Precision Inhibition of Class IIA Histone Deacetylases for Pulmonary Arterial Hypertension

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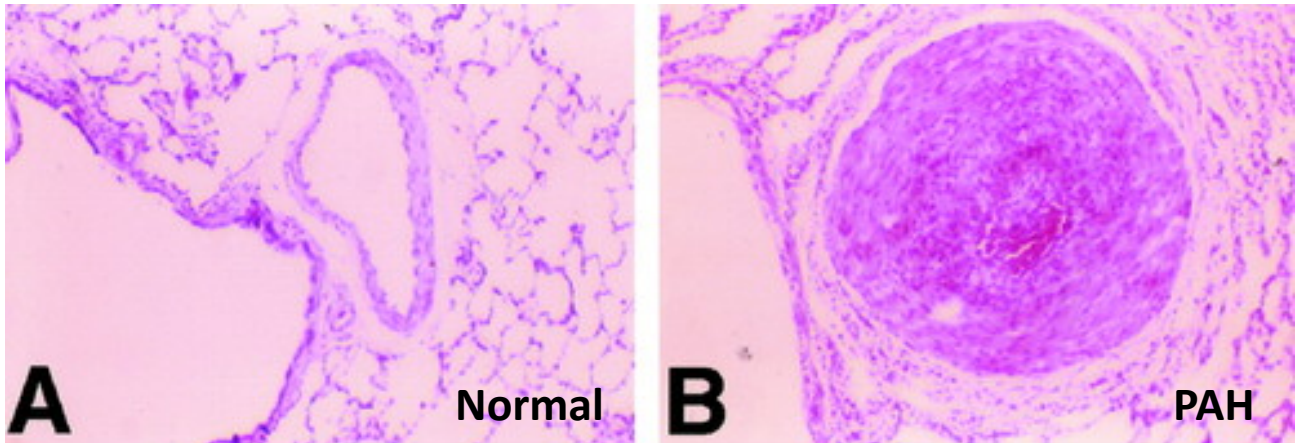
Disclosures:
Co-founder, Verso Therapeutics
Inventor, US 10,213,422, 9,340,787
Consultant, AstraZeneca, TranslateBio

Introduction

- **Purpose:**

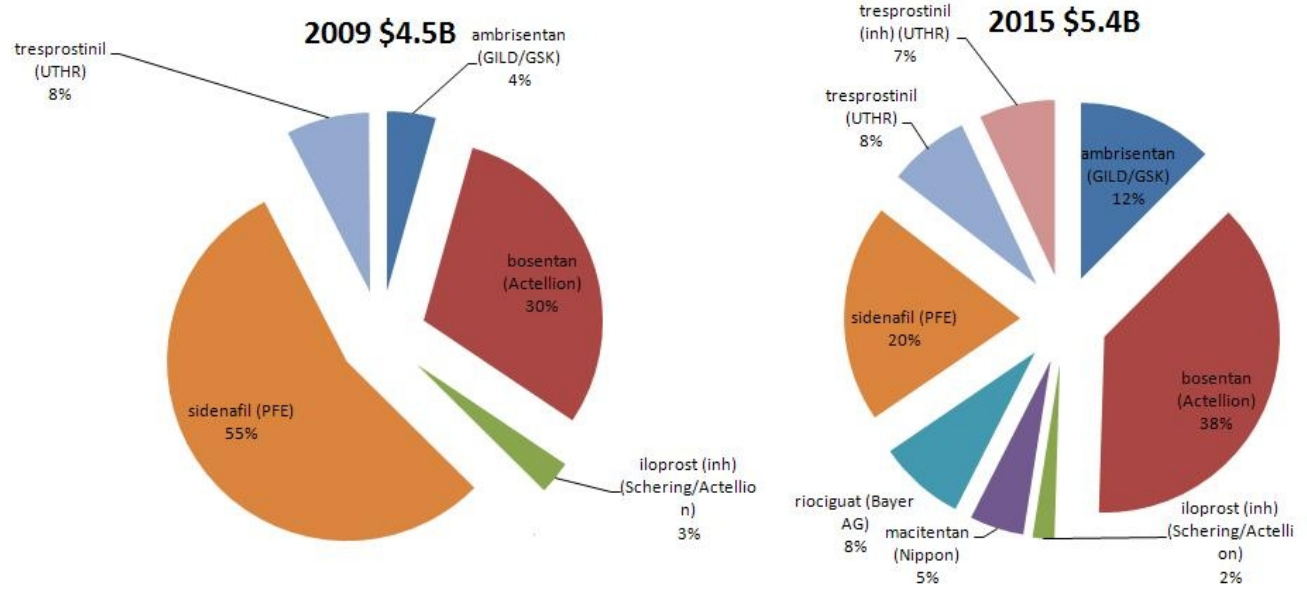
  Development of a novel disease modifying therapeutic agent for **pulmonary arterial hypertension (PAH)** to achieve restoration of normal pulmonary vascular architecture



