Protection and Repair After Spinal Cord Injury: Accomplishments and Future Directions

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It was an honor for me to present the 2014 G. Heiner Sell Memorial Lecture at the annual American Spinal Injury Association (ASIA) meeting in San Antonio. For this purpose, I provided a comprehensive review of the scope of research targeting discovery and translational and clinical investigations into spinal cord injury (SCI) research. Indeed, these are exciting times in the area of spinal cord research and clinical initiatives. Many laboratories and clinical programs throughout the world are publishing data related to the pathophysiology of SCI and new strategies for protecting and promoting recovery in both animal models and humans. For this lecture, several topics were discussed including neuroprotective and reparative strategies, neurorehabilitation, quality of life issues, and future directions. In the area of neuroprotection, pathophysiological events that may be targeted with therapeutic strategies, including pharmacological and targeted temperature management were reviewed. For reparative approaches, the importance of both intrinsic and extrinsic mechanisms of axonal regeneration was highlighted. Various cell therapies currently being tested in preclinical and clinical arenas were reviewed as well as ongoing US Food and Drug Administration approved trials for SCI patients. Neurorehabilitation is an evolving research field with locomotive training strategies, electrical stimulation, and brain-machine interface programs targeting various types of SCI. The importance of testing combination approaches including neuroprotective, reparative, and rehabilitative strategies to maximize recovery mechanisms was therefore emphasized. Finally, quality of life issues that affect thousands of individuals living with paralysis were also presented. Future directions and specific obstacles that require attention as we continue to move the SCI field forward were discussed.

Introduction

Traumatic spinal cord injury (SCI) is a devastating neurological problem that affects over 12,000 people each year in the United States.¹⁻³ SCI is a worldwide problem with thousands of individuals in many countries sustaining injury from a variety of mechanisms including vehicular accidents, sporting events, and violence.⁴ In addition to civilian casualties, military personnel have a high incidence of SCI due to recent wars that saw an increase in spinal injuries due to roadside explosions resulting in lacerations and blast injuries. SCI can result in a spectrum of neurological problems including the loss of motor and sensory function, bowel and bladder dysfunction, spasticity, neuropathic pain, and autonomic dysreflexia.^{2,5} Although a great amount of information is known about the pathophysiology of SCI and the cellular and molecular events that lead to cell death and neurological deficits, there is a lack of successful therapies in the clinic that

protect or promote recovery after injury.⁶ This lack of successful treatments is the result of numerous factors including the complexity of clinical SCI.^{7,8} The heterogeneous nature of the human SCI population requires that specialized treatments be considered based on the neurological and imaging assessment procedures. Nevertheless, specific treatments have been shown to be effective in preclinical models of SCI with various degrees of improvement. These studies have resulted in an impressive collection peer-review articles in high-tier journals.⁶⁻¹⁷ Only through the continued investigation into the pathophysiology of SCI and the rigorous testing and translation of the treatments will successful therapies be identified and tested in well-planned clinical trials.

As previously mentioned, SCI research incorporates a number of areas that relate to new and chronic injuries. Many laboratories are concentrating on testing treatment strategies that can be given in the early injury setting to limit

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secondary injury mechanisms known to be active in acutely injured patients.^{7,18,19} Neuroprotection is an active research area and has provided treatment strategies that have or are currently being tested in the clinic.¹⁸⁻²¹ Cell transplantation approaches and novel strategies to promote axonal regeneration are active areas of neuroscience research being conducted internationally.²²⁻³⁰ A multitude of cellular and molecular processes including cell-signaling cascades, genetic factors, and the involvement of specific transcriptional factors have been reported to be important in successful neurite growth and axonal regeneration in various experimental settings. Thus, the testing of growth-promoting factors and cellular therapies is an active area of study.³¹⁻³³

In addition to enhancing reparative strategies using novel treatments, neurorehabilitation is known to improve the strength and function of people living with SCI.³⁴⁻³⁷ New strategies including robotic training and electrical stimulation studies are providing evidence for these approaches enabling spinal cord circuits to respond to stimulation and participate in recovery mechanisms after SCI.³⁸⁻⁴⁰ In parallel, treatments including neuroprotection, regeneration, and neurorehabilitation are targeting motor recovery and influencing quality of life issues that are so important to the SCI community. Many of these strategies are moving toward clinical studies including US Food and Drug Administration (FDA)–approved trials that will ultimately determine the safety and efficacy of these approaches. The continued cross-fertilization of information among multiple research areas and between different scientific disciplines targeting various neurological disorders and diseases are helping to stimulate new ideas and progress in the field of SCI.

