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“Dancing Molecules” Successfully Repair Severe Spinal Cord Injuries

Northwestern University researchers have developed a new injectable therapy that harnesses “dancing molecules” to reverse paralysis and repair tissue after severe spinal cord injuries. In a study, which included research at the U.S. Department of Energy’s Advanced Photon Source (APS), the team administered a single injection to tissues surrounding the spinal cords of paralyzed mice. Just four weeks later, the animals regained the ability to walk.

By sending bioactive signals to trigger cells to repair and regenerate, the breakthrough therapy dramatically improved severely injured spinal cords in five key ways: (1) the severed extensions of neurons, called axons, regenerated; (2) scar tissue, which can create a physical barrier to regeneration and repair, significantly diminished; (3) myelin, the insulating layer of axons that is important in transmitting electrical signals efficiently, reformed around cells; (4) functional blood vessels formed to deliver nutrients to cells at the injury site; and (5) more motor neurons survived. After the therapy performs its function, the materials biodegrade into nutrients for the cells within 12 weeks and then completely disappear from the body without noticeable side effects. This is the first study in which researchers controlled the collective motion of molecules through changes in chemical structure to increase a therapeutic’s efficacy.

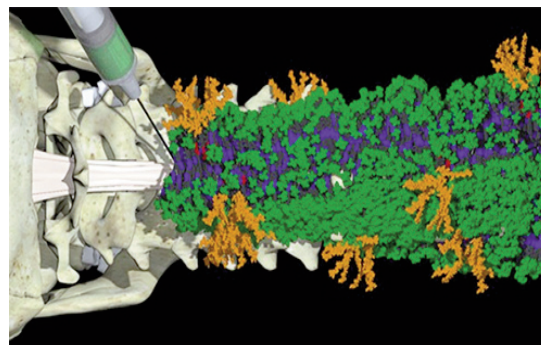
“Our research aims to find a therapy that can prevent individuals from becoming paralyzed after major trauma or disease,” said Northwestern’s Samuel I. Stupp, professor of Materials Science and Engineering, Chemistry, Medicine and Biomedical Engineering and founding director of the Simpson Querrey Institute for BioNanotechnology, who led the study.

The secret behind Stupp’s new breakthrough is tuning the motion of molecules, so they can find and properly engage constantly moving cellular receptors. Injected as a liquid,

the therapy immediately goes into a complex network of nanofibers that mimic the extracellular matrix of the spinal cord. By matching the matrix’s structure, mimicking the motion of biological molecules, and incorporating signals for receptors, the synthetic materials are able to communicate with cells. Stupp and his team found that fine-tuning the molecules’ motion within the nanofiber network to make them more agile resulted in greater therapeutic efficacy in paralyzed mice. They also confirmed that formulations of their therapy with enhanced molecular motion performed better during in vitro tests with human cells, indicating increased bioactivity and cellular signaling.

Once connected to the receptors, the moving molecules trigger two cascading signals, both critical to spinal cord repair. One prompts the long tails of neurons in the spinal cord, called axons, to regenerate. Similar to electrical cables, axons send signals between the brain and the rest of the body. Severing or damaging axons can result in the loss of feeling in the body or even paralysis. Repairing axons, on the other hand, increases communication between the body and brain. The second signal helps neurons survive after injury because it causes other cell types to proliferate, promoting the regrowth of lost blood vessels that feed neurons and critical cells for tissue repair. The therapy also induces myelin to rebuild around axons and reduces glial scarring, which acts as a physical barrier that prevents the spinal cord from healing.

While this therapy could be used to prevent paralysis after major trauma (automobile accidents, etc.), as well as from diseases, Stupp believes the underlying discovery — that “supramolecular motion” is a key factor in



A new, injectable therapy forms nanofibers with two different bioactive signals (green and orange) that communicate with cells to initiate repair of the injured spinal cord. Illustration by Mark Seniw

bioactivity — can be applied to other therapies and targets. This fundamental discovery about controlling the motion of molecular assemblies to enhance cell signaling could be applied universally across biomedical targets.

The team employed a wide range of experimental techniques to characterize the synthetic materials, including nuclear magnetic resonance imaging; transmission electron microscopy; cryogenic transmission electron microscopy; scanning electron microscopy; circular dichroism spectroscopy; Fourier transformed infrared spectroscopy; and synchrotron solution small-angle x-ray scattering, which was carried out at the DuPont-Northwestern-Dow Collaborative Access Team x-ray beamline station 5-ID-D at the APS.

See: Z. Álvarez, A. N. Kolberg-Edelbrock, I. R. Sasselli, J. A. Ortega, R. Qiu, Z. Syrgiannis, P. A. Mirau, F. Chen, S. M. Chin, S. Weigand, E. Kiskinis, S. I. Stupp, “Bioactive scaffolds with enhanced supramolecular motion promote recovery from spinal cord injury,” *Science* **374**, 848 (2021). DOI: 10.1126/science.abh3602

CALL FOR APS GENERAL-USER PROPOSALS

The Advanced Photon Source is open to experimenters who can benefit from the facility’s high-brightness hard x-ray beams.

General-user proposals for beam time during Run 2022-2 are due by March 4, 2022.

Information on access to beam time at the APS is at http://www.aps.anl.gov/Users/apply_for_beamtime.html or contact Dr. Dennis Mills, DMM@aps.anl.gov, 630/252-5680.

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