

C-terminal Src Kinase Inhibits Endothelial Fibrosis and is Upregulated in Early-Stage Experimental Pulmonary Arterial Hypertension

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DISCLOSURES

Presenter: Bradley M. Wertheim, MD
Change Healthcare: Consulting

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Deerfield: Investigator-initiated research

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Verve Therapeutics: Stock

Patents: Anti-NEDD9 antibody (US Patent ID# PCT/US2019/059890), Plasma NEDD9 ELISA (US Patent ID# PCT/US2020/066886)

Co-author: Bradley A. Maron, MD
Actelion Biosciences: Steering committee
Deerfield: Investigator-initiated research



BACKGROUND AND OBJECTIVE

Background

- Inflammation, endothelial dysfunction, and pulmonary arteriolar fibrosis promote irreversible right heart failure in advanced-stage pulmonary arterial hypertension (asPAH).¹
- Identifying mechanisms that regulate vascular fibrosis in early-stage PAH (esPAH) may have therapeutic importance.

Objective

- We hypothesized that profibrotic molecular pathways differentiate esPAH from asPAH.

MATERIALS AND METHODS

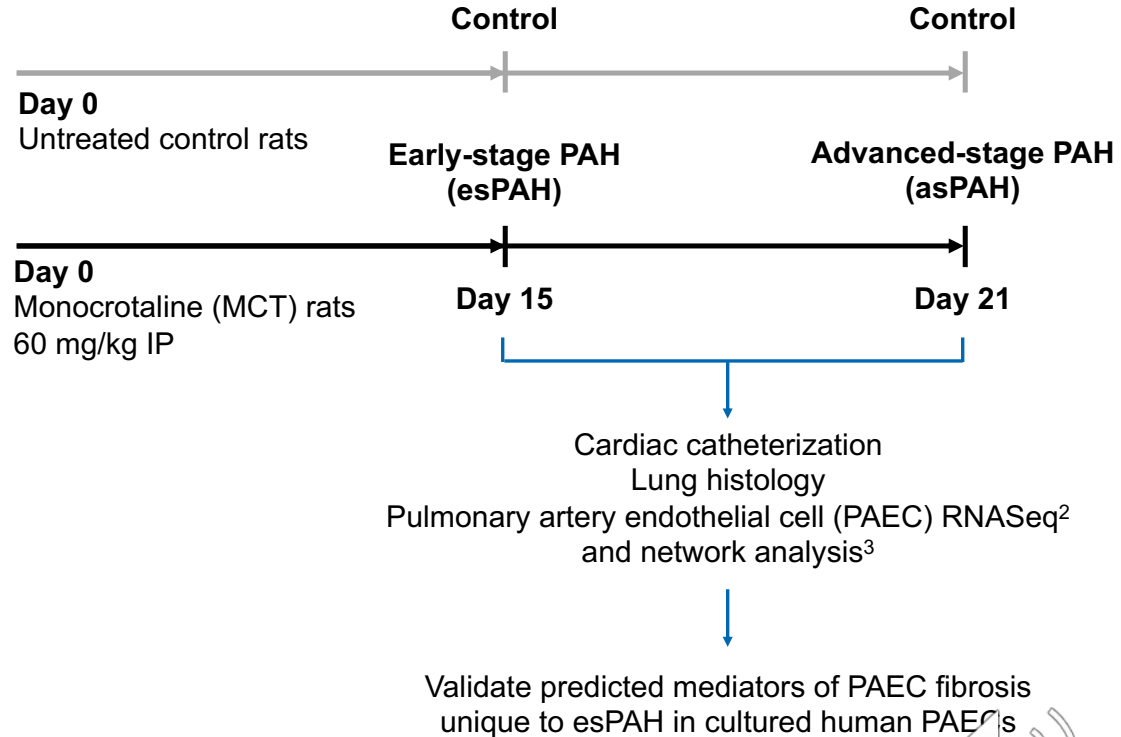
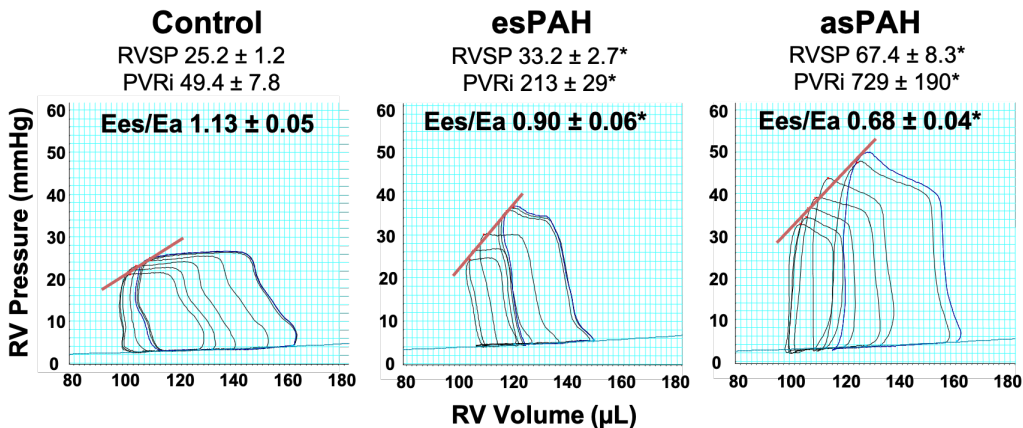
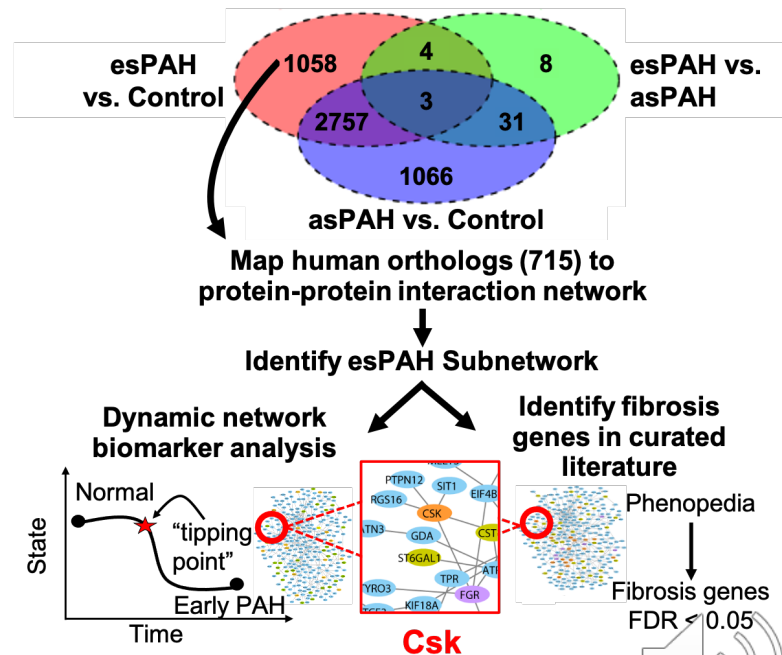