Many research groups continue to emphasize bench-to-bedside programs so that new discoveries can be ultimately moved to the clinical arena and tested for efficacy and safety. These types of programs include discovery or basic science research, preclinical translational studies, and clinical investigations leading to multicenter clinical trials. These types of approaches have the long-term goal of altering treatment guidelines and recommendations for therapeutic interventions and thereby changing how we provide medical treatment for our subjects and patients. An

important ingredient of the bench-to-bedside approach is also an emphasis on the potential for bedside-back-to-bench strategies that take information from the clinic and effectively move it to animal studies to more effectively focus on clinically relevant questions. Thus, the bench-to-bedside/bedside-back-to-bench research program has the advantage of producing an ongoing communication between the basic, translational, and clinician scientists to maximize opportunities for studying clinically relevant questions that may be important in protection and repair. Only through such a coordinated multidisciplinary program can critical information come together to provide an integrated program to successfully move new treatments forward.

For this reason, many laboratories are utilizing a multidisciplinary approach where established investigators with expertise from different research areas work together as an extended team to advance science. The Miami Project to Cure Paralysis, a Center of Excellence at the University of Miami Miller School of Medicine, was established in 1985 to bring together leading international neuroscientists interested in central nervous system (CNS) injury and repair to focus on this problem of SCI paralysis. One characteristic of this evolving program is that several neurological disorders including SCI, traumatic brain injury, cerebrovascular disease, and stroke as well as neurodegenerative diseases are investigated. The cross-fertilization of new information among these various neurological disorders in terms of research discoveries is helping to exchange new ideas from one field to the next to help provide novel strategies for affecting outcome after SCI. Although the various parts of an envisioned scientific puzzle directed toward a cure for paralysis continue to be clarified, it is clear that a multidisciplinary approach using combination strategies will ultimately be required to maximize our chances of good clinical outcomes.

Neuroprotective Strategies and Treatments

The pathophysiology of SCI is complex and involves numerous injury processes.^{7,22,41,42} Initially, direct mechanical injury to cell membranes including axon projections, cell bodies, and blood vessels occurs after traumatic SCI. This initial

trauma leads to brain edema and subsequent damage associated with the excitotoxic and oxidative damage that is commonly seen after different types of traumatic injury. Cellular and molecular mechanisms leading to cell death include necrosis, apoptosis, and autophagy. Primary and secondary injury mechanisms activate inflammatory cascades and glial reactivity associated with a robust immune response to damage. Vascular perturbations including breakdown of the blood-spinal cord barrier and intraparenchymal hemorrhage also aggravate injury mechanisms leading to expansion of the lesion area and ultimate spinal cord cavitation associated with secondary inflammatory events. In addition to the initial mechanical damage, injury cascades lead to progressive damage associated with prolonged cell death mechanisms with white matter damage including oligodendrocyte vulnerability and subsequent demyelination. Axonal pathology, which can be widespread after SCI, leads to associated events including Wallerian degeneration and subsequent axonal dieback. The activation of glial cells contributes to the inflammatory response and the formation of a glial scar and production of inhibitory factors that can influence regenerative processes. Together, these posttraumatic events provide a complex target for therapeutic interventions that may reduce these detrimental consequences.

With the realization of this complex pathophysiology of SCI, it is also important to consider treatment windows during which specific pathophysiological events are active, as well as the role of injury severity and location in selecting therapeutic treatments.^{43,44} As damage becomes more severe, pathophysiological events can be aggravated leading to accelerated cell death with subsequent severe and prolonged neurological deficits. A well-defined sequence of pathological events has been described that include early, intermediate, and late processes. In thinking about the temporal profile of these pathophysiological events, it is therefore important to consider specific injury targets when assessing therapeutic windows for treatment. In this regard, pathomechanisms that may be activated early after injury are difficult to treat because of the narrow therapeutic window. In contrast, other injury mechanisms including

apoptosis and inflammatory cascades may be more delayed and prolonged, with wider therapeutic windows being therefore available for targeted therapeutic interventions.

