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Researchers show value of tissue-engineering to repair major peripheral nerve injuries

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Peripheral nerve injury (PNI) is a common consequence of traumatic injuries, wounds caused by an external force or an act of violence, such as a car accident, gun shot or even surgery. In those injuries that require surgical reconstruction, outcomes can result in partial or complete loss of nerve function and a reduced quality of life. But, researchers at Penn Medicine have demonstrated a novel way to regenerate long-distance nerve connections in animal models using tissue-engineered nerve grafts (TENGs). Their work was presented earlier this month at the annual meeting of the American Society for Peripheral Nerve (ASPN) at the Atlantis Resort, Paradise Island, Bahamas.

Nerve cells or neurons work by growing axons, long fibrous projections that connect neurons and form the body's signal transmission and communication structure. Although new neurons are born, the long axon cables that connect them do not regenerate effectively over long distances, yet they are necessary for normal function. Researchers have been working for decades to coax damaged axons to regenerate, with little success in getting enough axons to grow to the right places.

"Despite considerable progress in research and surgical techniques, treatment of peripheral nerve injury remains challenging," said D. Kacy Cullen, PhD, assistant professor of Neurosurgery at the Perelman School of Medicine at the University of Pennsylvania. "Our results demonstrate for the first time some promise for patients who experience a loss of peripheral nerve function as a result of surgery or traumatic injury, including those experienced by members of the military."

TENGs are lab-grown nervous tissue comprised of long axonal tracts spanning neurons. The ability to generate TENGs is based upon a mechanism of axon "stretch growth" established by Douglas H. Smith, MD, Robert A. Groff Professor of Teaching and Research in Neurosurgery and director of the Center for Brain Injury and Repair at Penn. These tissues are not only similar in structure to endogenous nerves, but suitable for transplantation upon removal from custom bioreactors.

There are currently no commercially available nerve grafts capable of consistently facilitating axon regeneration across major nerve lesions, generally considered to be a loss of a nerve segment five centimeters or longer. In one of two new studies, the Penn team demonstrated the success of TENGs in driving axon regeneration across five centimeter nerve lesions in the legs of pigs (in 10 out of 10 subjects). The living TENGs were surgically attached to bridge a missing segment of nerve and were shown to accelerate the regeneration of axons, allowing a population of axons to cross the graft within five weeks. At three months, the bulk of axons had crossed the graft into the existing nerve structures opposite the lesion. Target muscle reinnervation was confirmed via an evoked hoof twitch as early as seven months following TENG repair, and over nine to eleven months post-repair there were steady increases in muscle electrical activity and muscle force generation. Microscopic examination of the regenerated nerves revealed a high density of regrown axons bridging the lesion zone and progressing the length of the repaired nerve to innervate target muscle.

In a separate study, Cullen, Smith and colleagues were able to show the value of living neurons in TENGs to maintain the pro-regenerative capacity of degenerated nerve segments, relevant for even longer peripheral nerve injuries. As time passes after injury, the nerve's capacity for potential regeneration diminishes, so Cullen and team looked to TENGs to "babysit" the support cells – referred to as Schwann

cells (SCs) – that are necessary to facilitate ultra-long distance axon regeneration. The team was able to implant living TENG neurons in a rat model of chronic axotomy – mimicking the state of nerve segments far distal from a primary nerve injury which do not see axons for the many months necessary for axons to regenerate – to prolong the pro-generative capacity of nerves.

SCs initially assumed a pro-regenerative alignment, which was maintained over two to four weeks. However, in the control group (which did not receive TENGs), this pro-regenerative structure was gradually lost, with significant degeneration seen at six to eight weeks and a complete absence of SC alignment by 16 weeks. Conversely, in animals receiving TENGs, surviving graft neurons were observed, as well as graft axon penetration into the nerves and interaction with host SCs. With TENG treatment, pro-regenerative host SCs were maintained to at least 16 weeks post-axotomy, demonstrating the promise of living axonal constructs to maintain the regenerative capacity in the distal nerve segment.

The team is currently assessing the ability of their unique tissue-engineering based bridging strategy together with their babysitting strategy in an even more challenging peripheral nerve injury model in pigs. Ultimately, the Penn research team is confident that this joint approach may provide functional recovery following currently untreatable peripheral nerve injuries, allowing full limb function and sensation to improve the quality of life for afflicted patients.

The studies were completed in collaboration with Axonia Medical, Inc., of Kalamazoo, Michigan and funded jointly by Axonia Medical and the Armed Forces Institute of Regenerative Medicine.

Axonia Medical was founded by Dr. Smith through PCI Ventures' Upstart program, a virtual incubator dedicated to supporting technology

commercialization within the Penn community. Since 2010, Upstart has worked with over 100 faculty and staff members to form and launch new companies based on selected inventions and innovative technologies. PCI Ventures is part of the Penn Center for Innovation (PCI), the University of Pennsylvania's commercialization organization.

Drs. Smith and Cullen are inventors on multiple patents licensed to Axonia and hold equity in the company, from which they may benefit financially. They also receive sponsored research funding from Axonia.

Provided by University of Pennsylvania