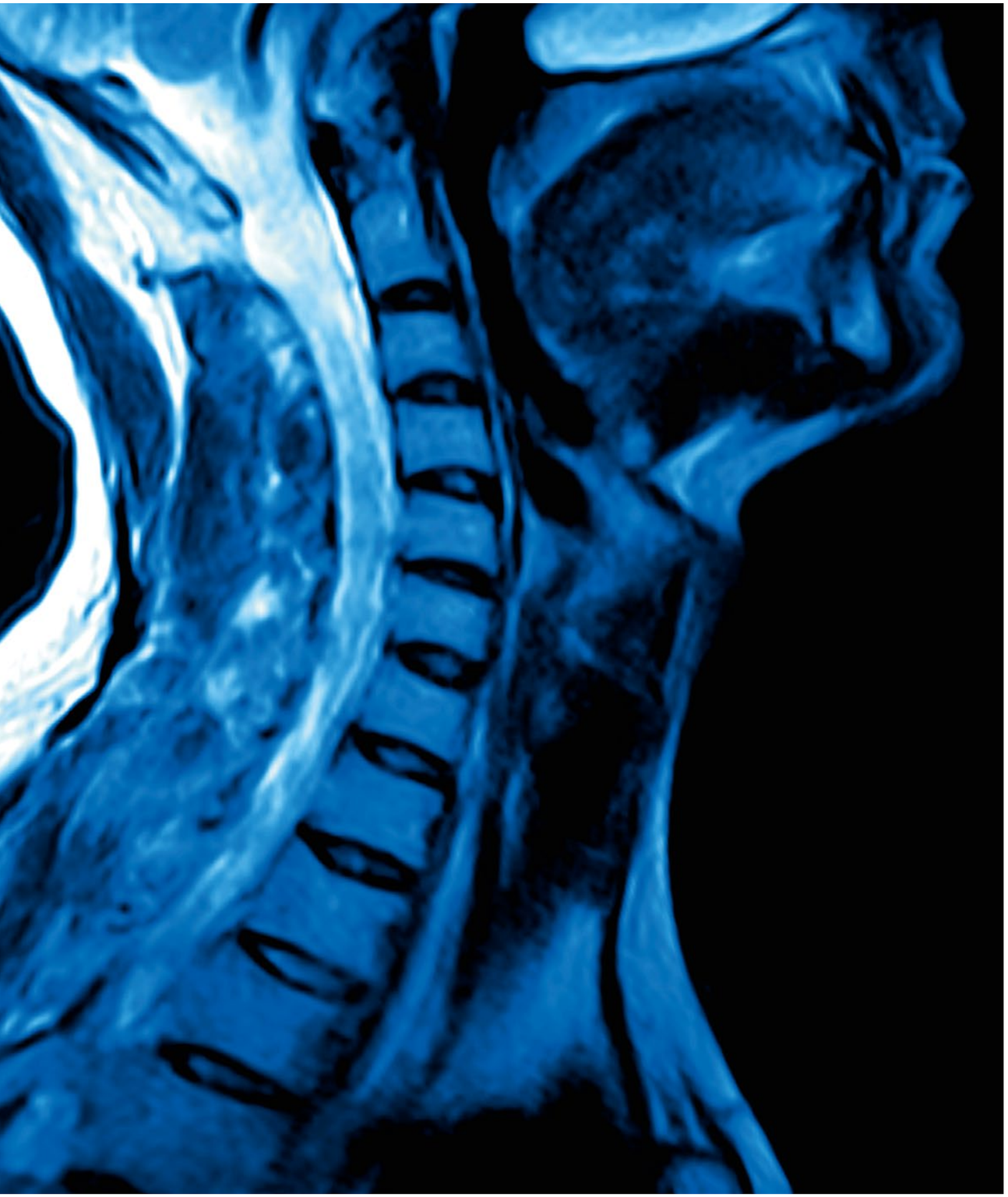

Cell transplantation for neural repair: improving outcomes following spinal cord injury

Dr Paul J Reier of the University of Florida began working in spinal cord repair research over 30 years ago. He and his former postdoctoral fellow, **Dr Michael Lane** of Drexel University, Philadelphia, are pursuing ways to improve outcomes for those suffering from spinal cord injury. They are currently exploring a promising experimental cell therapy approach, which has proven clinical safety and feasibility in both academic and biotechnology sectors.

