THE FRONT ROW at Scripps Research

100 YEARS — A Century of Science Changing Life

# Regenerating tissues to treat disease


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### ABOUT THE LECTURE

Unlike axolotls and zebrafish, humans are unable to regrow organs—at least, not on their own. But by harnessing the body's ability to repair tissue, associate professor Michael Bollong, PhD, is developing drugs to regenerate human organs ranging from the lungs to the heart. In his Front Row lecture, Bollong explained how regenerative medicine can replace cells that are damaged from aging or disease with healthy ones.

### TOP TAKEAWAY POINTS

1. As we age or become ill, the capacity for our cells to regenerate diminishes. By identifying and targeting pathways that control the body's ability to repair tissue, regenerative medicines can intervene in processes that cause various ailments, including fibrosis and heart disease. But regenerating a specific cell type first requires identifying a molecule that has the potential to become an effective therapeutic.
2. Using ReFRAME—a drug repurposing library built by Calibr-Skaggs Institute for Innovative Medicines—Bollong and colleagues determined that a drug class known as DPP4 inhibitors could potentially help activate production of lower airway stem cells. Insufficient division of these cells can lead to idiopathic pulmonary fibrosis (IPF), which causes the lungs to develop scar tissue and makes breathing increasingly difficult. Although DPP4 inhibitors are often used to control blood sugar in cases of type 2 diabetes, the dose required to effectively repair the lungs would be significantly higher and unsafe.
3. Bollong's solution was to develop a new drug that directly targets the lungs without seeping into other organs. This lung-retained therapeutic candidate, called CMR316, was created by modifying preexisting DPP4 inhibitors to remain in the lungs for extended periods. CMR316 requires a very low dose that's inhaled through a medicinal mist about once to twice per week. The drug, which also synergized with standard care treatments for IPF, is now entering a phase 1 clinical trial.
4. A known regenerative pathway in humans is called the yes-associated protein (YAP) pathway. It influences the Hippo signaling pathway, which controls organ size and tissue regeneration. Bollong wondered whether activating YAP when it should be "turned off" would regenerate heart muscle cells. With the help of ReFRAME, Bollong's team found 15 drug-like small molecules that "turn on" YAP when the Hippo pathway is also activated. And in preclinical models, activating YAP promoted regenerative cardiac repair and reversed heart failure. A phase 1 clinical trial is anticipated over the next couple of years, with the team now developing a one-time injectable to deliver via the pericardial sac that surrounds the heart.
5. Bollong is also working on drugs to combat aging. As we get older, the ends of our chromosomes degrade a bit each time our cells divide. Although telomerase fills in chromosomes' missing sequences, the enzyme isn't expressed in most human tissue. But Bollong and his team identified a telomerase-activating compound that increased neuron production and decreased brain inflammation associated with aging in preclinical models.