Researchers grow functional network of blood vessels at centimeter scale for the first time

November 30 2018

Jason Gleghorn, assistant professor of biomedical engineering. Credit: University of Delaware

When someone has a deadly disease or sustains a life-threatening injury, a transplant or graft of new tissue may be the best—or only—treatment option. Transplanted organs, skin grafts and other parts need blood vessels to bring oxygen-rich blood their way, but for tissue engineers and

regenerative medicine experts, making a functional blood vessel network within large tissues in the laboratory has long been a major challenge.

Now, a research group at the University of Delaware has pioneered methods to grow a self-assembling, functional network of blood vessels at a size relevant for human use. Jason Gleghorn and his colleagues are the first to make this system work at this scale, and their results were recently published in the journal *Biomaterials*.

Gleghorn, an assistant professor of biomedical engineering at the University of Delaware, studies how the embryo builds tissues and organs during development with the goal of using this knowledge to define new regenerative medicine strategies. While other groups have made blood vessel networks that span millimeters in size, the UD system works across centimeter scales, necessary for functional tissue replacement. With more development and refinement, Gleghorn's microfluidic system could someday be utilized to grow blood vessels for tissue and organ transplantation into humans.

How to build blood vessel networks

The team embedded human blood vessel cells into a gel made of collagen, a protein found in connective tissue such as skin and joints. The goal was to determine the physical conditions necessary to make the cells grow, multiply and connect with each other so that a network of blood vessels assembled itself.

Making blood vessel networks is tricky business because the system doesn't always behave how investigators expect. During his doctoral training, Gleghorn was part of the first team that developed techniques to create patterned blood vessel networks for tissue engineering using microfluidic techniques.

"As an engineer, we can say we think the cells need to be this far apart or the vessels need to be a certain size and spacing," Gleghorn said. "We can create a very precise environment and structure for the cells, but the problem is that biology doesn't work that way. The cells remodel everything. They change shape and size and push and pull on each other and the materials they are embedded in to rearrange our 'perfect' home that we think they need. The reality is we need to design systems that will encourage cells to remodel themselves and their environment to generate a functional tissue."

Instead, Gleghorn's group asked: "What is the fundamental initial starting point of the system that we need, and then can we kick it in the right direction to get it to evolve and build its own architecture similar to the way your body does it during development?" he said.

For one, using a powerful confocal microscope at the Delaware Biotechnology Institute, the group found that the density, or stiffness, of the collagen gel affected how the cells suspended within it behaved, ultimately affecting the size and connectivity of the vessels.

"It looks kind of like the holiday dessert with fruit suspended in Jell-O," said Gleghorn of the cells in the collagen gel. "You have a bunch of cells randomly distributed throughout the volume of the gel, and if they are sparsely distributed, it gets very hard for them to talk to each other and form connections to form vessels. The languages they use are chemical signals and physical forces." The key is to find the sweet spot of stiffness, stiff enough so that neighboring cells can interact with the material and each other, but not so stiff that the cells can't move.

The team also found that by perturbing their system in a specific way, they could affect the size and shape of the vessel networks under assembly.

"From larger vessels to much smaller microvessels, which are really hard to make, we can now tune the vessel network architecture with the initial starting parameters," said Gleghorn. This means that the new system could have applications from forming larger vessels deep within the body to tiny capillaries, the teeny vessels in your fingertips.

Gleghorn's team also found that their lab-grown blood vessels were perfusable, suggesting that blood could flow through them without leaking out of the vessels into surrounding gel. The vessel networks can also form throughout a variety of shaped gels, meaning that this system could be useful for building blood vessel networks in tissues with complicated shapes, such as the meniscus cartilage that pads your knees or a large skin graft for burn patients.

In addition to Gleghorn, authors on the new paper include Joshua Morgan, a former postdoctoral scholar at UD who is now an assistant professor at the University of California, Riverside; Jasmine Shirazi, a graduate student in biomedical engineering; Erica Comber, a former undergraduate research assistant who earned an honors degree in biomedical engineering from UD in 2017 and is now pursuing a doctoral degree at Carnegie Mellon University; and Christian Eschenburg, head of R&D at Orthopedic Technology Services GmbH active in Germany, who did research in Gleghorn's lab as part of the Fraunhofer-UD graduate student exchange program. This work was supported in part by grants from the National Institutes of Health, National Science Foundation, University of Delaware Research Foundation, the Oak Ridge Associated Universities Ralph E. Power Junior Faculty Enhancement Award and the March of Dimes Basil O'Connor Award.

Now, Gleghorn's group is learning even more about how blood vessel networks form so that they can refine their system. With Babatunde Ogunnaike, the William L. Friend Chair of Chemical Engineering, Gleghorn is mapping out mathematical formulas to describe how blood

vessels form and remodel in developing chicken embryos in the egg. "Then we plan to take the math and systems engineering and couple it with the biology—the molecules and the signaling pathways—that we know, and apply it to these 3-D tissue-engineered models to make more complex hierarchical blood vessel networks" said Gleghorn. That project is supported by an award from the University of Delaware Research Foundation.

More information: Joshua T. Morgan et al. Fabrication of centimeter-scale and geometrically arbitrary vascular networks using in vitro self-assembly, *Biomaterials* (2018). DOI: 10.1016/j.biomaterials.2018.10.021

Provided by University of Delaware

Citation: Researchers grow functional network of blood vessels at centimeter scale for the first time (2018, November 30) retrieved 19 April 2024 from https://phys.org/news/2018-11-functional-network-blood-vessels-centimeter.html

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.