Injuries to the spinal cord affect over 180,000 people worldwide each year. Their impact can be devastating, as the connections made by the nervous system between the brain and the rest of the body are disrupted.

A LIFE-CHANGING DIAGNOSIS

The majority of spinal injuries occur in the neck (~60% in the USA), mostly at the fourth and fifth spinal level. Troublingly, recent years have seen an increase in injuries at the higher, first to third, spinal level. These 'cervical' injuries can have particularly serious consequences, including pain, impaired use of and sensation in the limbs, effects on bladder and bowel function and even life-threatening impact on breathing. In addition to these disabilities are the tremendous lifetime costs of treatment and support, which can run into millions of dollars.

The changes that result from a spinal injury are highly variable in nature, extent, and degree of reversibility, making this a complex condition to treat. While the initial trauma results in cell death at and around the injury site, this is followed by a chain of physiological reactions which, in turn, leads to further cell loss. This includes the two main types of spinal tissue: grey and white matter (Figure 1 overleaf).

Grey matter forms the centre of the spinal cord and is composed mostly of cells called neurons, which are part of networks that relay sensory information from the body to the brain, and motor signals from the brain to the muscles. Other neurons in grey matter relay signals between neuronal networks at different levels of the spinal cord. On the other hand, white matter, running along the outside of the spinal cord, is composed of nerve fibres or 'axons' that are responsible for transmission of sensory signals to the brain and, conversely, motor commands from the brain to various levels of the spinal cord. Damage to those fibres accounts for paralysis and other functional deficits below the region of spinal cord injury.

Once believed to be an incurable condition, a wealth of laboratory and clinical information has demonstrated the potential for restoring useful functions after spinal cord injury without requiring the regrowth of injured axons. Researchers agree, however, that no single treatment will be sufficiently effective; instead a combination of complementary approaches will be needed. These will include physical rehabilitation, drugs to help prevent progressive tissue damage or promote repair, electrical stimulation, and robotics. The research being pursued by Drs Reier and Lane, however, focuses on perfecting transplantation techniques for immature nerve cells – commonly referred to as neural progenitors or stem cells.

HARNESSING NATURAL HEALING

After a spinal cord injury, many patients undergo some degree of spontaneous recovery and behavioural adaptation, resulting in partial restoration of function. This is attributed to 'neuroplasticity' – functional and/or physical changes in nerve cells and their connections as a response to environmental stimuli such as injury. However, the extent of rehabilitation that can be achieved by natural neuroplasticity is both variable and limited. One aim of Dr Reier's and Dr Lane's collaboration is to develop therapies that harness and enhance the body's natural neuroplastic potential. The current limit to plasticity in spinal cord injury is which tissues and connections have been spared by the trauma. If some repair of the spinal cord could be achieved, then there would be the potential for greater plasticity.

Drs Reier and Lane are therefore investigating how communication between the brain and spinal cord might be restored by introducing new connections at sites of tissue damage. Through the use of 'neural precursor cells' (immature cells similar to stem cells), the team hope to provide a meaningful degree of recovery.

Unlike embryonic stem cells, which may develop into any cell type in the body, neural precursor cells can become only neurons or glia. They therefore provide targeted building blocks for generating new spinal cord tissue. In a damaged spinal cord, neural precursor cells are envisioned to have potential for restoring communication across injury sites. By introducing neurons that can serve as functional bridges or relays (Figure 2 overleaf), they can effectively bypass any white matter pathways which do not regenerate.