FIG 1. IMPAIRED RIGHT VENTRICLE-PULMONARY ARTERY COUPLING PRECEDES SEVERE PULMONARY HYPERTENSION *IN VIVO*

FIG 2. NETWORK ANALYSIS IDENTIFIES C-TERMINAL SRC KINASE (CSK) AS A FIBROSIS MEDIATOR IN ESPAH PAECs

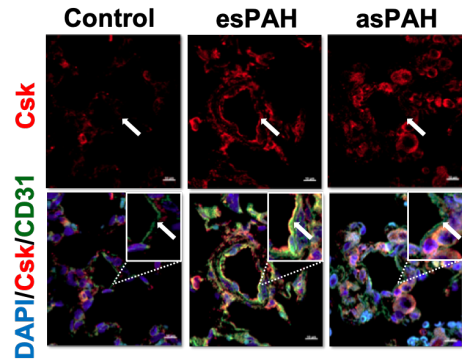


N=6 rats/condition, mean \pm SE. *P<0.05 vs control. Representative images shown.



Abbreviations: **asPAH**, advanced-stage pulmonary arterial hypertension; **Ea**, pulmonary arterial elastance; **Ees**, RV end-systolic elastance; **esPAH**, early-stage pulmonary arterial hypertension; **FDR**, false discovery rate; **PVRI**, indexed pulmonary vascular resistance in $\text{mmHg} \cdot \text{min} \cdot \text{mL}^{-1} \cdot \text{g}^{-1}$; **RVSP**, right ventricle systolic pressure

FIG 3. PULMONARY ENDOTHELIAL Csk EXPRESSION IS INCREASED IN esPAH AND CORRELATES WITH VASCULAR COLLAGEN QUANTITY



Arrow = PAECs. N =4 rats/condition, mean \pm SE. *P<0.05 vs control. Scale bar = 10 μ m.