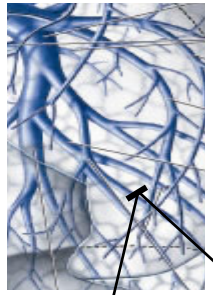
Nishimura, T., *Circ.* 2003

Opportunity

- **Pulmonary Arterial Hypertension (PAH):**
  - Rare, orphan disease
  - ~15,000-30,000 patients in the US
  - ~1000 new cases in the US each year
- **Once diagnosis is confirmed, a highly tenuous clinical course**
  - **Up to ~50% mortality at 3 years after diagnosis**



Opportunity

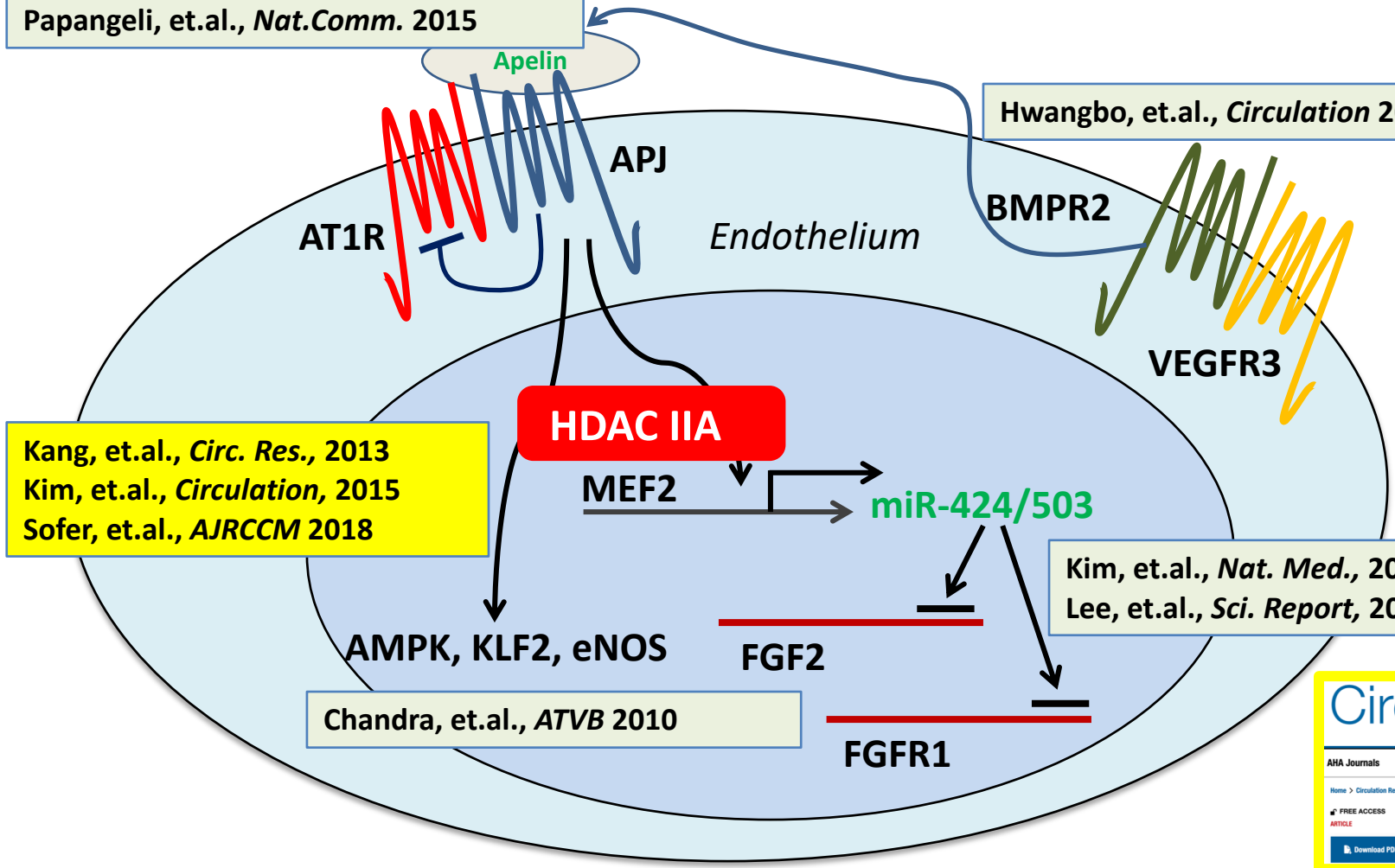


Proposed therapy:

Achieving disease modification through restoration of normal Pulmonary vascular architecture

Chun lab: Vascular pathways that promote can achieve disease modification in PAH

Chun, et.al., *JCI* 2009
Papangeli, et.al., *Nat.Comm.* 2015

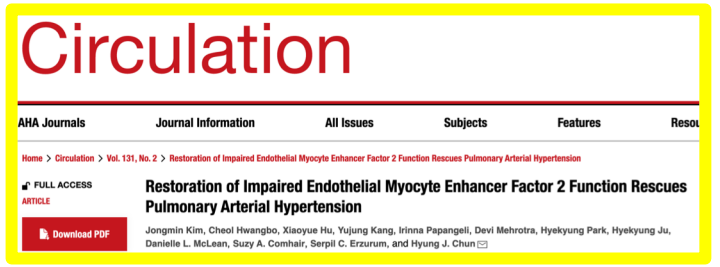


Hwangbo, et.al., *Circulation* 2017

Kang, et.al., *Circ. Res.*, 2013
Kim, et.al., *Circulation*, 2015
Sofer, et.al., *AJRCCM* 2018

Kim, et.al., *Nat. Med.*, 2013
Lee, et.al., *Sci. Report*, 2017

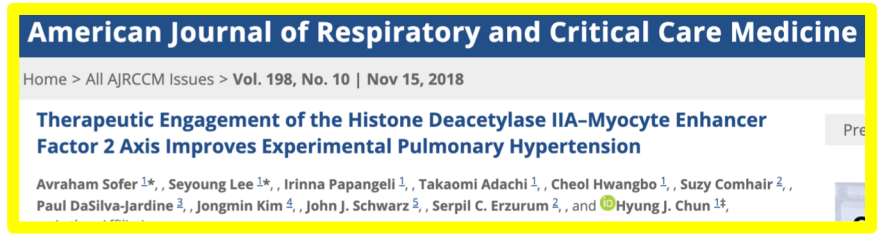
Chandra, et.al., *ATVB* 2010


Circulation

AHA Journals | Journal Information | All Issues | Subjects | Features

Restoration of Impaired Endothelial Myocyte Enhancer Factor 2 Function Rescues Pulmonary Arterial Hypertension

Jongmin Kim, Cheol Hwangbo, Xiaoyue Hu, Yujung Kang, Irinna Papangeli, Devi Mehrotra, Hyekyung Park, Hyekyung Ju, Danielle L. McLean, Suzy A. Comhair, Serpil C. Erzurum, and Hyung J. Chun


American Journal of Respiratory and Critical Care Medicine

Home > All AJRCCM Issues > Vol. 198, No. 10 | Nov 15, 2018

Therapeutic Engagement of the Histone Deacetylase IIA–Myocyte Enhancer Factor 2 Axis Improves Experimental Pulmonary Hypertension

Avraham Sofer, Seyoung Lee, Irinna Papangeli, Takaomi Adachi, Cheol Hwangbo, Suzy Comhair, Paul DaSilva-Jardine, Jongmin Kim, John J. Schwarz, Serpil C. Erzurum, and Hyung J. Chun


Circulation Research

AHA Journals | Journal Information | All Issues | Subjects | Features | Resources &