In investigating therapies that limit these harmful effects on spinal cord tissues, one must also consider the effects of treatments on numerous endogenous reparative strategies that may be activated after SCI. SCI can lead to the generation of reparative and potentially regenerative processes that may be promoted after SCI.⁴⁵⁻⁴⁸ Thus, it is important that drugs targeting early injury mechanisms do not interfere with endogenous reparative processes that could potentially aid in the recovery process. Most recently, cellular events including cellular proliferation, neurogenesis, oligodendrogenesis, axonal sprouting, and neovascularization have been associated with improved function after brain and SCI. Thus, treatments that reduce harmful events in parallel to promoting reparative or regenerative processes are the ultimate goal of neuroprotective therapies.

Various critical care and surgical approaches have been investigated that provide beneficial effects in animal models of SCI.^{5,7,49} In terms of early SCI management protocols, limiting critical secondary insults by providing adequate oxygen and stabilizing systemic blood and perfusion pressures are immediate concerns in the critical management of patients. Episodes of secondary hypoxia or systemic hypotension can adversely affect long-term outcome. Surgical interventions are also needed in the early injury setting to help stabilize the spinal column, improve spinal cord blood flow, and reduce ischemia and swelling. Early decompression surgical procedures after severe SCI have been examined in both preclinical and clinical studies.⁴⁹ Evidence suggests that these early surgical interventions are safe and effective, and they are currently recommended as an early intervention for patients with acute severe SCI.

A number of pharmacological treatments have been tested in preclinical models with some success and translation to the clinic.^{6,9,13,14,50-52} Methylprednisolone, an off-label steroidal anti-inflammatory agent, has been reported to have beneficial effects in terms of treating spinal cord trauma.¹⁵ Most recently, analysis of clinical data from these trials has been evaluated

and many treating physicians now feel that methylprednisolone may have significant adverse effects. Thus, although methylprednisolone continues to be given to patients with acute SCI, some physicians have decided not to administer based on the potential associated risk factors.⁵³ GM1-ganglioside was also tested clinically in hopes of improving outcome.¹⁶ However, in a large multicenter clinical trial, no significant effect in terms of long-term neurological outcome was reported. Thus, there continues to be a critical need to expand our portfolio of appropriate agents that can be moved to the clinic. In this regard, agents including erythropoietin, minocycline, cethrin, riluzol, and selective phosphodiesterase inhibitors are currently being investigated in the laboratory.

In terms of what specific drugs or other treatment strategies should be considered for translation to the clinic, the NIH/NINDS in 2003 initiated a program for the replication of published SCI findings as part of the Facilities of Research Excellence in SCI Research.⁵⁴ This program determined whether the successful replication of findings from published SCI studies could be accomplished and evaluated data reproducibility. Another aim sought to emphasize the potential for translation to clinical trials. Unfortunately, many of the published SCI studies that were selected could not be replicated to the extent in which they were originally published. Thus, there is a need in the preclinical arena to identify the most encouraging results prior to consideration of translation to the clinic.

Several clinical studies have been completed in terms of neuroprotective agents. The phase II placebo controlled randomized trial of minocycline treatment reported overall improvement, with motor complete cervical injuries showing the largest differences.¹³ Interesting, no significant changes were observed in incomplete SCI participants, a finding that was also reported in a previous replication study of incomplete SCI.⁵⁵ The pharmacokinetics, safety, and neurological outcome of riluzole treatment in severe SCI has also been conducted.^{12,56} In one study, no adverse effects were reported with riluzole treatment; there was an increase in mean motor scores compared to registry cervical SCI participants. Analysis of

the Cethrin clinical trial also showed a trend to improved sensory scores in patients with thoracic injury.⁵⁷ These studies are encouraging and provide a rationale for further clinical investigations possibly targeting specific SCI populations.

