Following computational predictions, scientists demonstrate that cancer drug counters pulmonary fibrosis

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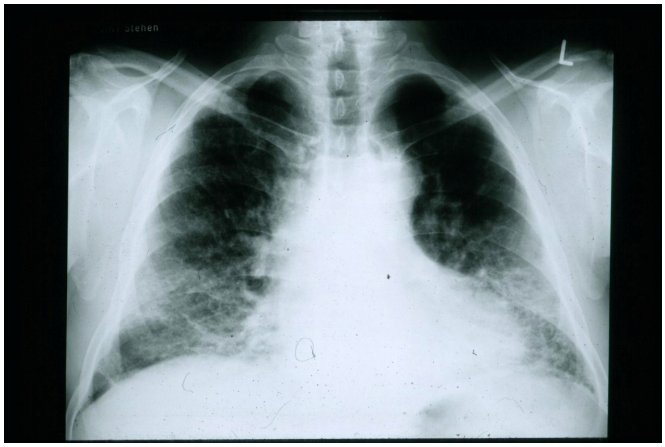

A chest radiograph of a patient with Idiopathic Pulmonary Fibrosis (IPF). Credit: Wikipedia/CC BY-SA 3.0

An experimental cancer drug with a favorable safety profile shows promise as a treatment for Idiopathic Pulmonary Fibrosis (IPF), according to a study published on August 23, 2022, in the *American Journal of Respiratory and Critical Care Medicine* by Yale School of Medicine, Mount Sinai, and National Jewish researchers. The drug, saracatinib, works as well or better than current FDA-approved treatments for IPF at countering fibrosis in preclinical models, including human lung cells in culture and fibrotic lung slices obtained from IPF patients who received transplants.

"To our knowledge, this is the first study that has used a computational approach to link a drug developed for another indications to IPF, and then validate the efficacy of the drug in multiple systems using in vitro, in vivo, and ex vivo models, resulting in a human clinical trial in IPF patients," said the study's corresponding author, Farida Ahangari, MD, assistant professor of medicine (Pulmonary, Critical Care and Sleep Medicine) at Yale School of Medicine.

In IPF, a progressive and currently incurable lung disease, scar tissue builds up around the lungs' air sacs, impeding the exchange of oxygen and carbon dioxide, making it difficult to breathe. Approximately 50,000 new cases of IPF are diagnosed in the U.S. each year, and patients survive a median of three to five years following diagnosis. Two FDA-approved drugs for IPF, nintedanib and pirfenidone, slow disease progression, but they can have side effects and do not ameliorate IPF symptoms or cure the disease.

"There is an urgent need for better drugs, and more effective therapies, that safely modify the course of IPF and restore quality of life to patients," said Ahangari.

The researchers identified saracatinib as a potential IPF drug by applying a novel strategy to determine whether previously developed drugs may have antifibrotic effects. They exposed human cell lines to 32 different drugs, determined the genes whose expression changed in response to the drugs, and compared those gene-expression signatures to 700 different diseases. They found that saracatinib was predicted to reverse the disease signature of IPF.

Ahangari and colleagues tested the effects of saracatinib on lung fibroblasts, the cells that accumulate in lung scarring. Saracatinib reduced the fibrotic response in cells obtained from a normal lung, as well as from patients with pulmonary fibrosis. In two preclinical models of pulmonary fibrosis, saracatinib reduced collagen as well as other measures of lung scarring as much or more than nintedanib and pirfenidone.

The researchers also used a novel approach that

allows testing drugs on lung slices. After demonstrating that saracatinib reversed fibrosis in preclinical models and human lungs stimulated with compounds that cause fibrosis, they aimed to establish that the drug reverses fibrosis in the actual disease. They did this by applying saracatinib in lung slices obtained from IPF patients who'd had lung transplants. Treatment with saracatinib reduced expression of pro-fibrotic genes and lowered collagen levels. "This finding that fibrosis is changed in tissue obtained from a human with the disease is very promising," Ahangari said.

On the strength of these findings, Yale, Mount Sinai, National Jewish Health, and Baylor Scott & White Research Institute, along with AstraZeneca, and with funding from the National Center for Advancing Translational Science, are collaborating on "STOP-IPF" phase 1b/2a clinical trial to test saracatinib in patients with IPF. In the trial, which began in 2020, IPF patients receive either saracatinib or a placebo. The trial's primary outcome is safety; evaluating saracatinib's efficacy at reducing fibrosis in patients is a secondary outcome. The researchers estimate that the trial will be completed in a year.

"Patient recruitment for the study has previously been slow because of the pandemic," said Danielle Antin-Ozerkis, MD, associate professor of medicine (pulmonary) and medical director of the Yale-ILD Center of Excellence who is one of the leaders of the clinical trial. "We are optimistic that now recruitment will increase even more. We know that IPF patients really want to participate in trials and to help move the field forward."

The clinical trial, "Saracatinib in the treatment of Idiopathic Pulmonary Fibrosis (STOP-IPF)", is underway.

More information: Farida Ahangari et al, Saracatinib, a Selective Src Kinase Inhibitor, Blocks Fibrotic Responses in Preclinical Models of Pulmonary Fibrosis, *American Journal of Respiratory and Critical Care Medicine* (2022). DOI: 10.1164/rccm.202010-3832OC

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