

Traditional Chinese medicine in modern healthcare

Integrating both worlds



Integrating TCM and western medicine
for cancer treatment

Are we close to finding a cure for HIV

Diseases in ageing



Injuries to the spinal cord can cause permanent paralysis and even lead to death, with little or no hope of regaining lost functions once the trauma has occurred. News of my spinal cord research first came to prominent public awareness in the 1980's with a front page story in The New York Times entitled, "Rat Nerves Repaired and Rejoined with Spine"¹ which chronicles our presentation at the annual Society for Neuroscience meeting, the first time crushed peripheral nerves were successfully regenerated back into the spinal cord.

Regeneration of the nerves inside the spinal cord itself after injury, a far more complex challenge, is coming closer to fruition as NervGen Pharma, a Canadian company I have partnered with, is tasked with developing my discoveries with the goal of conducting human clinical trials. My team at Case Western Reserve University medical school and I are working to understand why nerves that are damaged through spinal injury do not regenerate and to identify non-invasive, easy-to-administer strategies that can promote robust functional recovery.

My team and I found that this was possible, even long after the damage had occurred. To demonstrate this, we conducted a simple experiment.

First, we purified in cell culture, fully adult nerve cells that were genetically prelabelled with a fluorescent protein so that the cells could be easily visualised. The first step served not only to harvest the nerve cells but also to cut all the axons away from the cell bodies that, nevertheless, remain alive.

Next, we collected the axon-less nerve cell bodies and very gently re-implanted them into the pre-lesioned spinal cord of an unlabeled adult host animal so as not to create any damage or scarring at the implant site.

It was a huge surprise to the scientific community when we found that axons could, indeed, grow robustly in the spinal cord and reach out quickly over long distances. However, we also found that when the new axons reached the area of severe lesion damage and scarring, they stopped growing abruptly and started to deteriorate.

Emerging treatments for spinal cord damage

Can damaged nerves regenerate? by Dr. Jerry Silver

Can damaged nerves regrow?

My research began by investigating whether it was possible for an adult nerve cell to regrow within the environment of the damaged adult spinal cord. It had long been thought that this was impossible.

Nerve cells consist of elaborate long extensions (axons) that grow out from the main cell body. It is these axons that make the connections called synapses with other nerve cells, and it is the axons within the spinal cord that are severed when the bony spine is impelled into the cord when it is violently broken. Axons can be incredibly lengthy, some reaching almost the entire span of our bodies.

One challenge for researchers working in the field of spinal injury was to determine whether damaged axons have the intrinsic capacity (i.e., a strong enough growth motor) so that, in principle, they had at least the potential to replace the damaged ones.

We suspected that there was some sort of chemical produced by the scar tissue around the break itself that was hostile to axons and stops even exuberantly growing new ones from extending further.

Understanding scar tissue

Inflammatory damage to the spinal cord after the initial injury can continue to spread outward from the lesion epicenter into surviving tissue to cause further loss of function. The development of scar tissue encases the lesion core and plays an important role in the protection of the healthy nerve cells from further harm.

However, it is now clear that once the important task of protection is complete, the same structure that offered protection soon after the injury then develops into a barrier to the regrowth of the cut axons.



My team and I set out to identify the culprit in the scar that was stopping axon regrowth, and then see what we could do to reduce or overcome the growth inhibitory effect of the scar, once it had mitigated the danger of the initial injury. As we had already shown that axons can regrow once past or through the scar, we understood that this could be the key to returning or improving function to the injured area.

We found a particular family of potentially inhibitory molecules that were being produced in the scar tissue, and that when newly regenerating axons encountered them, it caused the growing tips of the axons to become so tightly stuck (similar to a fly on flypaper) that they could no longer move forward. These sticky molecules are known as chondroitin sulphate proteoglycans (CSPGs).

