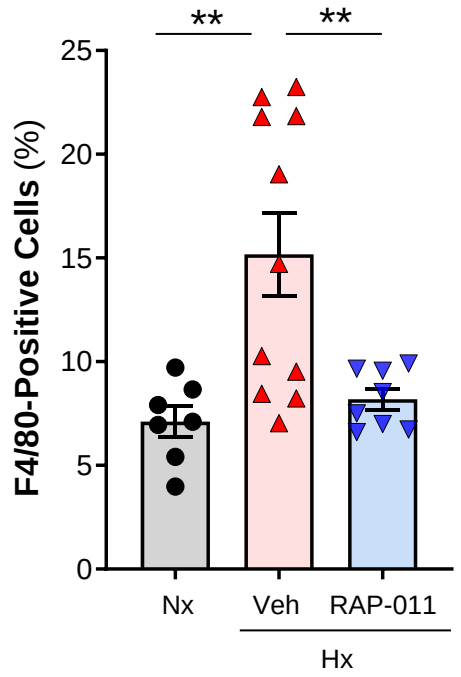
Nx: Normoxia Hx: Hypoxia

Results: RAP-011 Prevented Perivascular Inflammation

Macrophage Infiltration

- RAP-011 prevented macrophage infiltration in the lungs of *Bmpr2*$^{+/R899X}$ mice under hypoxic conditions ($P < 0.01$)





Nx: Normoxia
Hx: Hypoxia

Conclusions

- Treatment with RAP-011 improves cardiopulmonary structure and function and suppresses macrophage infiltration in a mouse model of heritable PAH arising from *Bmpr2* haploinsufficiency.
- Together with our previous studies of experimental PAH, these findings suggest that therapeutic benefits of RAP-011 are robust and observed across multiple experimental PAH models thus supporting evaluation of sotatercept broadly in heritable and idiopathic forms of human PAH.

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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