A LONG HISTORY OF SUCCESS

Dr Reier and colleagues first started working in spinal cord repair in the 1980s, and his laboratory studies tested the possibility of repairing damaged spinal cords with transplanted fetal spinal cord tissue. At the time, despite rapidly growing interest in the use of fetal tissue for treating Parkinson's disease, their proposition of utilising this material for treating spinal cord injury was met with scepticism. Nevertheless, those early studies demonstrated the primary requirements of this cell therapy: that embryonic cells could survive in, and integrate with, a damaged spinal cord. Moreover, they showed that even a relatively small number of

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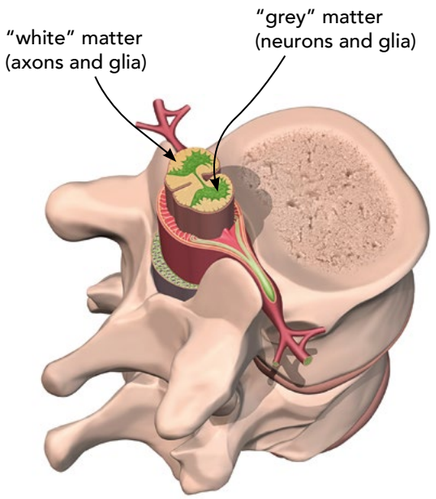

Figure 1

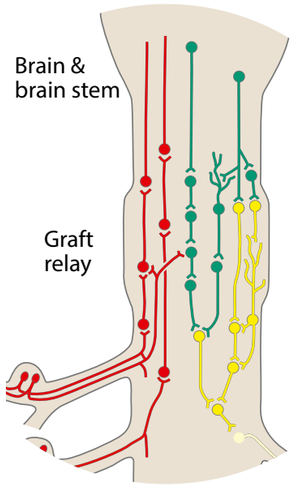

Figure 2

cells could grow, multiply and differentiate to replace damaged grey matter.

By the mid-1990s, Dr Reier's research had progressed to demonstrating the safety and feasibility of transplanting embryonic nerve tissue in a small number of people with spinal cord injuries. This was the first clinical translation of its kind in the United States, and only second worldwide to a single patient study conducted in Russia. This technique has now been reproduced by several others in both academic and biotechnological settings, using a variety of proprietary cell lines. The experimental and clinical replication of this treatment demonstrates the promising nature of the approach. Recently, other laboratories have also reported independent evidence of the potential to establish novel, functional relays by transplantation of neural precursor cells. However, significant technical and biological challenges remain.

NEW CHALLENGES, NEW SOLUTIONS

One major issue is how to encourage the formation of new neural connections in useful directions, as the current random growth of nerve fibres between the host and implanted tissues gives variable functional results. Modern scientific methods, including genetic modification, now permit tracking the distribution of neural precursor cells after transplantation and provide optimised conditions for selecting the most desired cell types for transplantation. There is also evidence that electrical stimulation of circuits silenced by spinal cord injury can promote neural activity, which may attract nerve fibre growth in a predetermined and functionally-relevant direction. Drs Reier and Lane are currently exploring new ways to incorporate advances in neurobiology and neuroengineering to optimise cell-based approaches for functional repair of the spinal cord. One way to incorporate recent technologies is to use optogenetic methods to stimulate transplanted cells. This very powerful method allows scientists to make donor neurons more active simply by shining light on them. Physiologically-patterned electrical activation of host and graft tissue may also enable more functionally relevant patterns of connectivity to be formed.

The restoration of sensory and motor abilities are what matters most to injured people, so promoting repair and neuroplasticity both aim to address this common goal. Putting an injured spinal cord together again to obtain useful, though not necessarily perfect, functions is clearly not a straightforward endeavour. Nevertheless, spinal cord injury research has made tremendous advances over the last three decades – the potential clearly exists for improving patients' quality of life and reducing the spiralling costs of spinal cord injury.

SPACE TO BREATHE

Dr Reier's and Dr Lane's current research focuses on using cell therapy to treat one of the most devastating consequences of cervical injury to the spinal cord (at the level of the neck) – its impact on breathing. Restoring respiratory function is clearly very clinically relevant, but is also an important proof-of-concept because the spinal circuitry involved with breathing is anatomically simple when compared with other networks involved in motor function. In addition, relatively short distances of repair would likely be necessary to restore communication between respiratory centres in the brain and the spinal circuit controlling the diaphragm (the primary muscle for breathing).

