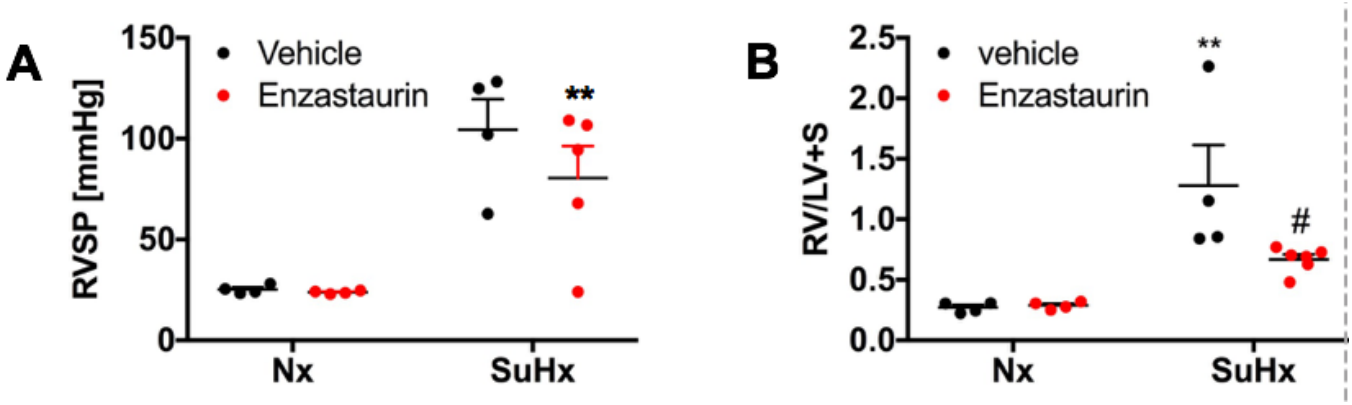
Docket #: S17-202

Enzastaurin and FHIT-elevating agents for the treatment of Pulmonary Hypertension

Stanford researchers have developed a method of reducing pulmonary hypertension (PH) in mammals by targeting FHIT (Fragile Histidine Triad), a gene not previously linked to PH but consistently reduced in blood of patients with pulmonary arterial hypertension (PAH). The second aspect of this invention is directed to the therapeutic use of the pharmaceutical Enzastaurin to increase FHIT levels and reduce PH in mammals. In certain embodiments, the method comprises administering Enzastaurin to a mammal having pulmonary hypertension with severe occlusive pulmonary vasculopathy at a dosage sufficient to reduce the pressure in the pulmonary arteries and the occlusive vasculopathy, improve right ventricular hypertrophy and reduce cardiac fibrosis.



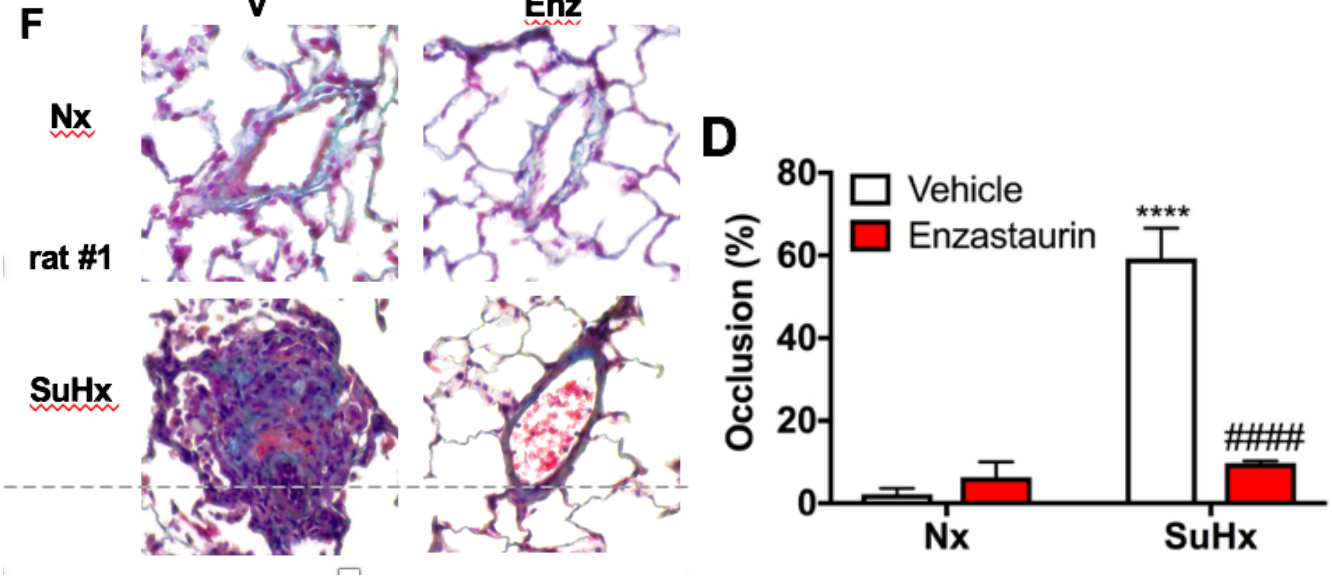


Figure description:
(A) Enzastaurin reduces pulmonary hypertension as assessed by reduced right ventricular systolic pressure (RVSP) as well as **(B)** reduced right ventricular hypertrophy (RV/LV+S). **(F)** Enzastaurin has anti-remodeling effects and opens previously occluded vessels **(D)**

Stage of Research

- Reduced FHIT lead to endothelial dysfunction levels which can be rescued by using Enzastaurin
- Mice with a lack of a novel signaling compound, FHIT, have more severe PH
- Treatment of rats with Enzastaurin after induction of PH using Sugen/hypoxia/Normoxia to reduce pulmonary hypertension

Applications

- Reduce established hypertension or emphysema in mammals
- Use Enzastaurin as a preventative measure for mammals with risk factors (i.e. positive mutation status for BMPR2 or FHIT, or BMPR2 or FHIT downregulation)

Advantages

- No current interventions or therapeutic strategies are available to cure pulmonary hypertension or reverse the obliterative vasculopathy so

characteristic of PAH. Thereby a drug that has anti-remodeling properties could be disease modifying.

Publications

- **Fragile Histidine Triad (FHIT), a Novel Modifier Gene in Pulmonary Arterial Hypertension**, *In revision*. Svenja Dannewitz Prosseda, Xuefei Tian, Kazuya Kuramoto, Mario Boehm, Deepti Sudheendra, Kazuya Miyagawa, Fan Zhang, David Solow-Cordero, Joshua C. Saldivar, Eric D. Austin, James E. Loyd, Lisa Wheeler, Adam Andruska, Michele Donato, Lingli Wang, Kay Huebner, Ross J. Metzger, Purvesh Khatri, **Edda Spiekerkoetter**.

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