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# Beyond the petri dish

# BEYOND THE PETRI DISH

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The creation of bioengineered organs has slowly made its way to the forefront of medical research. With the ability to construct fully functional organs will come the ability to decrease the current risk of mortality due to the scarce number of viable, obtainable organs. Through various mechanisms, engineers and doctors around the world have joined forces, creating artificial kidneys, arterial grafts, blood pumps, and even artificial hearts. However, despite the large demand for artificial cardiovascular apparatuses, the possibility of regenerating anything remotely related to neuroscience has long seemed unattainable. That was, until a few months ago, when scientists at Tufts University were able to regenerate brain tissue that was strikingly similar to functional brain matter, a feat thought to be impossible.

The problems that scientists faced in the past revolved around the structural complexity of the brain, including the compartmentalization of white matter, the axons of neurons, and grey matter, the neuronal cell bodies. Growing neurons in petri dishes neither allows for the separation of the two components, nor provides an ideal environment for healthy neurons to grow. Even after they optimized healthy neuronal growth, they couldn't maintain the neurons' viability for more than a few days, at best.[3]

The race to create the perfect brain tissue was on. Back in 1998, Dr. James Thomson, director of regenerative biology at the Morgridge Institute at the University of Wisconsin, was the first to isolate human embryonic stem cells. In 2008, collaboration between Thomson and another postdoctoral fellow divulged a mechanism of creating stem cells from adult cells, by inserting four genes exclusively active in embryos. These stem cells, called induced pluripotent stem cells, or iPS, were revolutionary, no human embryonic cells were needed to create them. In late 2013, researchers at the Institute of Molecular Biotechnology in Vienna were able to again genetically program these stem cells as neurons. The question remained how to optimize these neurons' growth, and provide them with an environment ideal for optimal functionality.

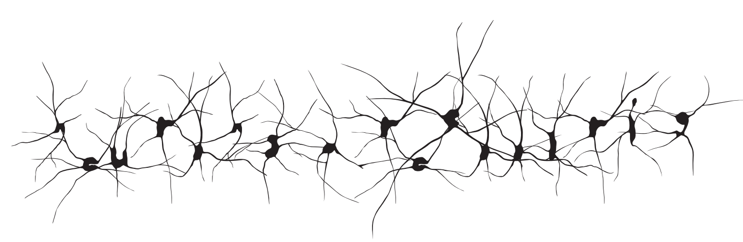
Spearheading a solution to this demanding problem was David Kaplan, Ph.D., and his team at the Tissue Engineering Resource Center at Tufts Boston, whose primary studies focused on the chemical and electrical changes that occur immediately following traumatic brain injuries in patients. In troubleshooting the growth of TBI models, he created the perfect biomaterial mixture of silk protein and a softer, collagen-based gel. The silk protein served as a scaffold onto which neurons could anchor, while the collagen-based gel was able to serve as a media for the axons to grow through. The cell bodies were taken from primary rat cortices, implanted in the mixture alongside structural support components, and were then stacked and sealed into three-dimensional shapes optimal for growth. In order to achieve compartmentalization, the team cut the scaffold model into a donut shape and implanted rat neurons, then filling the hole in the center with the collagen-based gel.

Over time, neurons created functional networks around the pores of the scaffold. The projections from the neuron wound through the center of the gel to synapse with neurons on the opposite side, creating a distinct white matter region in the center, separate from grey matter. Thus, compartmentalization was successful. Although the structure of these neurons seemed to resemble that of a human neuronal network, confirmation that the experimental network could express electrical activity was needed. Upon measurement of activity, the synthesized neural network exhibited electrical activity and responsiveness that resembled human neural circuits. The true test of viability, however, came when the synthesized neural network was treated with particular toxins. Indeed, the activity was altered, and the response was the same as human cerebellar neuron models.

With a man-made system this advanced and brain-like, this breakthrough bears weight in clinical applications, including the ability to study chemical and electrical changes that occur immediately following TBI. "With the system we have, you can essentially track the tissue response to traumatic brain injury in real time," said Kaplan. "Most importantly, you can also start to track repair, and what happens over longer periods of time." If all goes well, and the Kaplan model continues to improve in both longevity and function, a patient with traumatic brain injury may eventually be able to receive an implant of this scaffold. Their still in tact cells can adhere to the scaffold, grow, and contribute to neural tissue regeneration.

The Kaplan Lab is now starting to consider ways to make their creation more "brain-like." The ultimate goal is to create a fully functional cortex with six concentric layers, each populated with a variety of neurons whose functions are able to imitate those of the layers of the human brain. One of the main hurdles the Kaplan lab faces in their next steps is ensuring that the layers are constructed in the proper order and all function in harmony with one another without creating any spontaneous connections. The formation of large and small pathways will be a very complex feat, as any alterations or inconsistencies would alter the representation of the circuitry in the human brain.

The creation of a fully functional neocortex will allow individuals with traumatic brain injuries to essentially re-grow their brain. Before this innovation, when nerve cells were damaged, that was it. Those cells were gone, and they weren't coming back – end of story. A man that falls off a ladder and cuts his head open, lesioning his motor cortex, can regain that part of his brain back, and motor function can be restored. The ability to regain cognitive ability and motor function is priceless. The possibilities are endless. And to think – this all started in a petri dish.



*Untitled.* By Natalie Cherry

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**Anna** is a sophomore in the dual-degree program for Neuroscience and Human Physiology. Her interest in neuro is simple - she is fascinated by how much we don't know about the very thing that controls us.