The race to patch the human heart

Carolyn Beans, Science Writer

In the lab of biomedical engineer Nenad Bursac of Duke University, patches of human heart tissue beat rhythmically on their own accord. Each translucent patch—on some days up to about 15 patches, 4 centimeters by 4 centimeters each—sits suspended in its own dish on a gently rocking platform. A red broth washes over the cells as the tissues strengthen. If these patches can get strong enough, and functional enough, they may just revolutionize heart repair.

Heart tissue is challenging to generate in the lab but even more so in the adult body. During a heart attack, as many as one billion contracting heart cells known as cardiomyocytes can be lost (1). Those cells do not regenerate. Instead, the heart forms scar tissue that cannot transmit electrical signals or contract, putting patients at risk of heart failure.

According to the CDC, about 790,000 Americans have a heart attack each year (2). Because existing therapies cannot heal the heart and organ donations are scarce, patients are left with limited options. “If we could put back actively contracting cardiac muscle cells, then we believe we would be delivering the largest benefit,” Bursac says.

Bursac and other researchers are racing to fabricate a cardiac patch with ingredients, ranging from heart cells to thigh-muscle cells, and tools as diverse as rocking dishes and 3D bioprinters. But before heart patches become a real option for patients, researchers must overcome challenges ranging from the logistical—to mass produce and store them—to the biological—how to build a patch thick enough for powerful contractions and synchronize its rhythm with the heart’s own.

Patch Perfect

There’s more than one way to heal a heart. For decades, researchers have experimented with cardiomyoplasty—an early version of a sort of heart patch that involved wrapping the heart in muscle extracted from other parts of the body and stimulating it electrically (3). About 2,000 people have received a cardiomyoplasty in the course of many clinical trials. But efforts to date have failed to show a reliable benefit (3).

Researchers have also explored injecting stem cells directly into or near the heart. These cells release cytokines—enzymes and growth factors that help restore damaged tissue that isn’t yet dead. Although trials are ongoing, the technique has so far shown inconsistent results (4). “Traditional handheld injections were not a very efficient way of transferring cells,” says cardiac surgeon Philippe Menasché of the University of Paris Descartes. “Many of them die because of the surgical stress that they incur during the process of injection.”

An optimal heart patch would both contract in synch with the heart and release restorative cytokines, although researchers believe that either approach alone could be beneficial. In the late 1990s, researchers began taking steps toward engineering these patches (5).
In 1999, a team of Massachusetts-based researchers, with Bursac as the lead author, reported that they had constructed tissue from mammalian heart cells (6). In 2004, another author of this study, biomedical engineer Gordana Vunjak-Novakovic, now of Columbia University, showed that she could encourage neonatal rat muscle cells to form heart-like tissue if she stimulated the cells with electrical signals that mimicked the heart’s own (7). In 2009, after one of the earliest cardiac-patch tests in a living animal, Menasché reported that rats that received cells in two patch forms showed greater recovery of heart function than those that received cell injections (8).

Choosing Ingredients
To build heart tissue, Bursac takes a skin biopsy and, using genetic manipulations, converts human skin cells into a stem cell state. Using chemical cues, he coaxes these cells, known as induced pluripotent stem (iPS) cells, into multiple cell types that make up the heart.

When Bursac’s graduate student Ilya Shadrin first showed him the most recent version of the large beating patch made from these cells, Bursac was skeptical. “The first time you show me things, I always say it is beginner’s luck,” he says. “You show me three times and then I start believing you.” Previous versions of the team’s large patch hadn’t held together. Trying to get it right, they laboriously tweaked the exact combinations of cells, nutrients, and culture conditions.

One of the keys to success was rocking the tissues, sloshing the broth back and forth to better distribute nutrients and oxygen to the cells.

But not all researchers generate heart cells to make heart patches. Cardiac surgeon Yoshiki Sawa of Osaka University in Japan and his team often use cells from the thigh. “The skeletal muscle cells and heart muscle cells seem to be similar,” he says. “They hold similar cytokines.” The team removes a piece of thigh muscle and then cultures the muscle to encourage the proliferation of skeletal myoblasts, cells that repair damaged muscle. They culture 100 million of these cells, into multiple cell types that make up the heart. The bigger challenge is as-
vanting time and hindering mass production.

