The Research Strategy

The goal of *Spinal Research* is to develop treatments to cure spinal cord injury and we have an international reputation for funding some of the best experimental and clinical studies in this area. One reason for this is the group of expert scientists and clinicians who sit on the charity's Scientific Committee, guiding all our decisions on funding. Another is our Research Strategy. The Research Strategy has been developed by some of the best minds in neuroscience. Using the Strategy, the Scientific Committee identify key areas of research that are likely to deliver meaningful results.

The first Research Strategy was published in 1996, and the second in 2000. It has now been updated again and takes account of significant advances made in the past few years. These advances mean that two additional areas of research are identified in the list of promising approaches - Combinatorial therapies and Complementary therapies.

The 2006 Research Strategy identifies seven particularly promising research areas. It also outlines how research might be targeted most effectively by developing the infrastructure needed for effective collaborative research and clinical trials.

Research targets identified in the 2006 Research Strategy

- Neuroprotection
- Factors that either inhibit or promote growth
- Guiding regrowth
- Spared spinal cord cells and fibres
- Cell-based and gene-based therapies
- Combinatorial therapies
- Complementary therapies

The themes described in the Research Strategy are deliberately wide-ranging, and individual views on the relative importance of these approaches are likely to differ. By promoting this discussion, *Spinal Research* hopes to encourage debate between scientists, clinicians and patients about the many issues that surround this area of research.

The full Research Strategy is published in the journal *Spinal Cord* (http://www.nature.com/sc/journal/vaop/ncurrent/abs/3101963a.html)

Target 1. Neuroprotection

Minimising the deleterious effects of early trauma, inflammation and scar tissue

Neuroprotection aims to minimise the effects of early tissue damage and inflammation. These processes are part of the body's natural response to injury that, unfortunately, enlarge the size of the lesion and the resulting paralysis in the days after the initial injury. Neuroprotective strategies aim to contain the injury and prevent it from spreading, so minimising the overall loss of function.

Because many of the mechanisms responsible for these secondary processes are unknown, a high-priority target identified in the Research Strategy is to increase the basic understanding of the events involved soon after the spinal cord is damaged in humans. These events include immune responses and the formation of scar tissue. Increasing the basic understanding of how they impact on spinal cord injury is vital if we are to develop newer, more powerful therapies.

The Research Strategy also recognizes that spinal cord injury should not be considered in isolation. There are several common elements in the processes associated with damage to the spinal cord and with brain damage that follows stroke and head trauma, and potential neuroprotective therapies have already been tested in clinical trials following stroke. Therefore, as well as developing new therapies, it is important to encourage researchers from other fields to explore how their expertise might apply to spinal cord injuries. For example, a strategy that shows promise in stroke victims might also reduce cell damage following a spinal cord injury.

- Analyze in detail the natural injury-related responses that occur following different types of spinal cord injury, and the contribution each makes to the functional impairment in model injuries
- Fund research into assessing the extent of early trauma, inflammation and scar formation in humans
- Use this knowledge to promote research into reducing the deleterious effects of human injury

Target 2. Factors that either inhibit or promote growth

Many factors are now known to block the growth of nerve fibres in the spinal cord following injury. Nogo, the first of these to be identified, is present in the myelin sheath that normally surrounds nerve fibres and enables them to transmit nerve impulses. Many other inhibitory factors have now also been discovered, including chondroitin sulphate proteoglycans (CSPGs), which accumulate in the scar tissue at the injury site, and other molecules such as ephrins and semaphorins.

Inhibitory factors act at the surface of nerve cells to cause changes deep within the fibres that block regrowth. Although the details are still being worked out, it is clear that many different inhibitory factors cause similar if not identical changes inside the nerve fibres themselves. Therefore, the Research Strategy highlights the need to find out more about these common inhibitory pathways and target these for new therapeutic approaches.

In contrast to inhibitory factors, several growth factors boost nerve growth in the spinal cord and elsewhere. Transplanting genetically modified cells that secrete high concentrations of nerve growth factors into the injury site enhances regeneration. Having identified several of the genes and proteins that are responsible for this effect, scientists are now working to develop strategies that will benefit injured patients; an effective combination that enhances positive factors and reduces negative ones is an attractive goal for current research.

Based on this assessment, the Research Strategy highlights three categories of research into inhibitory and facilitatory molecules

- Discover molecules that contribute to inhibition and facilitation of axon growth
- Produce reagents that either counteract inhibition or increase facilitation
- Investigate how other approaches, such as cell- and gene-based therapies, interact with inhibitory/facilitatory molecular mechanisms

Target 3. Guiding regrowth

Experimentally, researchers have successfully used growth factors to stimulate significant regrowth of nerve fibres following injury. They are also developing synthetic guidance channels that provide a ‘bridge’ along which the regenerating fibres can grow. However, it is not sufficient merely to promote regrowth: to function effectively, regrowing fibres must also make connections with appropriate targets beyond the injury site because indiscriminate connections might be ineffective or, even, lead to unwelcome problems such as spasticity and pain.

The study of how nerve fibres are directed to their correct targets and how the appropriate connections between them are formed is fundamental to many different areas of neuroscience, not just spinal cord injury. The Research Strategy advocates integrating this knowledge into spinal injury studies and promoting research to

- Identify the key growth factors that exert significant effects on the regrowth and connectivity of nerve fibres in the damaged spinal cord
- Identify the mechanisms that control the production of these growth factors to encourage appropriate outgrowth

Target 4. Spared spinal cord cells and fibres

In most cases, injury does not completely destroy the spinal cord, even if it results in complete paralysis and loss of sensation. It is estimated that, patients might still be able to walk provided as few as 10% of nerve fibres in the spinal cord survive. This is encouraging because it indicates that functional recovery might only need a relatively small number of new nerve fibres to cross the lesion site and reconnect with undamaged fibres. With this in mind, it is important to encourage techniques that maintain the health of the spinal cord below the injury as far as possible in preparation for successful interventions.

