Medical Xpress

A new approach to growing heart muscle

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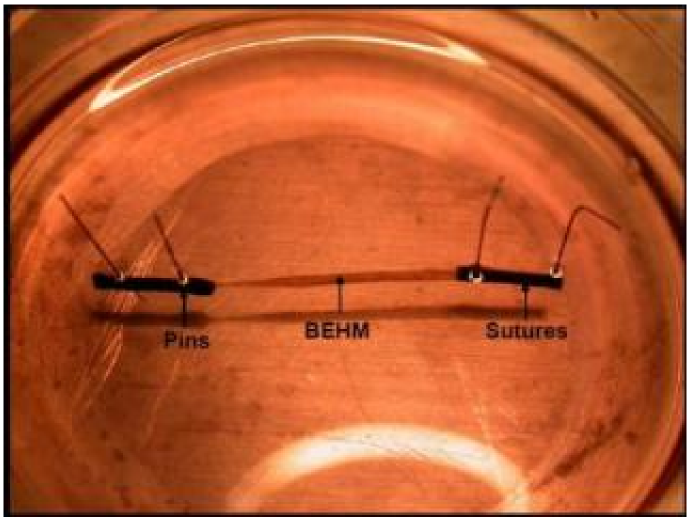

A length of bioengineered heart muscle, or BEHM, grown at the University of Michigan using rat cardiac muscle cells and a fibrin gel base. Credit: Ravi Birla, University of Michigan

It looks, contracts and responds almost like natural heart muscle – even though it was grown in the lab. And it brings scientists another step closer to the goal of creating replacement parts for damaged human hearts, or eventually growing an entirely new heart from just a spoonful of loose heart cells.

This week, University of Michigan researchers are reporting significant progress in growing bioengineered heart muscle, or BEHM, with organized cells, capable of generating pulsating forces and reacting to stimulation more like real muscle than ever before.

The three-dimensional tissue was grown using an innovative technique that is faster than others that have been tried in recent years, but still yields tissue with significantly better properties. The approach uses a fibrin gel to support rat cardiac cells temporarily, before the fibrin breaks down as the cells organize into tissue.

The U-M team details its achievement in a new paper published online in the *Journal of Biomedical Materials Research Part A*.

And while BEHM is still years away from use as a human heart treatment, or as a testing ground for new cardiovascular drugs, the U-M researchers say their results should help accelerate progress toward those goals. U-M is applying for patent protection on the development and is actively looking for a corporate partner to help bring the technology to market.

Ravi K. Birla, Ph.D., of the Artificial Heart Laboratory in U-M's Section of Cardiac Surgery and the U-M Cardiovascular Center, led the research team.

"Many different approaches to growing heart muscle tissue from cells are being tried around the world, and we're pursuing several avenues in our laboratory," says Birla. "But from these results we can say that utilizing a fibrin hydrogel yields a product that is ready within a few days, that spontaneously organizes and begins to contract with a significant and measurable force, and that responds appropriately to external factors such as calcium."

The new paper actually compares two different ways of using fibrin gel as a basis for creating BEHM: layering on top of the gel, and embedding within it. In the end, the layering approach produced a more cohesive tissue that contracted with more force – a key finding because embedding has been seen as the more promising technique.

The ability to measure the forces generated by the BEHM as it contracts is crucial, Birla explains. It's made possible by a precise instrument called an optical force transducer that gives more precise readings than that used by other teams.

The measurement showed that the BEHM that had formed in just four days after a million cells were layered on fibrin gel could contract with an active force of more than 800 micro-Newtons. That's still only about half the force generated within the tissue of an actual beating heart, but it's much higher than the forces created by engineered heart tissue samples grown and reported by other researchers. Birla says the team expects to see greater forces created by BEHM in future experiments that will bathe the cells in an environment that's even more similar to the body's internal conditions.

In the new paper, the team reports that contraction forces increased when the BEHM tissues were bathed in a solution that included additional calcium and a drug that acts on beta-adrenergic receptors. Both are important to the signaling required to produce cohesive action by cells in tissue.

The U-M team also assessed the BEHM's structure and function at different stages in its development. First author and postdoctoral fellow Yen-Chih Huang, Ph.D., of the U-M Division of Biomedical Engineering, led the creation of the modeling system. Co-author and research associate Luda Khait examined the tissue using special stains that revealed the presence and concentration of the fibrin gel, and of collagen generated by the cells as they organized into tissue.

Over the course of several days, the fibrin broke down as intended, after fulfilling its role as a temporary support for the cells. This may be a key achievement for future use of BEHM as a treatment option, because the tissue could be grown and implanted relatively quickly.

The U-M Artificial Heart Laboratory (www.sitemaker.umich.edu/ahl) is part of the U-M Section of Cardiac Surgery, and draws its strength from the fact that it includes bioengineers, cell biologists and heart surgeons – a multidisciplinary group that can tackle both the technical and clinical hurdles in the field of engineering heart muscle. Its focus is to evaluate different platforms for engineering cardiovascular structures in the laboratory. Active programs include tissue engineering models for cardiac muscle, tri-leaflet valves, cell-based cardiac pumps and vascular grafts. In addition, the laboratory has expertise in several different tissue engineering platforms: self-organization strategies, biodegradable hydrogels such as fibrin, and polymeric scaffolds.

Each approach may turn out to have its own applications, says Birla, and the ability to conduct side-by-side comparisons is important. Other researchers have focused on one approach or another, but the U-M team can use its lab to test multiple approaches at once.

"Fundamentally, we're interested in creating models of the different components of the heart one by one," says Birla.

"It's like building a house – you need to build the separate pieces first. And once we understand how these models can be built in the lab, then we can work toward building a bioengineered heart." He notes that while many other labs focus on growing one heart component, only U-M is working on growing all the different heart components.

Already, the U-M team has begun experiments to transplant BEHM into the hearts of rats that have suffered heart attacks, and see if the new tissue can heal the damage. This work is being conducted by Francesco Migneco, M.D., a research fellow with the Artificial Heart Laboratory. Further studies will implement "bioreactors" that will expose the BEHM tissue to more of the nutrients and other conditions that are present in the body.

Source: University of Michigan Health System