Stem cell drug screen yields potential alternative to statins

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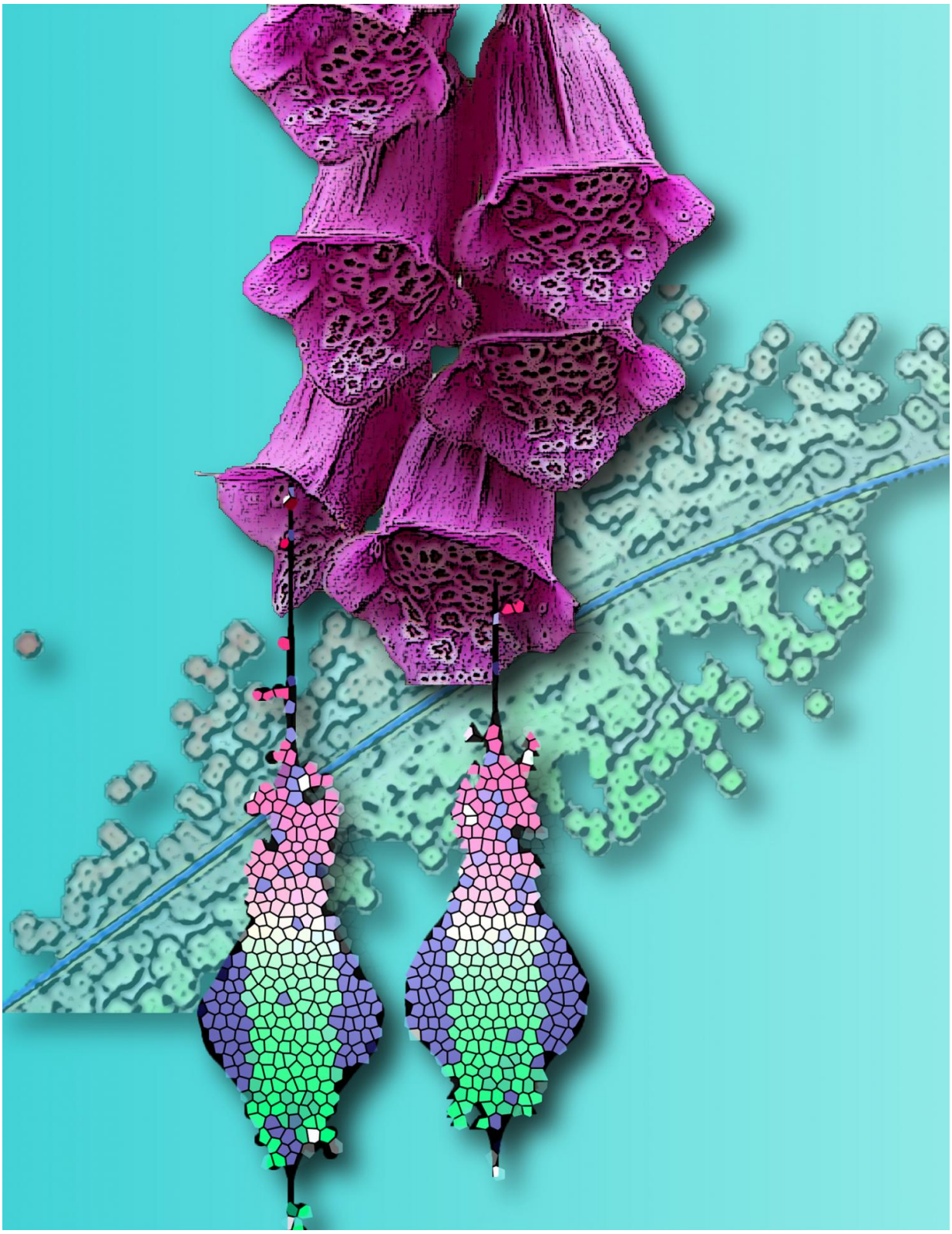

An illustration featuring foxglove, the plant from which cardiac glycosides are

derived. Credit: Dr. Stephen Duncan, Medical University of South Carolina

Scientists at the Medical University of South Carolina (MUSC) have found that a class of heart failure drugs might decrease low-density lipoprotein (LDL) cholesterol levels in patients who do not respond to statins. In a study appearing in the April 6, 2017 issue of *Cell Stem Cell*, cardiac glycosides reduced levels of a precursor of LDL in liver-like cells, and patients taking cardiac glycosides for heart failure had low LDL.

