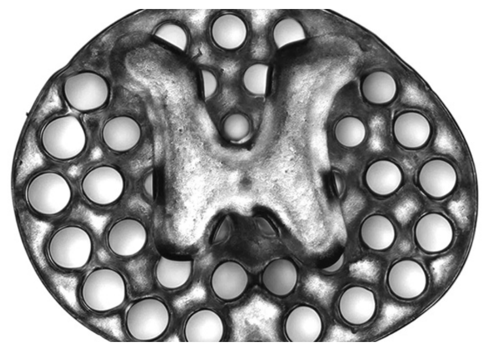
January 14, 2019 | By Scott LaFee and Liezel Labios

3D Printed Implant Promotes Nerve Cell Growth to Treat Spinal Cord Injury

In rat models, the novel scaffolding mimicked natural anatomy and boosted stem cell-based treatment; the approach is scalable to humans and advances effort toward clinical trials

For the first time, researchers at University of California San Diego School of Medicine and Institute of Engineering in Medicine have used rapid 3D printing technologies to create a spinal cord, then successfully implanted that scaffolding, loaded with neural stem cells, into sites of severe spinal cord injury in rats.



A 3D printed, two-millimeter implant (slightly larger than the thickness of a penny) used as scaffolding to repair spinal cord injuries in rats. The dots surrounding the H-shaped core are hollow portals through which implanted neural stem cells can extend axons into host tissues. Photo credit: Jacob Koffler and Wei Zhu, UC San Diego

The implants, described in a study published in the January 14 issue of *Nature Medicine*, are intended to promote nerve growth across spinal cord injuries, restoring connections and lost function. In rat models, the scaffolds supported tissue regrowth, stem cell survival and expansion of neural stem cell axons out of the scaffolding and into the host spinal cord.

“In recent years and papers, we’ve progressively moved closer to the goal of abundant, long-distance regeneration of injured axons in spinal cord injury, which is fundamental to any true restoration of physical function,” said co-senior author Mark Tuszynski, MD, PhD, professor of neuroscience and director of the Translational Neuroscience Institute at UC San Diego School of Medicine. Axons are the long, threadlike extensions on nerve cells that reach out to connect to other cells.

“The new work puts us even closer to real thing,” added co-first author Kobi Koffler, PhD, assistant project scientist in Tuszynski’s lab, “because the 3D scaffolding recapitulates the slender, bundled arrays of axons in the spinal cord. It helps organize regenerating axons to replicate the anatomy of the pre-injured spinal cord."

Co-senior author Shaochen Chen, PhD, professor of nanoengineering and a faculty member in the Institute of Engineering in Medicine at UC San Diego, and colleagues used rapid 3D printing technology to create a scaffold that mimics central nervous system structures.

"Like a bridge, it aligns regenerating axons from one end of the spinal cord injury to the other. Axons by themselves can diffuse and regrow in any direction, but the scaffold keeps axons in order, guiding them to grow in the right direction to complete the spinal cord connection," Chen said.

Faster, More Precise Printing

The implants contain dozens of tiny, 200-micrometer-wide channels (twice the width of a human hair) that guide neural stem cell and axon growth along the length of the spinal cord injury. The printing technology used by Chen's team produces two-millimeter-sized implants in 1.6 seconds. Traditional nozzle printers take several hours to produce much simpler structures.

The process is scalable to human spinal cord sizes. As proof of concept, researchers printed four-centimeter-sized implants modeled from MRI scans of actual human spinal cord injuries. These were printed within 10 minutes.

"This shows the flexibility of our 3D printing technology," said co-first author Wei Zhu, PhD, nanoengineering postdoctoral fellow in Chen's group. "We can quickly print out an implant that's just right to match the injured site of the host spinal cord regardless of the size and shape."

Restoring Lost Connections

Researchers grafted the two-millimeter implants, loaded with neural stem cells, into sites of severe spinal cord injury in rats. After a few months, new spinal cord tissue had regrown completely across the injury and connected the severed ends of the host spinal cord. Treated rats regained significant functional motor improvement in their hind legs.

"This marks another key step toward conducting clinical trials to repair spinal cord injuries in people," Koffler said. "The scaffolding provides a stable, physical structure that supports consistent engraftment and survival of neural stem cells. It seems to shield grafted stem cells from the often toxic, inflammatory environment of a spinal cord injury and helps guide axons through the lesion site completely."

Additionally, the circulatory systems of the treated rats had penetrated inside the implants to form functioning networks of blood vessels, which helped the neural stem cells survive.

"Vascularization is one of the main obstacles in engineering tissue implants that can last in the body for a long time," Zhu said. "3D printed tissues need vasculature to get enough nutrition and discharge waste. Our group has done work on 3D printed blood vessel networks before, but we didn't include it in this work. Biology just naturally takes care of it for us due to the excellent biocompatibility of our 3D scaffolds."

The advance marks the intersection of two longstanding lines of work at the UC San Diego School of Medicine and Jacobs School of Engineering, with steady, incremental progress. The scientists are currently scaling up the technology and testing on larger animal models in preparation for potential human testing. Next steps also include incorporation of proteins within the spinal cord scaffolds that further stimulate stem cell survival and axon outgrowth.

Co-authors include: Xin Qu, Oleksandr Platoshyn, Jennifer Dulin, John Brock, Lori Graham, Paul Lu and Martin Marsala, all at UC San Diego; and Jeff Sakamoto, University of Michigan.

Funding for this research came, in part, from the National Institutes of Health (R01EB021857, R21HD090662), the National Science Foundation (1644967, 1547005), the California Institute for Regenerative Medicine (RT3-07899) and the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation.

Disclosure: Chen and Zhu have co-founded the startup, Allegro 3D, to commercialize their rapid bioprinting technology.

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