Molding Tissue
For Bursac, there’s nothing special about cardiomyocytes beating in a dish; beating and contraction is their fundamental property. “Seeing it contract is really the very beginning,” he says. The bigger challenge is assembling the cells into functional tissue. Bursac begins by mixing heart cells with a hydrogel made largely from fibrin, a protein that helps blood clot. He then lets this gelatinous solution set within a flexible frame held in place by a mold. After a few days, the patch is firm enough to be transferred to a rocking dish where the nutrient-rich broth helps it develop further.

Like Bursac, many researchers use fibrin or other natural materials as a sort of scaffold for cells. Others use synthetics (5). Bioengineer Kelly Stevens of the University of Washington in Seattle sometimes goes without any scaffold, relying only on cells. “Nature doesn’t use plastic,” she says. Working with collaborator and professor of pathology, Charles Murry, who directs the Institute for Stem Cell and Regenerative Medicine at the University of Washington, Stevens has shown, for example, that cardiomyocytes alone make a weak patch that quickly falls apart. But by adding other cell types also present in a developing embryo, the cells can signal to one another and construct small blood vessels. After attaching to the rat heart, these vessels deliver blood to cells in the patch, keeping those cells alive longer (12).

But cell-only approaches need not follow nature. Cardiac surgeon Narutoshi Hibino of Johns Hopkins University uses a 3D bioprinter to skewer tiny balls of cells known as cell spheroids onto needles all pointing upward in a dense array. After cells on neighboring needles develop connections to one another, the
team lifts the tissue from the needles and allows it to continue maturing (13).

**Keeping the Beat**
When Bursac transplanted rodent-sized versions of his patch into a mouse model, the patch kept beating. When he tested the patch in rat hearts, he found no added risk of heart arrhythmias, a serious concern when attaching beating tissue with its own rhythm to a heart (1). Bursac is now testing the human-sized version in pigs. But he hasn’t yet achieved the perfect patch.

One issue is synchrony. “What we most count on is that this patch will be able to synchronize with the heart, electrically, mechanically,” he says. But there’s an insulating layer of non-heart cells between the heart and the patch that doesn’t conduct electrical signals. The heart and engineered tissue remain separate, each beating to its own rhythm. One way to overcome that issue might be to make the insulating layer become electrically conductive, Bursac explains. In a proof-of-concept in vitro study, his team placed sodium channels from bacteria into nonconductive human cells, which enabled these cells to conduct the sort of electrical signals that trigger heart beats (14).

Another challenge is thickness. To make up for lost contractions, you really need a thick piece of functional tissue, says Bursac. His current patch is five to eight cell layers thick. He can stack a few patches, but that still leaves him with a tenth of the cells lost as a result of a typical heart attack. To go thicker, he needs veins and arteries. “If you don’t have vasculature, then everything in the center of a tissue will die because there are not enough nutrients and oxygen,” he says. Bursac is exploring ways to grow the patch after it’s implanted on the heart so that, as it thickens, the heart’s own vasculature could support it. Hibino’s team is working on a technique for bioprinting blood vessels. And Stevens is also experimenting with bioprinting, as well as genetically engineering cells to organize themselves into vessels.

In the meantime, researchers are beginning to test non-beating patches in humans. Although they cannot themselves strengthen contractions, these patches could help save some of the heart’s own contracting tissue if applied soon after a heart attack. Menasché reported this year that his team transplanted a cardiac patch made of cardioprogenitor cells derived from human embryonic stem cells onto the hearts of six patients (15). Last year Sawa’s team reported results from a clinical trial involving 27 patients who received heart patches made of cells cultured from their own thighs muscles (16). In both trials, many patients improved their capacity to exercise. But the researchers couldn’t attribute the response to patches alone. All of the patients in Menasché’s study also received coronary artery bypasses. And Sawa notes that the extent of recovery might depend in part on the remaining viability of the patient’s own heart. The trials did prove, however, that there were no obvious negative side effects. In May, Sawa received approval from Japan’s health ministry to treat three patients with a different patch made from heart muscle cells derived from iPS cells (17).

Bursac hopes to test his team’s beating heart patch in humans within 15 years. “To make a human heart patch and make it highly functional is not trivial,” says Bursac. “Everyone is trying to accelerate their research as fast as possible.”

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