It is also important to learn how to measure how much remains of spinal cord function and how this can be enhanced most effectively. This requires identifying strategies to strengthen the surviving connections between individual nerve fibres in the spinal cord, as well as how to stimulate the surviving fibres to develop new connections with other fibres. However, it is important that any new connections are helpful – encouraging the wrong sort of connections might increase the pain, called neuropathic pain, and muscle spasms that are experienced by many injured people.

Another aspect to be considered is the role of the brain in processing sensation. Studies have shown that several areas of the brain undergo large-scale reorganization after injury, which might account for the ‘phantom’ sensations that are sometimes associated with spinal cord injury. Therefore, functional recovery after SCI might involve strategies that reorganize brain circuits, as well as regeneration and functional reconnection in the spinal cord.

The Research Strategy highlights the main research areas associated with spared spinal cord cells and fibres

- Establish reliable measurements of how much of the spinal cord remains and its function
- Develop techniques to promote functional reconnection and identify strategies that increase reorganization in the CNS
- Fund research to enhance and modify the function of undamaged connections
- Fund the development of techniques to reduce unwanted effects such spasticity and neuropathic pain

Target 5. Cell-based and gene-based therapies

There has been major progress in both cell therapy and gene therapy in the past few years. Cell-based therapies include transplanting olfactory ensheathing cells (OECs) to encourage regrowth of damaged nerve fibres as well as other types of cells, including stem cells, to replace the tissue that is lost by injury.

Cell-based therapies have the potential to act in several, distinct ways. For example, they are a potential source of growth factors (see Targets 2-4). Transplanted cells such as OECs can also act as a 'bridge' that supports the growth of regenerating fibres. Alternatively, transplanted stem cells have the potential to either provide the myelin needed to surround regenerating nerve fibres or develop into functional nerve fibres to replace those damaged by injury. Although this latter approach might seem a particularly attractive strategy, the use of stem cells is still relatively new and early studies document some potential disadvantages. For example, transplanting neural stem cells can lead to an increase in pain. Although this is overcome by forcing stem cells to form non-neural cells before transplantation, it is a reminder that the adverse effects of cell therapies should be examined.

Gene therapy is a powerful technique that has the potential to block the production of inhibitory factors and to increase the production of growth factors. Gene-based therapies have been developed in which the DNA that produces a particular growth factor (or other protein) is added directly to cells in the spinal cord. Alternatively, transplanted cells can be genetically modified before transplantation.

To progress in the area of cell and gene therapy, the Research Strategy recommends funding research that will

- Determine which cell types are most effective in restoring defined spinal cord functions such as myelin repair and regeneration, and generate a usable source of these cells
- Developing improved markers to study cell transplantation, especially those that are compatible with non-invasive imaging techniques
- Optimise when and where cells are transplanted, and the number of cells needed for successful repair
- Develop and optimise systems to introduce therapeutic DNA into cells

Target 6. Combining therapies

We know that many mechanisms including inhibitory factors, scar tissue and inflammation, contribute to the outcome of spinal cord injury. Therefore, a combination of therapies each directed at different mechanisms is likely to be more effective than targeting each individual mechanism alone. Proof of this concept is provided by recent studies that combine cell transplants with drugs that increase the connections between nerve fibres. It is likely that more effective combinations are possible, and combination therapy is likely to be a cornerstone of future strategies to treat spinal cord injury.

- The potential complementarity of different therapies is crucial. For combined therapies to be effective it is vital that combinations of individual therapies are studied in highly reproducible injury models that are relevant to humans

Target 7. Complementary therapies

Complementary therapies, which include functional electrical stimulation (FES), treadmill training and intensive physiotherapy, have been developed to improve quality of life following injury rather than repair the damaged spinal cord. As the aim of *Spinal Research* is to develop a long-term, effective treatment for spinal cord injury, FES and other forms of intensive physiotherapy were not included in the original Research Strategy because they were not thought to involve actual repair of the injury. However, in the past few years this has been re-assessed.

FES uses electrical implants to activate paralysed muscles, giving patients control of, for example, bladder function and hand grasp. In addition, intensive physiotherapy helps maintain bone and muscle mass, which is important for general health. Recently, it has become clear that, as well as these direct effects, FES also has long-term 'secondary' effects in the brain and spinal cord that might allow surviving fibres to function more effectively. Thus, although complementary therapies do not directly repair nerve fibres in the spinal cord, they cause beneficial changes in the strength of connections between nerve fibres, which leads to specific improvements in function. FES and other forms of electrotherapy might also complement the therapeutic effects of other, more invasive, therapies.

Given that the principal aim of *Spinal Research* is a treatment that repairs spinal cord injury, it should promote research that

- Investigates the effects of non-invasive therapies, including FES, on functional recovery, particularly those that complement other therapeutic approaches
- Adds to understanding how functional improvement occurs
- Develops more convenient ways to deliver these sorts of therapy

In order to meet the ambitious experimental targets outlined above, *Spinal Research* realizes that the infrastructure required for effective experimental and clinical research also needs to be encouraged. The Research Strategy also addresses these issues by encouraging experimenters to

- Develop and study models that are relevant to injuries in humans using models give robust, objective and reproducible results

- Develop and refine methods to measure change in function in humans that occur either spontaneously or following treatment. Accurate assessment methods are crucial for identifying a successful repair strategy. This is the remit of Stage 2 of the Clinical Initiative.
- Follow international guidelines on how to develop clinical trials of potential treatments in the most accurate and effective manner
- Encourage collaborations between the researchers it funds and others, including both clinical and basic scientists.