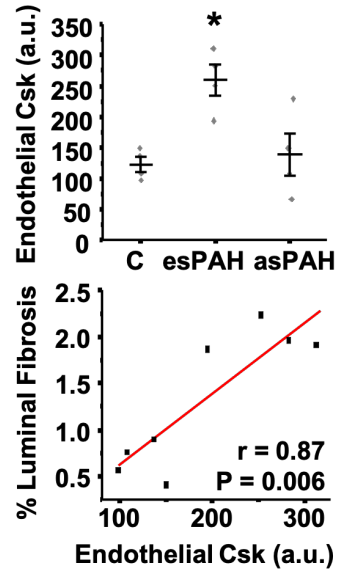
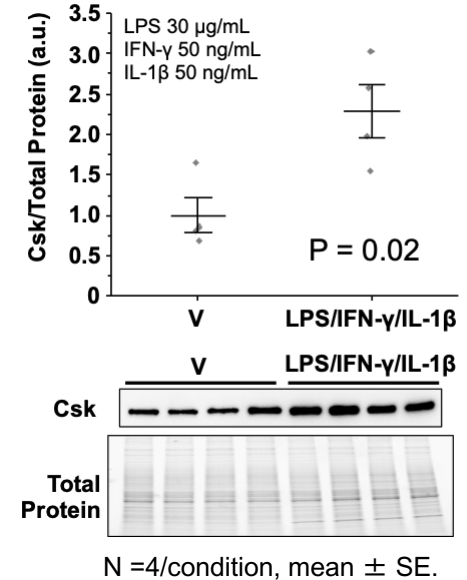
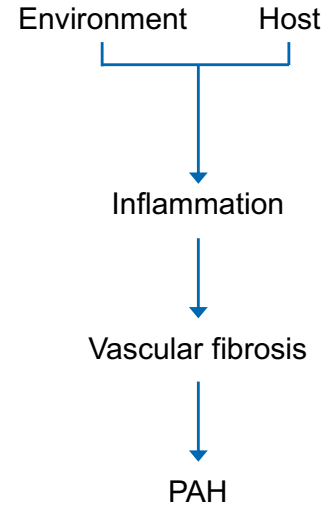


FIG 4. INFLAMMATION INDUCES Csk ACCUMULATION IN HUMAN PAECs



N =4/condition, mean \pm SE.

Abbreviations: **asPAH**, advanced-stage pulmonary arterial hypertension; **a.u.**, arbitrary units; **C**, control; **esPAH**, early-stage pulmonary arterial hypertension; **IFN- γ** , interferon gamma; **IL-1 β** , interleukin-1-beta; **LPS**, lipopolysaccharide; **M.F.I.**, mean fluorescence intensity.



FIG 5. INFLAMMATION INCREASES HUMAN PAEC HYDROXYPROLINE, AN INDICATOR OF COLLAGEN ABUNDANCE

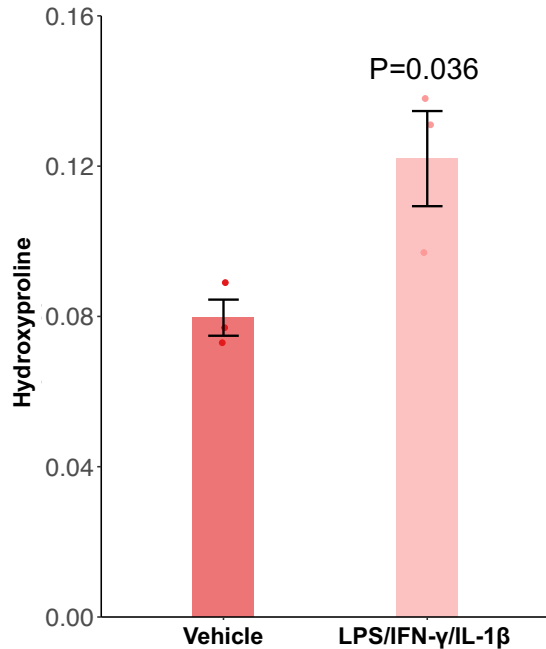
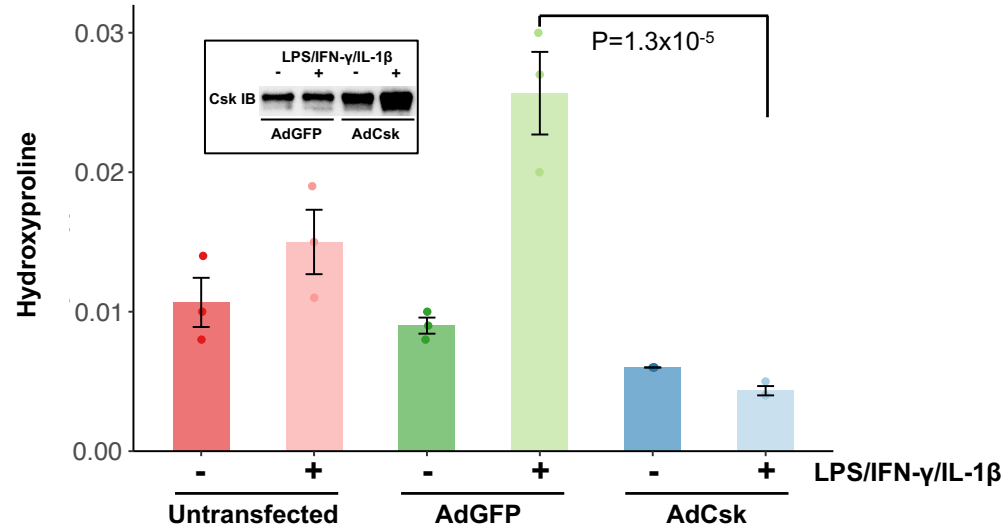