As previously noted, a potential hurdle in terms of treating SCI is the high degree of heterogeneity of the injured patient population.⁵⁸⁻⁶⁰ Although individuals are routinely initially divided into ASIA Impairment Scale (AIS) A, B, C, and D based on the completeness and severity of their motor and sensory deficits, they can vary greatly in structural injury as indicated by imaging approaches and the potential for spontaneous recovery. Even in the complete AIS A group, individuals can have very different patterns of tissue damage and neurological recovery potential over weeks to months after SCI.^{61,62} An active area of research directed at this problem is the use of surrogate markers to help evaluate injury severity and predict long-term outcomes. State-of-the-art MRI imaging, for example, can evaluate areas of structural damage, sites of contusion formation, detailed white and gray matter damage, tissue swelling, and hemorrhage.⁶¹ However, these studies can be relatively time-consuming and costly. In addition, serum and cerebral spinal fluid (CSF) sampling for biomarker analysis may also help in the assessment of injury severity in the very heterogeneous populations. Dr. Pouw and colleagues⁶² have investigated various inflammatory and structural serum biomarkers in patients after acute SCI. Their findings demonstrate variations in concentrations of CSF biomarkers depending on injury severity. It is possible in the future that these types of biomarker assays may be used in concert with other strategies to help predict injury severity and most importantly help guide treatment strategies.

In addition to pharmacological agents, therapeutic hypothermia and targeted temperature management protocols are gaining support in the experimental and clinical arena in terms of its potentially beneficial effects in acute SCI.^{18,19,63-65} In the 1960s, investigators tested the potential benefits of producing profound local hypothermia in SCI patients. Although these studies were limited in terms of assessing small numbers of subjects

undergoing confounding treatment variables, they did report that local hypothermia could be produced in these patients and in some instances provided benefits. Over the last decades, work by many laboratories reported that relatively small variations in the temperature of the CNS tissue had a critical impact in terms of structural damage and behavioral outcomes in models of cerebral ischemia, traumatic brain injury, and SCI.^{18,19} In those studies, small reductions in temperature of 2°C–3°C were beneficial in terms of protecting vulnerable neurons and improving functional recovery. In contrast, mild elevations in CNS temperature had adverse effects on outcome. These types of studies emphasized the importance of CNS or body temperature in the pathophysiology of CNS injury and indicate the need for the establishment of targeted temperature management protocols in the human injury situation. Temperature fluctuations may have such profound effects on traumatic outcome by targeting many of the pathomechanisms that have been described after cerebral ischemia and trauma.^{18,19} Thus, reductions in temperature reduce cerebral metabolism, neurotransmitter release, blood-brain and spinal cord barrier permeability, edema formation, free radical activation, and inflammation, all representing important secondary injury mechanisms.

Based on encouraging findings, several groups tested the beneficial effects of modest systemic hypothermia in models of compressive or contusive SCI.^{67–73} Yu and colleagues⁶⁸ first demonstrated that reducing spinal cord temperature to 33°C after severe thoracic SCI led to improvement in overall motor function and reduced structural damage compared to normothermic animals. Based on the clinical need to study therapeutic hypothermia in models of cervical injury, Lo and colleagues⁶⁷ next reported that posttraumatic hypothermia after severe cervical SCI also improved outcome by enhancing upper limb mobility and strength and reducing histopathological damage with increased motor neurons survival. Laboratories throughout the world using different SCI models have now reported that mild systemic hypothermia improves outcome and reduces structural damage.¹⁸ Recently, a systemic review and meta-analysis

of therapeutic hypothermia in animal models of SCI was reported.⁷⁴ Batchelor and colleagues reviewed 3 databases to assess the beneficial effects of both systemic and regional hypothermia after experimental SCI. In both cases, hypothermia was reported to be a promising method of treating SCI on the basis of this meta-analysis.

In the 1990s, the clinical application of modest systemic hypothermia after human SCI was first investigated after clinical guidelines and protocols were established.^{75–78} In these single institution studies, modest hypothermia (33°C) was induced via an intravascular cooling catheter and maintained for a 48-hour period followed by a slow rewarming phase. In 2009, Levi and colleagues⁷⁵ published the first findings from 14 subjects using systemic modest hypothermia. A positive correlation between core temperature and heart rate was reported with no significant increase in risk factors associated with modest hypothermia. This study was important because it provided critical baseline data for proposed multicenter randomized trials. The cooling protocol that included an early temperature reduction, sustained controlled hypothermia followed by a controlled rewarming period, was based on preclinical data reporting the importance of each phase in the therapeutic treatment effects. More recently, Levi and colleagues^{76,77} have reported the clinical outcomes in a larger number of cooled subjects. Importantly, at 1 year after severe cervical SCI, an approximate 43% conversion of AIS As to Bs and Cs was reported. Taken together, these results are encouraging and indicate that this experimental therapeutic approach is safe. Currently, there is need for a multicenter trial to be conducted that will include SCI patients randomized between normothermia and hypothermia.⁷⁹ Hopefully, with future funding, the beneficial effects of therapeutic hypothermia and targeted temperature management protocols specifically for human SCI can be critically evaluated.