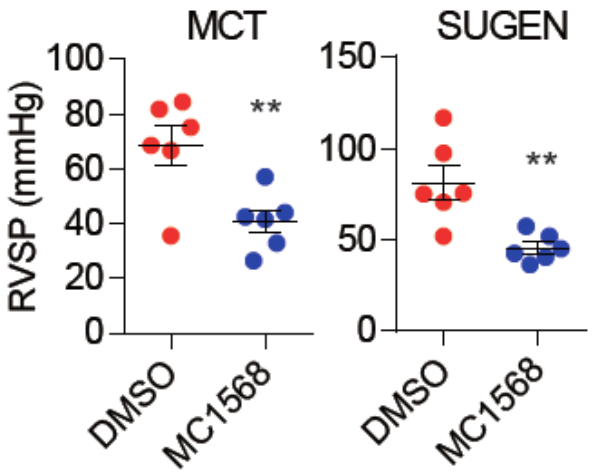
Apelin-APJ Signaling Is a Critical Regulator of Endothelial MEF2 Activation in Cardiovascular Development

Yujung Kang, Jongmin Kim, Joshua P. Anderson, Jingxia Wu, Scott R. Gleim, Ramendra K. Kundu, Danielle L. McLean, Jun-dae Kim, Hyekyung Park, Suk-won Jin, John Hwa, Thomas Quertermous, and Hyung J. Chun

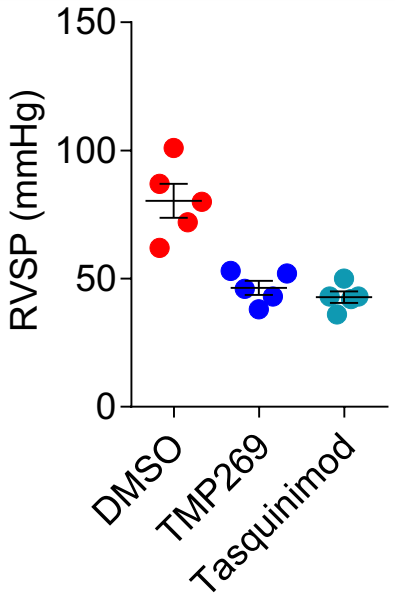
Precision Inhibition of Class IIa Histone Deacetylases

US 10,213,422: Compositions and Methods of Inhibiting Histone Deacetylases (issued 2/26/2019)

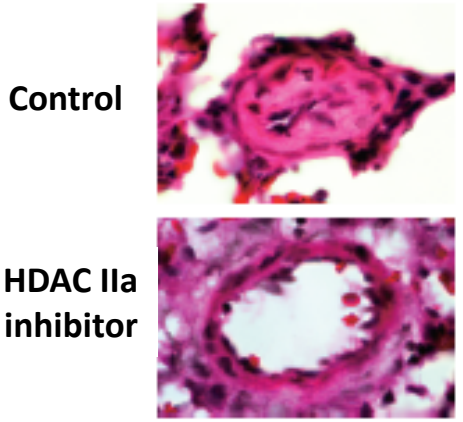
Efficacy in two independent rat severe PAH models



Three independent HDAC IIA inhibitors w/ robust efficacy



Restoration of normal pulmonary vascular architecture



Three distinct HDAC IIa inhibitors can rescue experimental models of PAH

Foundation for Start-up Verso Therapeutics ($1.2m seed funding)

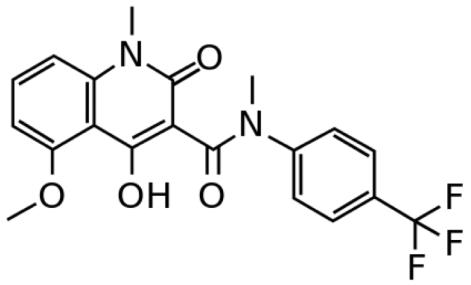
- Target validated by 2 independent CROs