Not everyone with high LDL cholesterol responds to statins. Statins increase levels of a cell surface receptor that removes LDL cholesterol from the bloodstream. However, statins do not work in patients with familial hypercholesterolemia (FH), who have a rare mutation in that receptor. FH patients have very high cholesterol and die of cardiovascular disease by their forties. The existing drugs for FH can cause fatty liver disease, and the best treatment is a liver transplant.

Stephen A. Duncan, D. Phil., SmartState Chair of Regenerative Medicine at MUSC, and his colleagues developed a drug screen to identify an alternative to statins. They focused on apolipoprotein B (ApoB), a molecule that liver cells use to make LDL and which is normal in patients with FH. Drugs that decrease ApoB could potentially lower cholesterol independently of the LDL receptor in FH patients and also in patients with other forms of high cholesterol.

FH was a perfect model for testing alternatives to statins. Yet the rarity of FH meant these liver cells were scarce. Duncan's group obtained skin cells from a patient with the rare disorder from the Next Generation Genetic Association Studies consortium of the National Heart, Lung, and Blood Institute, which studies genetic mutations linked to cardiovascular

diseases. Next, they generated induced pluripotent stem cells from these skin cells. Stem cells continually double their numbers while in culture. This meant that a sample of converted skin cells from a single patient with FH provided a renewable source of liver-like cells that retained the mutation.

The team treated their liver-like cells with the SPECTRUM drug library, a collection of 2300 pharmaceuticals, many of which have reached clinical trials. In a surprising finding, all nine cardiac glycosides in the library, some once widely prescribed for heart failure, reduced ApoB levels in liver-like cells from the patient with FH, ranging from 29 percent (ouabain) to 38 percent (digoxin) to 73 percent (gitoxin). In further tests, they also lowered ApoB levels in human hepatocytes and reduced them by 30 percent in mice engineered to grow normal human livers without the FH mutation at doses eight times below their toxicity thresholds. Molecular tests revealed that glycosides shorten the lifetime of the ApoB molecule, in part by increasing how quickly it is degraded.

As everyone needs ApoB to make LDL cholesterol, this was proof that cardiac glycosides could potentially also work in patients with other forms of high cholesterol. To find out, the team combed through more than five thousand records of patients prescribed cardiac glycosides for heart failure who also had LDL cholesterol records. On average, LDL cholesterol levels were lower in those taking a cardiac glycoside (reduction of 9 mg/dL) or a statin (reduction of 14 mg/dL) than in those not taking any drug. No difference in LDL cholesterol levels was noted between those taking an angiotensin-converting enzyme inhibitor, another heart failure drug with no known role in cholesterol production, and those not taking any drug. Duncan's team also found patients who had LDL measurements recorded both before and after being prescribed a cardiac glycoside. LDL cholesterol dropped in 16 out of 21 patients and by an average of nearly 26 points, which was similar to the 32-point drop seen in a matching group of patients prescribed statins.

This study contains the first evidence to date that cardiac glycosides could potentially reduce LDL cholesterol independently of the LDL receptor, where statins act, by promoting ApoB degradation.

It is not clear from this study whether cardiac glycosides decrease LDL cholesterol in patients who do not have heart failure or at what dose they should be used. The cardiac glycosides have narrow ranges of efficacy for the treatment of heart failure, above which they can be toxic. However, they could offer inexpensive, life-saving options for patients with FH. Digoxin, the cardiac glycoside most commonly prescribed for heart failure, costs less than one dollar per day. Additionally, a cardiac glycoside in a low dose could conceivably provide an added benefit to patients already taking a statin. Finally, using stem cell-based screens of drugs that are already on the market is an innovative way to investigate treatments for rare liver diseases.

"There are so few livers available for transplant," says Duncan. "Having the stem cell model where we make liver cells in the culture dish opens up a possibility of using this not only to investigate a disease, but also as a way to discover drugs that could fix a disease."

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