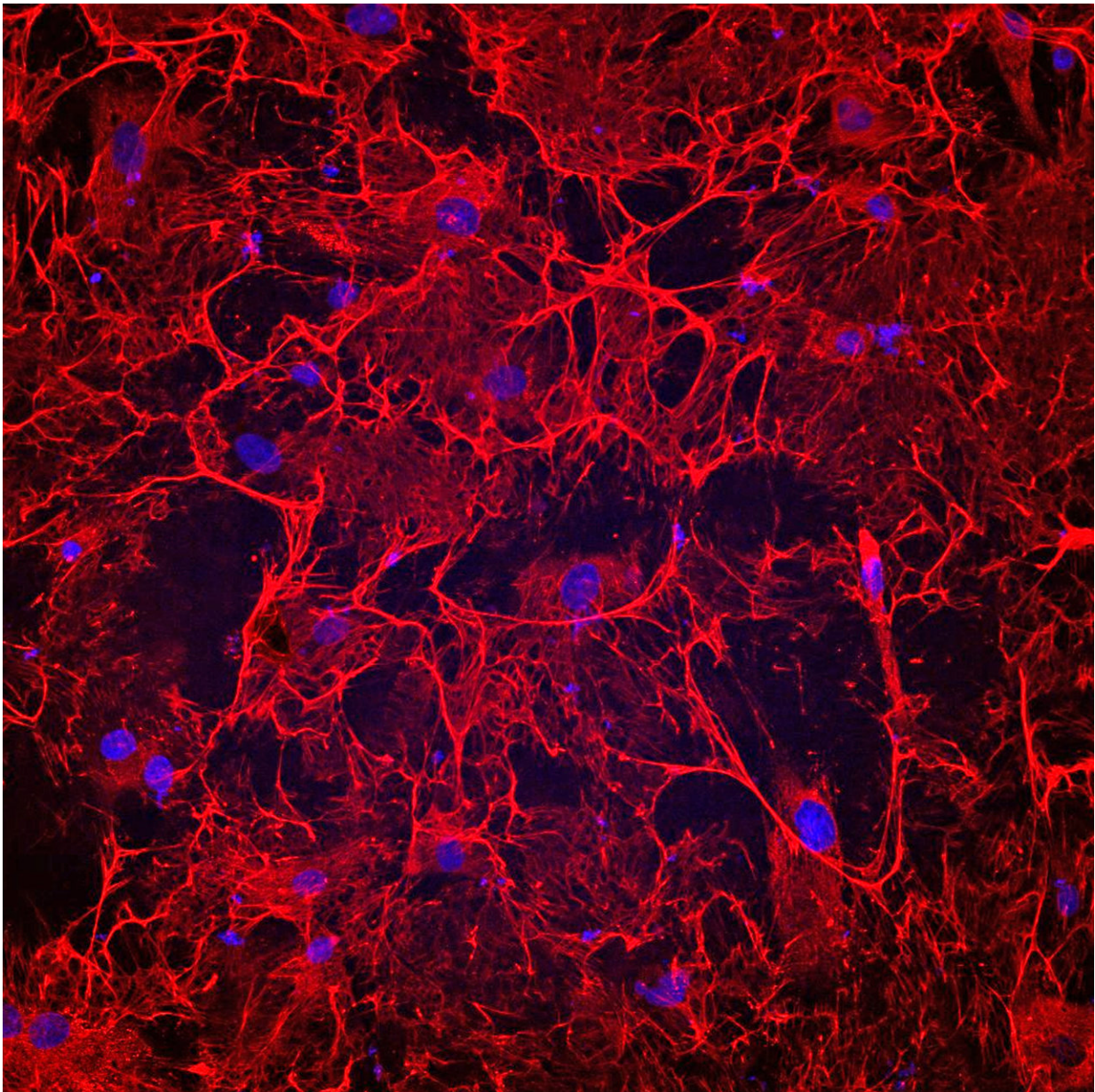


Blocking matrix-forming protein might prevent heart failure

April 13 2018



This microscopic image shows donated fibrotic heart cells from a patient who had heart failure. The cells have an elaborate fibronectin matrix (shown in red) which causes fibrosis and heart damage. In a study published by *Circulation*, researchers demonstrate a novel therapeutic peptide stops the process and heart fibrosis in mice with heart injury and human heart failure cells. Credit: Cincinnati Children's