ATLAS VENTURE

NIH National Heart, Lung, and Blood Institute

Vascular Interventions/Innovations and Therapeutic Advances (VITA) Program

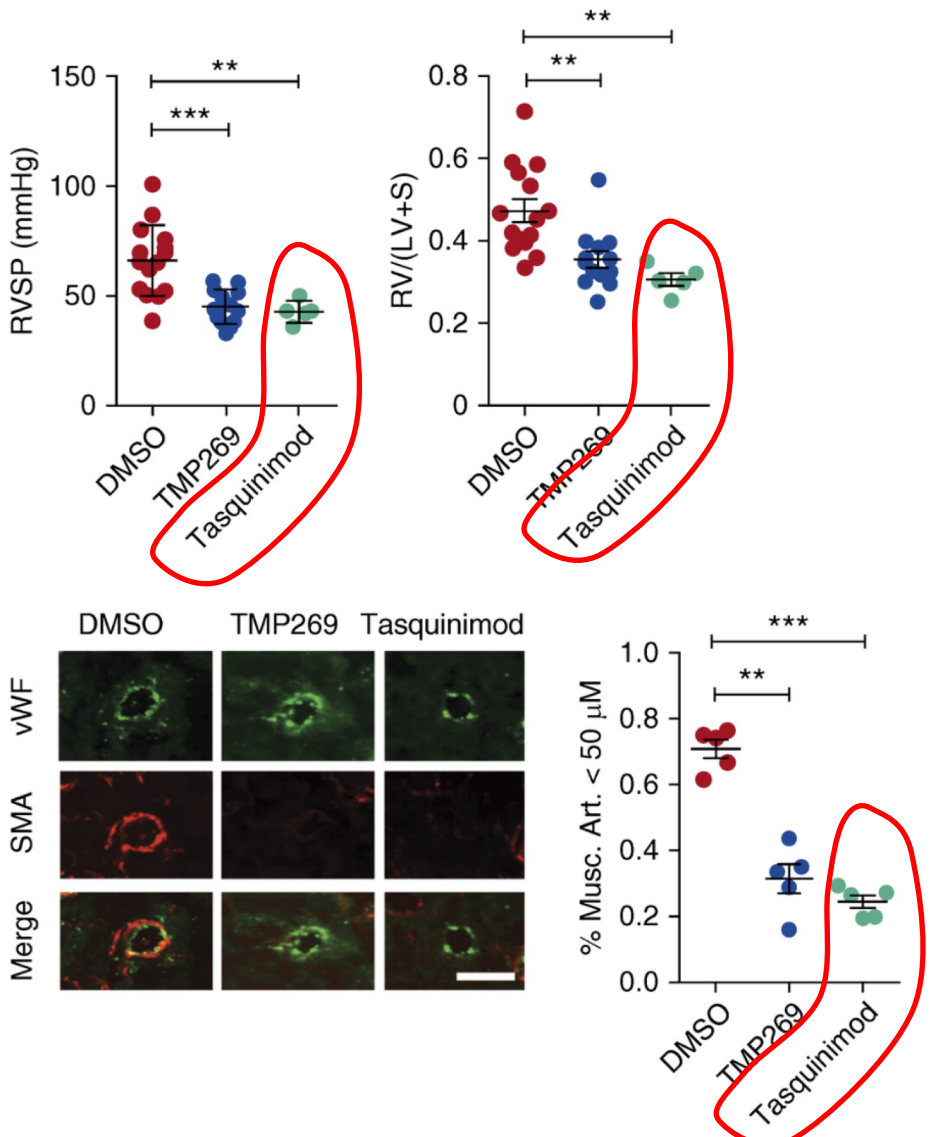
Repurposing Tasquinimod for Treatment of PAH



- A clinical stage small molecule compound
- Selective inhibitor of HDAC 4 (class IIA)
- Found to have robust anti-angiogenic effect
- Phase III Clinical Trial in Prostate Cancer (1245 patients): significant improvement in progression free survival (36% relative risk reduction), but did not demonstrate overall survival
- **No evidence of toxicity (overall good tolerability through more than 650 person-years of exposure to compound in humans,** GI disorder, fatigue, muscle pain

Repurposing Tasquinimod for Treatment of PAH

- Robust efficacy in multiple models of experimental pulmonary hypertension
- Marked reduction in pulmonary vascular muscularization
- Use in pulmonary hypertension covered by issued patent to Yale University
- Ongoing conversations with three biotech/pharma in the PH field regarding repurposing/licensing