THE LONG ROAD AHEAD

Drs Reier and Lane emphasise that the work is still at an experimental stage. Cell therapy techniques are both logistically feasible and procedurally safe, but there is still a great deal that scientists do not understand about how to maximise the use of cells for therapy. Several cell types have shown promise and some are now undergoing clinical trials, but continued research effort is required to ensure that the correct cells are being used, at the right time, in the right dose, and for the right purpose. As Dr Reier puts it: "Encouraging findings have been obtained, but there remains a great need to better understand the biology of this approach."

Challenges include practical and ethical considerations surrounding the source of neural precursor cells; the ability to culture sufficient numbers of cells for transplant; optimising the timing and delivery of the transplant procedure; and ensuring that the possibility of adverse outcomes is minimal. The main goal of the research at present is simply to bridge the gap between discovery phase and clinical application by enhancing promising research strategies and developing effective protocols for treatment.

Both Dr Reier and Dr Lane are convinced that cell therapy will, in the long term, become an essential part of the toolkit for treating spinal cord injury, alongside drug treatments, engineering strategies and physical therapy. The remarkable potential of transplanted neural precursor cells to build upon neuroplasticity and aid functional recovery from spinal cord injuries will help to improve recuperation times and, ultimately, quality of life.

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Q&A

How does a typical spinal injury progress from the initial trauma to the chronic phase?

There is a cascade of molecular and cellular events that follow a traumatic spinal cord injury, which promote inflammation, attract other cells to the site of injury, and initiate a 'wound-healing' like response. This removes cellular debris from the injury site, but may also contribute to further tissue loss and limit the potential for plasticity and repair.

What exactly is meant by 'neuroplasticity' and why is it important in this field?

There are many ways to define this word. To address this we default to a definition that we proposed in a recent research paper of ours by Hormigo et al (2017): "Neuroplasticity can be defined as the ability of the nervous system to make anatomical and functional changes that lead to persistent alterations in sensory-motor function. These changes can be mediated by a range of factors, such as prior synaptic activity (e.g., activity-dependent learning), persistent physical activity (e.g., rehabilitative training), or injury (e.g., SCI). Furthermore, this plasticity can also occur 'spontaneously' (without external interference) following traumatic SCI. An important goal for SCI treatments is that they either: i) do not impair spontaneously occurring, beneficial plasticity, ii) limit any detrimental aspects of plasticity (e.g., spontaneously occurring pain), or even more preferably, iii) act synergistically to enhance intrinsic neuroplasticity and optimize the extent of lasting functional improvement."

How do neural precursor cells help stimulate the spinal cord to repair itself?

As developing cells of neural lineage – which are therefore destined to become cells of the nervous system – they serve as building blocks for repair. They can replace cells that are lost, they are capable of releasing molecules that promote growth and limit inflammation, and they provide a substrate for growth of host axons (where there might otherwise be a scar or a cavity).

What improvements can cell therapy bring to the life of a spinal injury patient?

The extent of improvement that can be achieved will depend on where and when the cells are transplanted, which cells are used, which survive transplantation, whether the host neurons connect with them, and how donor neurons become integrated with host cells. The molecules they release may limit cell loss if transplantation occurs early on, which may also limit the extent of functional loss a patient may encounter. If the appropriate neurons survive and connect with the correct neuronal pathways within the injured spinal cord, they can enhance motor or sensory functional outcomes. It is likely, however, that no cellular therapy alone will provide profound recovery from spinal cord injury though, so it is important to understand what cells are used and how other treatments may optimise therapeutic potential.

What is the biggest challenge to putting cell therapy into practice for treating spinal cord injuries?

There are many technical and biological issues; not just one. Optimising the formation of useful, new connections is clearly one challenge we are now keenly interested in resolving. Beyond that, there is always the issue of developing transplantation strategies without risking adverse outcomes such as pain.

Detail

RESEARCH OBJECTIVES

Drs Reier and Lane are especially interested in optimising regenerative strategies, such as neurotransplantation, to effectively promote spinal cord repair.

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BIO

Dr Paul J Reier obtained his PhD in Anatomy from the Case-Western Reserve University in 1972. He is currently a Professor and Eminent Scholar at the University of Florida, where Dr Michael Lane joined his laboratory as a postdoctoral fellow in 2006. Dr Lane subsequently advanced to Research Assistant Professor there three years later, and then in 2013 moved to become an Assistant Professor at Drexel University, Philadelphia.

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