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Spinal cord regeneration enabled by stabilizing, improving delivery of scar-degrading enzyme

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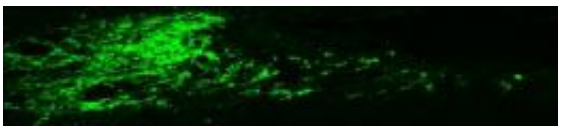

This image shows the extent of new nerves (green) that regenerated after treatment with the enzyme. Credit: Image courtesy of Ravi Bellamkonda

Researchers have developed an improved version of an enzyme that degrades the dense scar tissue that forms when the central nervous system is damaged. By digesting the tissue that blocks re-growth of damaged nerves, the improved enzyme - and new system for delivering it - could facilitate recovery from serious central nervous system injuries.

The enzyme, chrondroitinase ABC (chABC), must be supplied to the damaged area for at least two weeks following injury to fully degrade scar tissue. But the enzyme functions poorly at body temperature and must therefore be repeatedly injected or infused into the body.

In a paper published November 2 in the early edition of the journal Proceedings of the National Academy of Sciences, researchers describe how they eliminated the thermal sensitivity of chABC and developed a delivery system that allowed the enzyme to be active for weeks without

implanted catheters and pumps. This work was supported by the National Institutes of Health.

"This research has made digesting scar clinically viable by obviating the need for continuous injection of chABC by thermally stabilizing the enzyme and harnessing bioengineered drug delivery systems," said the paper's lead author Ravi Bellamkonda, a professor in the Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University.

At physiological body temperature, chABC enzyme loses half of its enzymatic activity within one hour and their remaining functionality within three to five days. To thermostabilize the enzymes, Bellamkonda, Emory University cell biology associate professor Robert McKeon and Georgia Tech graduate student Hyun-Jung Lee mixed the enzyme with the sugar trehalose. The result -- the enzyme's activity was stabilized at internal body temperature for up to four weeks during in vitro tests.

The researchers then used a lipid microtube-hydrogel scaffold system to deliver the thermostabilized enzymes into animals via a single injection. The scaffold provided sustained delivery of the enzyme for two weeks, with the microtubes enabling slow release and the hydrogel localizing the tubes to the lesion site. This delivery system also allowed the enzyme to diffuse deeper into the tissue than did catheter delivery.

In animal studies, the enzyme's ability to digest the scar was retained for two weeks post-injury and scar remained significantly degraded at the lesion site for at least six weeks. The researchers also observed enhanced axonal sprouting and recovery of nerve function at the injury site when the thermostabilized enzyme was delivered.

The delivery system also enabled the combination of therapies. Animals treated with thermostabilized chABC in combination with sustained

delivery of neurotrophin-3 -- a protein growth factor that helps to support the survival and differentiation of neurons -- showed significant improvement in locomotor function and enhanced growth of sensory axons and sprouting of fibers for the neurotransmitter serotonin.

"These results bring us a step closer to repairing spinal cord injuries, which require multiple steps including minimizing the extent of secondary injury, bridging the lesion, overcoming inhibition due to scar, and stimulating nerve growth," added Bellamkonda, who is also deputy director of research for GTEC, a regenerative medicine center based at Georgia Tech and Emory University, and a Georgia Cancer Coalition Distinguished Cancer Scholar.

Source: Georgia Institute of Technology