Scientists used an experimental targeted molecular therapy to block a matrix-forming protein in heart cells damaged by heart attack, reducing levels of scarred muscle tissue and saving mouse models from heart failure.

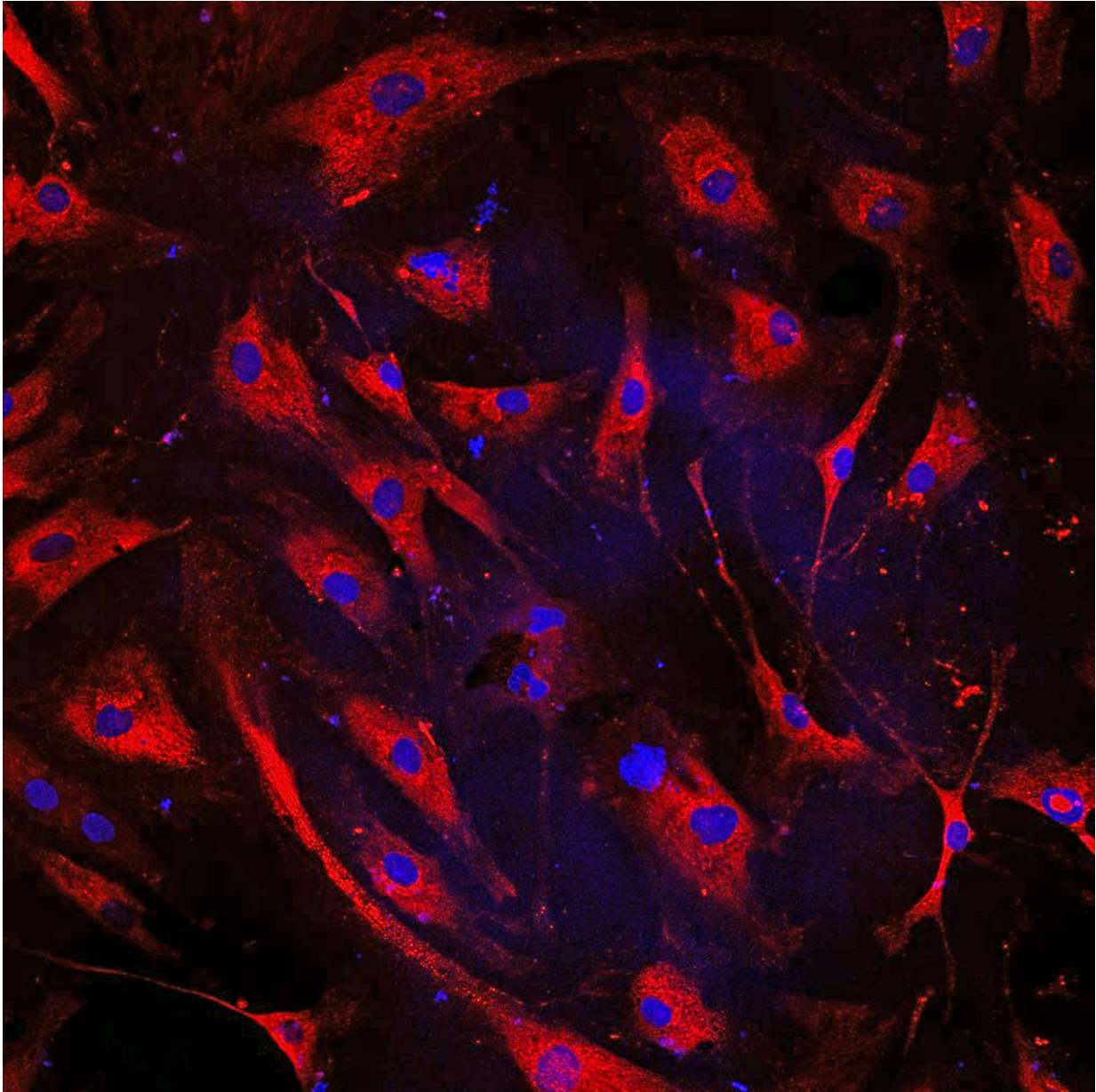
Researchers at the Cincinnati Children's Heart Institute report in the journal *Circulation* testing a manufactured peptide called pUR4 to block the fibronectin protein in human [heart cells](#) donated by [heart failure](#) patients. The treatment prevented the human [heart cells](#) from failing and restored their function. The treatment also reduced fibrosis and improved heart function after a simulated heart attack in mice.