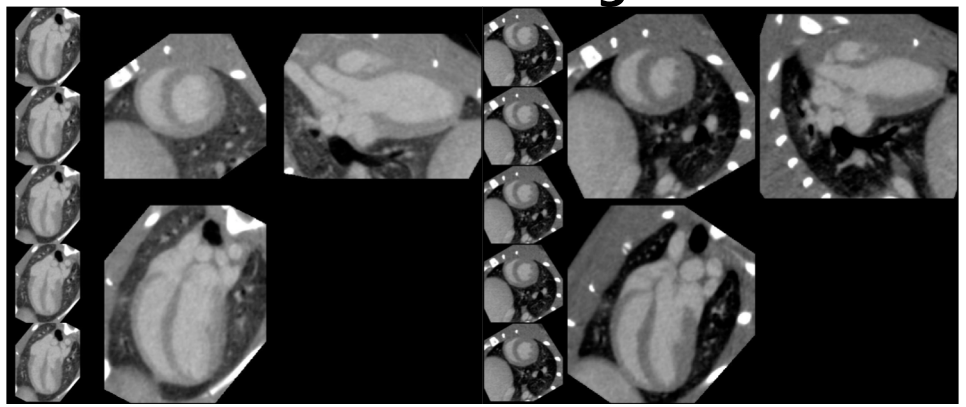
Goals for Blavatnik Fund

- **$100K: Validation studies in severe PH models**
  - **Project 1**: Establish survival benefit of Tasquinimod using a more severe, chronic model of PAH in rats
  - **Project 2**: Demonstrate additive effect of Tasquinimod above and beyond standard of care.

- **$300K: Extended studies to determine cardiac impact of Tasquinimod**
  - **Project 1: Test efficacy of Tasquinimod in a** novel model of severe PAH in rats with right heart failure
  - **Project 2: Test** efficacy of Tasquinimod in improving right heart function in a right heart failure model in pigs

Rat Cardiac CT

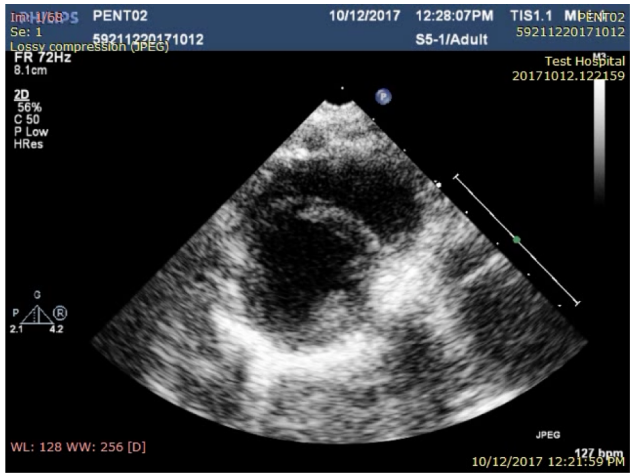
PH with RV failure **Drug intervention**

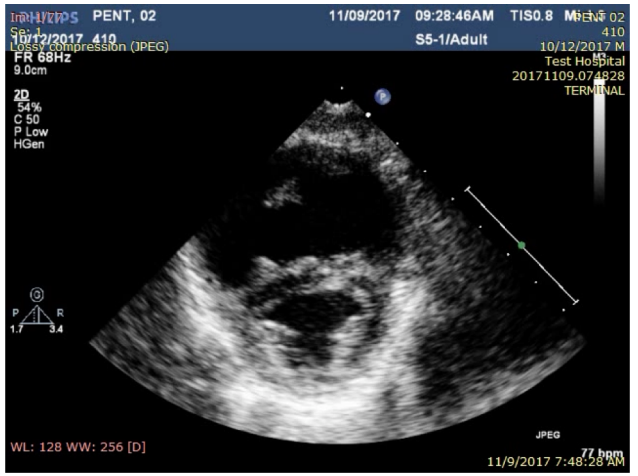


EF: 38% **EF: 56%**

Pig Cardiac Echocardiogram

Baseline **RV failure**





Pathway towards drug approval in PAH

- **Relatively “short” clinical trial periods (all Phase III):**
  - PATENT-1 trial (Ghofrani, et.al., NEJM 2013): **12 weeks**
  - SUPER trial (Galle, et.al., NEJM 2005): **12 weeks**
  - Bosentan trial (Rubin, et.al., NEJM 2002): **12 weeks**

- **Relatively “small” clinical trials**
  - PATENT-1: **443 patients**
  - SUPER: **278 patients**
  - Bosentan trial: **213 patients**

Hyung J. Chun MD FAHA

- *Associate Professor of Medicine and Pathology with Tenure*
- *Internal Medicine and Cardiology Fellowship,* Stanford University
- *MD*, Johns Hopkins School of Medicine
- *AB,* Harvard College
- Co-founder, Verso Therapeutics for novel therapeutics for PAH
- 4 US Patents (2 issued, 2 pending) on novel therapies and devices for cardiovascular disease