Regenerating the kidney

By Kai-Jye Lou, Staff Writer

Researchers at **Harvard Medical School** and **Massachusetts General Hospital** have shown that their previously described platform for creating transplantable bioengineered organs from decellularized matrices can be used to create a functional kidney.[1] The researchers are refining the process to improve kidney functionality and hope to begin large-animal testing within five years.

In the U.S., the kidney is the most commonly transplanted organ and the one for which there are the highest numbers of patients on waiting lists, according to the Organ Procurement and Transplantation Network website.

Decellularization is a process in which detergents and enzymes are used to remove cells from an organ or piece of tissue. What remains is an extracellular matrix (ECM) scaffold that retains both the 3D architecture of the original part and the associated vascular networks, which can then be seeded with cells to create bioengineered organs and tissues.[2]

In 2008, MGH's Harald Ott and collaborators at the **University of Minnesota** first reported on the use of their platform to engineer a beating rat heart from a decellularized heart ECM.[3] His group has since reported on the creation of bioengineered lungs and pancreases.[4,5]

"Our ongoing work is focused on showing that our approach is a platform technology and not just applicable to a single organ," said Ott, a fellow in cardiothoracic surgery at MGH and an instructor in surgery at HMS.

Although replacement bladders and tracheas built upon decellularized matrices have been tested in patients by investigators and companies such as **Tengion Inc.**, such organs have relatively low functional complexity compared with most other internal organs, including the kidney.

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—Stephen Badylak, University of Pittsburgh Medical Center

Indeed, according to Stephen Badylak, deputy director of the **McGowan Institute for Regenerative Medicine** at the **University of Pittsburgh** and director of the institute's Center for Preclinical Tissue Engineering, the cells seeded onto the scaffolds of bioengineered bladders and tracheas support the regeneration of the organ's tissues but do not persist to become a part of the new tissue.

"The approach taken by Dr. Ott and colleagues is different in that they would want and actually require the seeded cells to persist and become a part of the transplanted organ," he said.

Badylak also is a professor in the Department of Surgery at the **University of Pittsburgh Medical Center**. His group is working on a bioengineered liver created with an approach similar to the one being developed by Ott.[6]

Ott added that increased complexity makes the process of repopulating the ECM scaffolds for organs such as kidneys more challenging than it is for bladders and tracheas.

To create bioengineered kidneys, Ott and his team first perfused cadaveric rat kidneys with a detergent solution to generate decellularized kidney ECMs. The resulting matrices were reseeded with a mix of rat neonatal kidney cells and human umbilical vein endothelial cells. The researchers then cultured the seeded scaffolds in a bioreactor under whole-organ culturing conditions for up to 12 days before transplantation.

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—Jeffrey Ross, Miromatrix Inc.

In rats, the resulting bioengineered kidney grafted at an orthotopic position had filtering functionality, produced urine and did not show bleeding or clot formation for the duration of the short-term experiment. The functionality of the bioengineered kidney was higher than that of a decellularized kidney not reseeded with cells but lower than that of a cadaveric kidney.

Results were published in *Nature Medicine*.

"The real excitement from this study is in showing that the engineered organ has the ability to filter blood and form urine, which is what the kidney is supposed to do," said Badylak.

"The current study demonstrates the ability of cells introduced into a decellularized matrix to migrate to their native niche, thereby facilitating the re-creation of a very complex tissue structure," said Jeffrey Ross, VP of product development at **Miromatrix Inc.** "Many had thought the complexity of the kidney nephron would be too high to achieve functional recellularization."

Miromatrix has licensed exclusive, worldwide rights to a patent application from the University of Minnesota that covers the decellularization and recellularization process. The company is using the technology to develop engineered tissue and organ products for transplant but declined to provide details.

Badylak added that in addition to potentially addressing the shortage in donor organs, the underlying approach also could decrease the need for immunosuppressive therapy following transplant because the organ scaffolds could be seeded with a patient's own cells.

Refining protocol

Ott told *SciBX* that his group is now trying to refine the protocols for seeding and culturing the bioengineered organs. The researchers also are trying to adapt their approach to generate pig and human organs.

He said the goal is to test one of the bioengineered organs in a large-animal model within five years.

"Right now, researchers need to figure out the order in which to replace the cells during the seeding process and whether there will be a need to replace most of the cell types of the kidney or just a few of the cell types and let the body take care of the rest," said Badylak.

Badylak thinks the most immediate challenge is to maintain long-term blood flow through the bioengineered organs without also causing blood clots. He said this could be especially challenging for the kidney because the organ has an intricate vascular network.

M. Korkut Uygun, an assistant professor of surgery at HMS who is not part of Ott's team, agreed that preventing clot formation and poor circulation remain key technical challenges that still need to be addressed. He said that ideally, the vascular network of the decellularized organ scaffold needs to be lined with endothelial cells prior to transplantation because blood clots can form at exposed patches of ECM.

Uygun also said strategies such as using heparin or giving anticlotting drugs after transplantation have produced mixed results.

He thinks the next major milestone would be to show that a bioengineered organ can rescue the host animal from problems associated with loss of the host organ's function.

"Right now, what we see is that the transplanted organs only remain functional for a short period of time, usually a few hours," said Uygun. "The next major goal would be to show that we could keep one of these engineered organs functional inside an animal for weeks, months or even years."

Uygun's group is developing a transplantable bioengineered liver created with an approach similar to the one being developed by Ott.[7]

"I think the bioengineered organ most likely to reach human trials first will either be a kidney or a liver," Ross told *SciBX*. "This is based on multiple factors including cell sourcing, prolonged organ donor waiting list times, mortality rates and the lack of end-stage therapies. An engineered liver or kidney, even providing only 20% of the original organ function, would be effective and life changing."

MGH has filed a patent application covering methods for generating the bioengineered kidney. The technology is available for licensing.

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COMPANIES AND INSTITUTIONS MENTIONED

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