Fusion protein holds promise for treating pulmonary arterial hypertension

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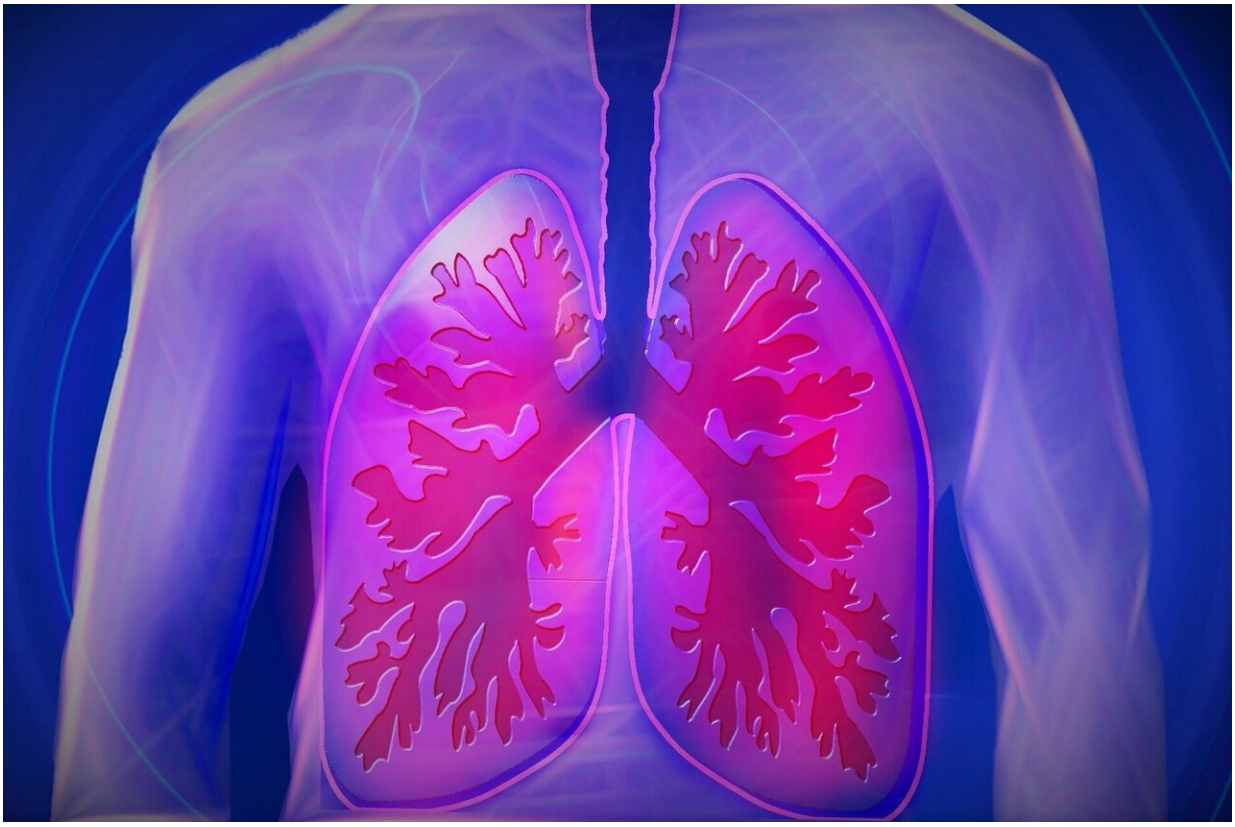

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Pulmonary arterial hypertension (PAH) is an insidious disease. Symptoms may begin slowly, and even before they appear, extensive damage has caused the obstruction of small arteries leading to increased

blood pressure in the lungs. By the time symptoms—most notably, shortness of breath—become severe enough for someone with PAH to seek care and obtain a definitive diagnosis, the patient's chances of survival at five years are slightly better than 50 percent on currently available treatments.