Bridging the scar tissue and repairing the nerve damage

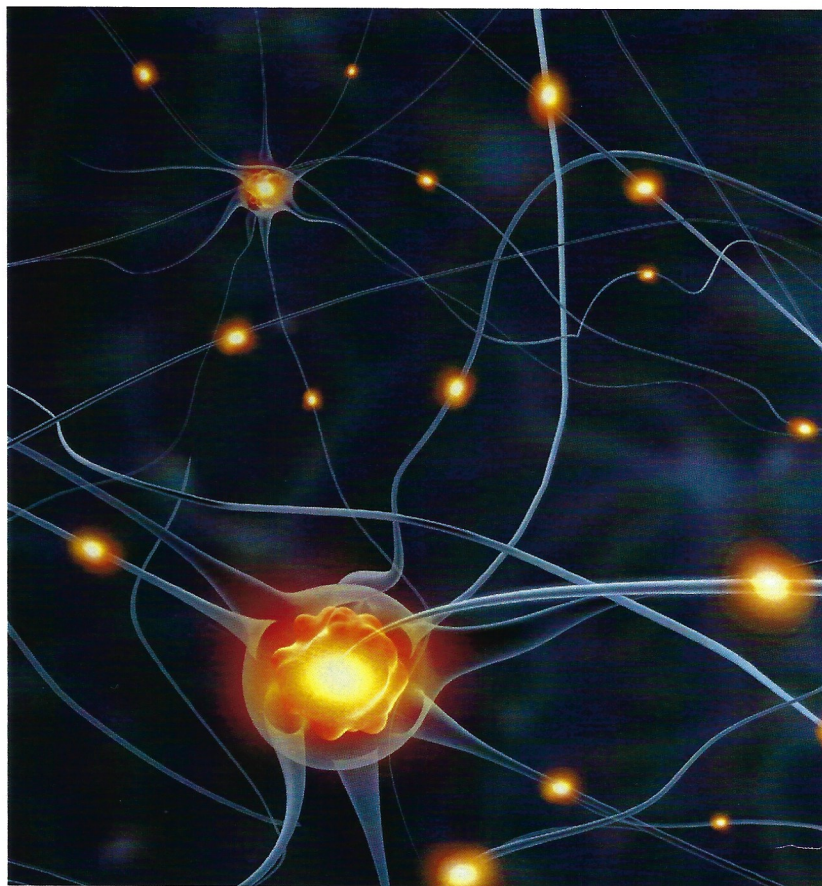
Having identified the culprit that stops the growth of axons near the scar tissue, our next step was to find a way to selectively eliminate CSPGs. My team and I investigated the use of a special enzyme (chondroitinase) that consumes the CSPGs once injected into the cord, stopping them from having such detrimental effects.

Using these enzymes, we found success in re-growing axons and improving function in animals that had problems with their limbs, bladder and diaphragm (which was hampering them from breathing). As these are common and potentially fatal conditions in humans following paralysis, the improvements in these areas were especially promising.

The use of enzymes to breakdown CSPGs has been widely investigated, with researchers attempting to optimise various factors, including the timing of administration and appropriate amount of targeted physical therapy. Benefits have been shown in many different animal models, including non-human primates and at long chronic timepoints post-injury.

However, problems still exist as the enzyme is of bacterial origin, must be injected directly into the spinal cord, and acts only over a very short distance. Supplementary treatments may also be required to ensure optimal spread of the enzyme and that the regrown axons go on to make the right connections. Studies are ongoing by a variety of research teams around the world to overcome these challenges.

To overcome the need to directly inject a molecule into the spinal cord, my colleagues and I tested a novel systemic approach to see what effect it would have on axon regrowth. We identified a receptor molecule called protein tyrosine phosphatase sigma ($PTP\sigma$) on the axons that acted as a 'helper' to cause CSPGs to be overly adhesive. This newly discovered $PTP\sigma$ receptor provided a way for the axons to detect CSPGs, signaling them to stop and become entrapped.



