

How a new drug prototype regenerates lung tissue

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Pulmonary diseases are a leading cause of morbidity and mortality worldwide. For many progressive lung diseases like idiopathic pulmonary fibrosis (IPF), a key issue is a low supply of new stem cells to

repair and reverse damage. These cells are responsible for regenerating and increasing the growth of healthy tissue—without them, lung function decreases and a range of severe illnesses can take hold.

But a team of scientists at Scripps Research and its drug discovery arm, the Calibr-Skaggs Institute for Innovative Medicines, has now developed a lung-targeted, druglike small molecule to stimulate the growth of lung stem [cells](#). These new findings, [published](#) in the *Proceedings of the National Academy of Sciences*, provide a biological proof of concept for activating one of the body's regenerative pathways and restoring damaged lung tissue.

This approach could transform the treatment of severe pulmonary diseases, notably as CMR316—Calibr-Skaggs' similar therapy for treating IPF—is set to enter a phase 1 clinical trial this summer.

"My approach toward [regenerative medicine](#) has been figuring out how to promote regenerative, proliferative repair of organs using druglike molecules that act on endogenous stem cell populations," says co-senior author Michael J. Bollong, Ph.D., an associate professor and the Early Career Endowed Roon Chair for Cardiovascular Research in the Department of Chemistry at Scripps Research. "We chose the lung because the stem cell population of the lower airway doesn't regenerate as effectively as one ages."

That means more scar tissue is secreted, which can lead to IPF—a disease that affects up to 20 per 100,000 people worldwide, according to the National Library of Medicine. However, there currently are no available treatment options that regenerate damaged lung tissue.

"Most drugs act by slowing the progression of disease—our approach is to make drugs that control cell fate to stop or reverse the disease process," says Peter G. Schultz, Ph.D., co-senior author and the

President and CEO of Scripps Research.

To see whether existing drug mechanisms could increase growth of lung stem cells, the team turned to ReFRAME, a drug repurposing library built by Calibr-Skaggs. ReFRAME permits researchers to rapidly sort through thousands of existing FDA-approved drugs and determine whether they could treat any other major diseases. This approach is particularly useful for cellular systems that aren't easily amenable to large-scale screening campaigns.

"ReFRAME allowed us to understand what the target was immediately, to start understanding how that biology made sense in the context of the lung, and to test the concept directly in vivo," says Bollong.

Using ReFRAME, the team—which also includes Scripps Research and Calibr-Skaggs researchers Sida Shao, Nan Zhang, Sean B. Joseph, Arnab K. Chatterjee and Jeffrey Jian Chen—determined that a drug class known as DPP4 inhibitors could potentially help activate production of lower airway stem cells, called type 2 alveolar epithelial cells (AEC2).

Although DPP4 inhibitors are often used as medications for type 2 diabetes to control blood sugar, the researchers found that the inhibitors promoted production of AEC2 in mice with damaged lungs. However, the dose required when using existing inhibitors for lung repair would be too high and unsafe for humans, meaning it wouldn't be possible to directly repurpose approved inhibitors for [clinical use](#), especially when used in combination with other anti-fibrotic drugs.

"To effectively repair the lungs, the dosing would be roughly 50 to 100 times as much, so we needed to make a drug that inhibited DPP4 in the lung only," explains Bollong. "That's why we went after a lung-targeted and lung-retained approach."

Bollong and his team developed NZ-97, a DPP4 inhibitor that persists in the lungs and promotes AEC2 growth in mice with lung damage. While NZ-97 is a prototype drug, it's chemically similar to CMR316, Calibr-Skagg's drug that will be entering a phase 1 clinical trial in a few months.

Unlike preexisting DPP4 inhibitors, CMR316 will be administered once weekly via a nebulizer—a machine that generates a medicinal mist to inhale—so it's delivered directly to the lungs. The research team also chemically modified these agents to remain in the lungs for long periods, such that the drug selectively inhibits DPP4 only in this organ.

"What that ultimately allowed us to do is have a drug that could be administered at very low doses," Bollong says. In fact, the projected dose for humans is inhaling 1 mg to 2 mg over the span of a couple of minutes once per week. "People have been making DPP4 inhibitors for more than 20 years, so we could leverage that known chemical matter to make a very good version of the drug that's efficacious, lung retained and safe."

Bollong, Schultz, and the rest of the research team are hopeful that CMR316 will also be able to assist with lung damage from a range of other pulmonary illnesses, including influenza, COVID-19 and [chronic obstructive pulmonary disease](#), the third leading cause of death around the globe, according to the World Health Organization.

"IPF makes the most sense as the first disease to investigate because it's driven by a deficiency in this stem cell population," Bollong explains, adding that NZ-97 showed generalizable efficacy across a wide array of lung damage models. "What we also show in this paper is that we've taken stem cells from IPF patient donors and replenish their capacity to grow at an ex vivo format." That's why NZ-97 is a key component in showing how CMR316 works from a pharmacological perspective.

With CMR316 poised to enter the clinic shortly, the research team is also moving forward compounds with novel mechanisms that help heart cells regenerate and repair damage from heart failure, as well as using small molecule drugs to replenish cells in organs ranging from the cornea to the kidney to the colon.

In addition to Bollong and Schultz, authors of the study are Sida Shao, Nan Zhang, Gregory P. Specht, Shaochen You, Lirui Song, Qiangwei Fu, David Huang, Hengyao You, Alain Domissy, Shuangwei Li, Van Nguyen-Tran, Sean B. Joseph, Arnab K. Chatterjee and Jeffrey Jian Chen of Scripps Research; and Jian Shu of Harvard University.

More information: Sida Shao et al, Pharmacological expansion of type 2 alveolar epithelial cells promotes regenerative lower airway repair, *Proceedings of the National Academy of Sciences* (2024). [DOI: 10.1073/pnas.2400077121](https://doi.org/10.1073/pnas.2400077121)

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