Paul B. Yu, MD, Ph.D., a cardiovascular medicine specialist at Brigham and Women's Hospital, has been studying PAH for more than 15 years to better understand the fundamental process in which blood vessels in the lungs are lost to the disease. In a paper published in *Science Translational Medicine*, members of Yu's lab and co-authors at Brigham and Women's Hospital and Acceleron Pharma illuminate the underlying biological pathways that may lead to vessel destruction. Their results provide a biological explanation for why proteins called activins and growth and differentiation factors (GDFs) might contribute to pulmonary vascular disease, and provide an explanation of how the activin/GDF-blocking drug sotatercept, currently in clinical trials, may help treat patients with pulmonary arterial hypertension.

"We were delighted to contribute to the pre-clinical validation of sotatercept, and improve our understanding of the signaling molecules that drive pulmonary arterial hypertension." said Yu. "We hope these advances will lead to new treatment options for this incredibly vexing disease."

Currently, PAH is treated with vasodilators to widen lung blood vessels and increase blood flow. Yu and his team have uncovered biological insights that may help to affect the underlying disease process more directly. Previous studies have shown that there are heritable forms of PAH—mutations in certain genes may impact the development, maturation and remodeling of arterial circulation. These genes are involved in two pathways: bone morphogenetic protein (BMP) signaling and transforming growth factor-β (TGFβ) signaling. It was thought that

BMP was protective and higher levels TGF-β were destructive, but the specific mechanisms involved remain unclear. There were also indications that two other closely related ligands, known as GDFs and activins, were involved. These play important roles in reproductive biology, but what were they doing in the context of PAH?

In their *Science Translational Medicine* paper, Yu and colleagues present data from both human and rodent models to cohesively connect these various protein players. The team found increased levels of activin A, GDF8, and to a lesser degree GDF11 in lung lesions from patients with PAH and rodent models of the disease. The team then tested what would happen when they added a "ligand trap"—a fusion protein that captures GDF and activin, blocking their activity. The team found that the fusion protein was more effective than vasodilators at treating PAH and preventing blood vessel remodeling, by restoring a more normal balance between proliferation and cell death of the cells that make up blood vessel walls. When mouse models were treated in the later stages of severe disease, the treatment increased the number of open lung vessels despite previous damage, in contrast to vasodilators which did not have this effect.

"It was unexpected to find such a prominent role for GDF and activin in PAH, but if they are helping to drive pulmonary vascular disease, it may help explain why a therapy that targets these ligands may be effective against PAH. Our research demonstrates that this central genetic pathway of PAH is tractable and can be exploited as a drug target," said co-lead author Peiran (Brian) Yang, Ph.D., a senior member of Yu's group at Brigham.

The ligand trap is currently under investigation as a treatment for PAH. The human version of this trap, known as sotatercept, was recently granted both Orphan Drug and Breakthrough Therapy designation by the United States Food and Drug Administration (FDA).

Acceleron Pharma, the manufacturers of sotatercept, recently announced the results of PULSAR, a phase 2 trial in patients with PAH. Patients treated with sotatercept experienced a statistically significant reduction in pulmonary vascular resistance (PVR), the trial's primary endpoint, compared to placebo. A second Phase 2 trial, SPECTRA, sponsored by Acceleron and led in part by Brigham investigators, will continue assessing the efficacy and safety of sotatercept in patients with PAH. The SPECTRA trial is ongoing and currently recruiting patients.

"There are still many unanswered questions, but with the clinically relevant degree of change seen in the clinical trial, coupled with our deeper understanding of the biology of the disease, the story of what drives this disease and how we may be able use that knowledge to treat are coming together in a way that is coherent," said Yu.

More information: Lai-Ming Yung et al, ACTRIIA-Fc rebalances activin/GDF versus BMP signaling in pulmonary hypertension, *Science Translational Medicine* (2020). DOI: 10.1126/scitranslmed.aaz5660

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