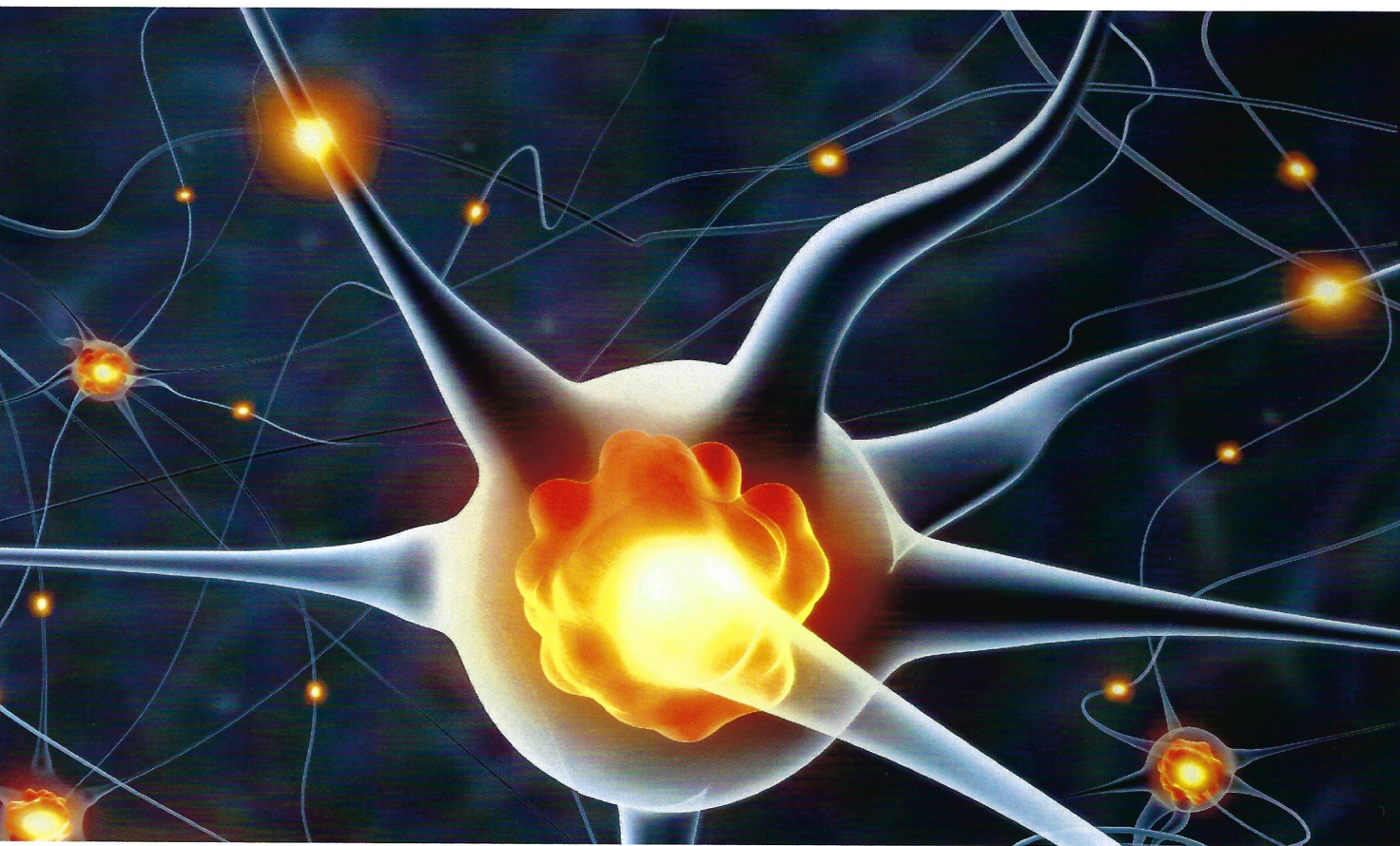
We developed a molecule that negates this signal, allowing the regenerating axons to ignore and bypass CSPGs. When the molecule, known as intracellular sigma peptide (ISP), was administered noninvasively via injections under the skin, it interfered with the CSPG/receptor signaling within the spinal cord, allowing for robust axon regrowth resulting in greatly improved bladder function and improved locomotion in animal models of spinal cord injury.

Beyond spinal cord injuries

In working to understand what controls the regrowth of axons after spinal cord injury, we also discovered several medical conditions involving nerve injury where scarring also occurs and CSPGs impact axon regrowth.

Axons that are severed in the peripheral nerves, such as those found in the arms and legs, do have a limited capacity to regrow. However, when the lesion is severe and closer to the body, a CSPG laden scar also hinders recovery because damaged peripheral axons also upregulate the same $PTP\sigma$ receptor. My team and I were able to show that ISP can help heal injuries to peripheral nerves by speeding up the growth of injured nerves across and beyond the scar to the muscles they control.

Multiple sclerosis (MS) is an inflammatory mediated nervous system disease that affects both the brain and the spinal cord. It damages the myelin, the material that wraps



and insulates the nerve cells. The loss of myelin slows down or blocks the electrical message that travels between the brain and the body, leading to MS.

Again, CSPG filled scar-like plaques that form in the damaged areas play a critical role in preventing recovery by blocking migration of immature, potential myelin-forming stem cells that exist in huge numbers within the central nervous system. In animal models, we recently found that ISP promotes the migration of the stem cells into the lesion with return of the myelin sheath leading to functional recovery.

We also teamed up with investigators who study scars that form after heart attack. When a heart attack occurs, sympathetic axons that control the heart rate are damaged in the vicinity of the forming scar.

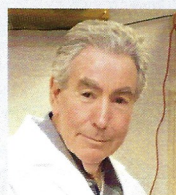
Just like in the spinal cord, these cut axons die back away from the lesion core and their regenerating tips become entrapped within the outer edges of the scar, causing irregular heartbeats known as arrhythmias which can be lethal. In animal models of heart attack, systemic treatment with ISP promoted new growth of the damaged axons back into the scar, stopping the arrhythmias.

In concert with NervGen Pharma, my team and I are creating innovative solutions for the treatment of nerve damage. Together, we have identified an ISP analogue known as NVG-291 to treat human patients. It is our hope

that this technology can improve the lives of the many people living with debilitating nerve damage. **APBN**

Reference

1. www.nytimes.com/1987/11/14/us/rat-nerves-repaired-and-rejoined-with-spine.html



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