Fibronectin is normally a good actor in the body. It helps form a cell-supporting matrix for the body's connective tissues, aiding tissue repair after injury.

But after a heart attack, fibronectin overreacts, it polymerizes and helps produce too much connective matrix. It also causes hyperactive production of clogged and dysfunctional cardio myofibroblast cells that damage the heart. The pUR4 compound is designed so it will attach to surface points on fibronectin, effectively inhibiting its effects in injured heart cells.

"Our data are a strong proof of principle and the first to show that

inhibiting fibronectin polymerization preserves heart function, reduces left ventricle remodeling and limits formation of fibrotic connective tissue," said the study's lead investigator Burns Blaxall, PhD, director of translational research in the Heart Institute and the Center for Translational Fibrosis Research.



In this image, human heart cells treated with a novel therapeutic peptide exhibit

dramatically reduced fibrosis. The experimental treatment prevented the human heart cells from failing and restored their function. Credit: Cincinnati Children's

Testing a Tiny Solution for a Big Problem

Although heart disease is the leading cause of death in the world, few effective treatment options are available for patients—many having had a previous heart attack or [congenital heart disease](#). The pUR4 molecular treatment used in the current study is one of several compounds Blaxall and his colleagues are testing that show promise in preliminary preclinical research data.

Heart fibrosis and cardiac remodeling are medical challenges that are also faced by children with congenital heart disorders, and ongoing medical challenges requiring specialized care often follow these children into adulthood.

A key question in the current *Circulation* study was verifying the results of pUR4 targeted molecular therapy in both the mouse models and human heart failure cells. In mice with simulated heart attack that as a control experiment received a placebo therapy, the animals developed significant fibrosis and heart failure. When researchers treated mice with pUR4 for just the first seven days after [heart attack](#), or genetically deleted fibronectin activity from the heart cells of mice, these reduced fibrosis and improved cardiac function. Treatment of human failing heart cells with pUR4 also reduced their fibrotic behavior.

Next Steps

The researchers emphasize it's too early to know whether the experimental therapy in this study can one day be used to treat human

heart patients clinically. Extensive additional research is needed first, including proving pUR4's safety in larger animal models and then moving on to establish proof-of-principal effectiveness treating heart failure in those models, according to Blaxall.

Researchers also are working to refine the pUR4 peptide to enhance its capabilities for localized administration to the heart and for extended-release in patients.

More information: Iñigo Valiente-Alandi et al, Inhibiting Fibronectin Attenuates Fibrosis and Improves Cardiac Function in a Model of Heart Failure, *Circulation* (2018). [DOI: 10.1161/CIRCULATIONAHA.118.034609](https://doi.org/10.1161/CIRCULATIONAHA.118.034609)

Provided by Cincinnati Children's Hospital Medical Center

Citation: Blocking matrix-forming protein might prevent heart failure (2018, April 13) retrieved 26 April 2024 from <https://medicalxpress.com/news/2018-04-blocking-matrix-forming-protein-heart-failure.html>

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