FIG 6. CSK OVEREXPRESSION ATTENUATES INFLAMMATION-MEDIATED HYDROXYPROLINE ACCUMULATION IN HUMAN PAECs

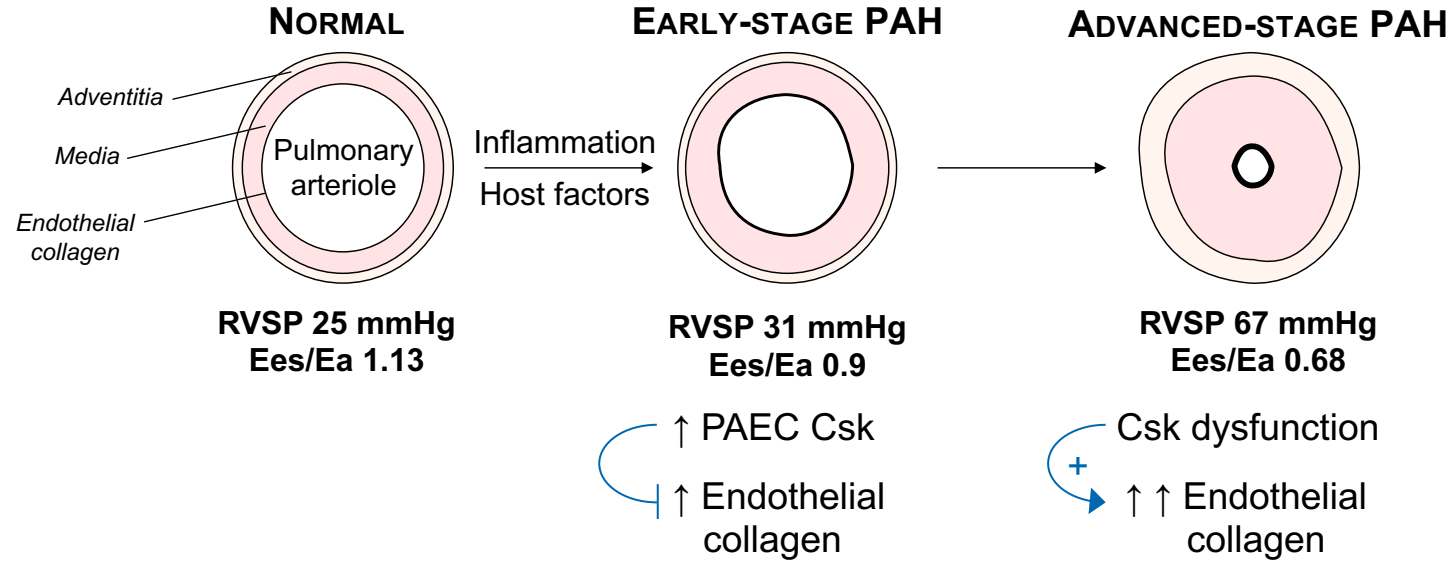


Mean +/- SE
 N = 3/condition
 Micrograms hydroxyproline/100,000 live PAECs

Abbreviations: **AdGFP**, adenovirus expressing GFP; **AdCsk**, adenovirus expressing Csk, **IB**, immunoblot; **IFN- γ** , interferon gamma; **IL-1 β** , interleukin-1-beta; **LPS**, lipopolysaccharide.



SUMMARY AND CONCLUSIONS



Csk regulates PAEC fibrosis in the setting of inflammation.

If impaired Csk activity is validated in human esPAH, this may have therapeutic implications for the prevention of fibrotic vascular remodeling and PAH progression.



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