Precision Inhibition of Class IIA Histone Deacetylases for Pulmonary Arterial Hypertension

Hyung J. Chun, M.D.
Associate Professor of Medicine and Pathology
Director of Translational Research,
Pulmonary Vascular Disease Program
Co-Director, T32 in Vascular Biology
Section of Cardiovascular Medicine
Yale University School of Medicine

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

Normal pulmonary artery

Remodeled pulmonary artery in PAH

Current therapies:
Inducing vasorelaxation
Not disease modifying!

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
- Kim, et.al., *Circulation*, 2015
- Sofer, et.al., *AJRCCM* 2018

**Key Components:**

- **Apelin**
- **miR-424/503**
- **FGF2**
- **FGFR1**
- **AMPK, KLF2, eNOS**
- **HDAC IIA**
- **MEF2**
- **BMPR2**
- **VEGFR3**

**References:**

- Chun, et.al., *JCI* 2009
- Papangeli, et.al., *Nat.Comm.* 2015
- Kim, et.al., *Circulation*, 2015
- Sofer, et.al., *AJRCCM* 2018

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**Diagram Notes:**

- Chun lab studies vascular pathways that promote disease modification in PAH.
- Key molecules and pathways are highlighted:
  - Apelin
  - miR-424/503
  - FGF2
  - FGFR1
  - AMPK, KLF2, eNOS
  - HDAC IIA
  - MEF2
  - BMPR2
  - VEGFR3

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**Selected Publications:**

- Hwangbo, et.al., *Circulation* 2017
- Papangeli, et.al., *Nat.Comm.* 2015
- Kim, et.al., *Circulation*, 2015
- Sofer, et.al., *AJRCCM* 2018
- Chandra, et.al., *ATVB* 2010
- Kim, et.al., *Nat. Med.*, 2013
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
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
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