UC San Diego Health

UC San Diego Researchers Reverse Pulmonary Arterial Hypertension in Mouse Models

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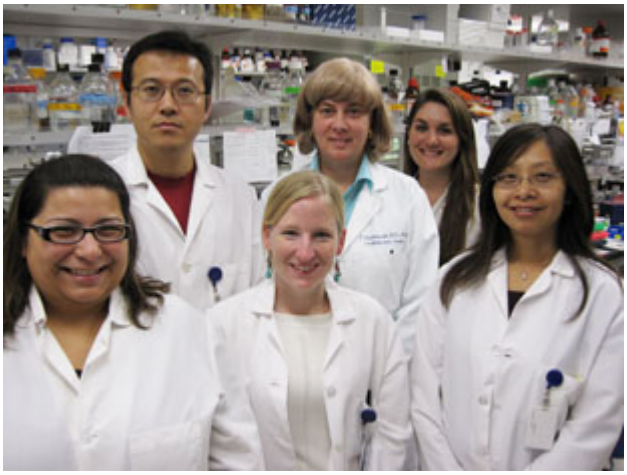
Researchers at the University of California, San Diego, have identified a key protein that promotes the development of pulmonary arterial hypertension in humans and mice. This groundbreaking discovery has implications for future drug therapies that may extend the life of patients with pulmonary arterial hypertension and prevent the need for lung transplantation, currently the only cure for this debilitating disease.

Patricia Thistlethwaite, MD, PhD, Professor of Surgery and Cardiothoracic Surgeon in UCSD's Department of Surgery

In a paper to be published online in *Nature Medicine* on October 25, Patricia Thistlethwaite, MD, PhD, Professor of Surgery and cardiothoracic surgeon in UCSD's Department of Surgery, and colleagues describe the genetic pathway by which vascular smooth muscle cells associated with pulmonary arterial hypertension are switched on to proliferate by a receptor protein called Notch-

3. With this finding, the researchers were able to block and reverse the pathway of disease in mice.

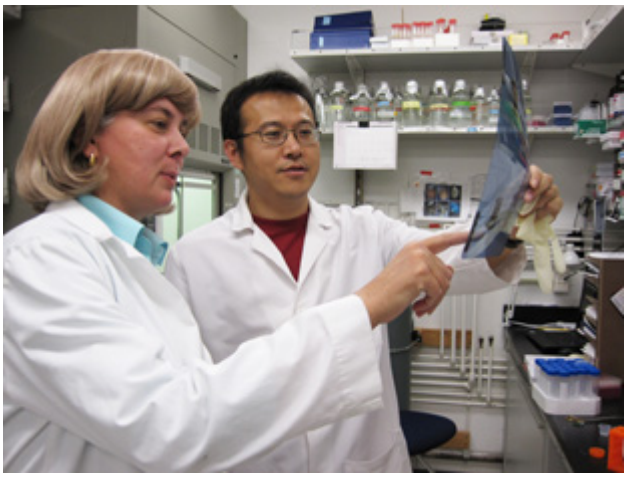
"The UCSD team found that pulmonary hypertension is characterized by overexpression of Notch-3 and that the severity of the disease correlates with the amount of this protein in the lung," said Thistelthwaite. "We showed that a mouse model lacking this protein does not develop pulmonary hypertension, and in addition, that the disease can be effectively treated with an enzyme called γ-secretase inhibitor, which blocks Notch-3 activation."



Thistlethwaite's research team at UC San Diego identified a protein that promotes pulmonary arterial hypertension

In Thistlethwaite's laboratory, mice with pulmonary arterial hypertension that were treated with the γ-secretase inhibitor showed reversal of the disease. Forms of this drug are currently in use in Phase 1 trials for the treatment of Alzheimer's disease.

Pulmonary arterial hypertension is a form of high blood pressure in the lung's arteries. The disease begins when tiny arteries in the lungs become narrow, blocked or destroyed causing resistance to blood to flow. As the pressure builds, the heart's lower right chamber becomes overworked and weakens, leading to ventricular failure. The condition afflicts more than 100,000 patients in the United States, causing 20,000 deaths per year.



Patricia Thistlethwaite, MD, PhD, and first author Xiaodong Li, PhD

"Pulmonary arterial hypertension is more common in the human population than is currently realized, and unfortunately, is often fatal," said co-author Stuart Jamieson, MB, FRCS, Distinguished Professor of Surgery and Chair of Cardiothoracic Surgery at UC San Diego Medical Center. "Current drugs to treat pulmonary arterial hypertension focus on dilating the arterial vessels but do not address the eventual thickening of the artery walls. Fortunately, by identifying this drug target it seems we are now on the right path to developing an intervention that prevents abnormal cell proliferation."

Additional contributors to the paper from UC San Diego Health Sciences are first author Xiaodong Li, Xiaoxue Zhang, Robin Leathers, Ayako Makino, Chengqun Huang, Pouria Parsa, Jesus Macias, Jason X-J Yuan, Stuart W. Jamieson, and Patricia A. Thistlethwaite. The research was supported by a grant from the National Institutes of Health.

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