Reparative Strategies

An active area of neuroscience includes strategies to repair the CNS after injury in the subacute or chronic injury settings.^{26–31,80,81} In addition to

transplanting cells or testing bridging strategies, researchers have uncovered the capacity of endogenous cells or specific regions of the adult nervous system to respond to injury or treatments by inducing reparative strategies that may promote spontaneous recovery mechanisms.⁸²⁻⁸⁹ In situations where the injury is severe, these endogenous mechanisms including cell proliferation, axonal sprouting, or release of growth promoting factors may not necessarily lead to clinically relevant improvements. Nevertheless, active investigations are clarifying strategies that may enhance these endogenous processes to help convert nonpermissive environments for regenerations and repair into permissive ones.^{22,46-48,80-89} Multiple mechanisms may be considered when attempting to repair the spinal cord after injury including enhancing regenerating axons, restoring neurocircuitry, the remyelination of demyelinated fibers, and increased expression of neurotrophins/cytokines leading to regeneration and repair. To accomplish these goals, various strategies including the addition of neurotrophic factors, cell transplantation, blockers of inhibitory molecules and bridging strategies have all been considered useful approaches for repair. Indeed, many investigators feel that a combination of these types of approaches may ultimately be required to provide significant improvements in regeneration with the long-term goal of providing clinically relevant improvements after SCI.

One important strategy for promoting repair includes the transplantation of different types of “helper cells” that may help convert the injured environment into one that will support repair processes.^{22,80-89} The different types of transplanted cells that have been investigated include peripheral nerves, Schwann cells, olfactory ensheathing glia, astrocytes, and activated macrophages. Research in stem cell biology has helped clarify how to utilize embryonic, fetal, or adult stem cells to promote repair in the nervous system. The identification of stem and progenitor cells in the adult nervous system and the field of induced multipotent stem cells (iPS) are also gaining acceptance.⁸³⁻⁸⁹ Finally, genetically engineered cells may help provide growth-promoting factors that could maximize the benefits of cellular transplantation.⁹⁰ One of the major limitations of this line of research is

that there are multiple cell populations that could potentially be used in the clinic to target SCI. Thus, it will be difficult in the future to consider translating many of these different types of cells into humans due to cost of trials and availability of eligible participants. Thus, a strategy needs to be adapted by the SCI community to help the field move forward with efficacy and safety testing in people.

The SCI research community has recently discussed strategies for demonstrating efficacy in preclinical studies of cellular therapies for SCI to help determine the types of data required to determine whether a particular therapy should be translated to the clinic.^{27,91} Uncertainty exists on the extent to which a cellular therapy needs to demonstrate efficacy in a preclinical setting to justify the initiation of lengthy, expensive, and potentially risky clinical trial. For this purpose, SCI researchers were surveyed and discussed a number of translational issues. These included what animal models and mechanisms of actions should be considered, therapeutic window demonstrating efficacy, independent replication defining meaningful efficacy, and the overall expectation of therapeutic benefits for cellular interventions. These types of thought groups are providing guidelines for the field to consider as we move cell therapies forward.

In addition to a rich literature on preclinical studies using cell therapies, some clinical trials have been conducted and completed.²² One of the first involved autologous incubated macrophage therapy in acute complete SCI.¹¹ This phase II randomized controlled multicenter trial failed to show significant differences in outcome between treated and controlled cohorts. However, important standardization and measurement variables were identified that may be important for future clinical trials. In another recent study, the clinical application of olfactory ensheathing glia (OEG) for the treatment of SCI was evaluated in 8 participants.⁹² Interestingly, a return of substantial sensation and motor activity in specific muscles below the injury site was observed in a few participants as well as improved bladder function. Importantly, no serious complications of the cell therapy were observed.

In terms of stem cell therapies, there is rich data collection of different types of stem cells from a variety of sources including brain, spinal cord, skin, adipose tissue, muscle, and bone marrow. In addition to Geron, which initiated but did not complete a transplantation trial using embryonic stem cells pre-differentiated into oligodendrocyte precursors targeting SCI, other companies have emerged that are currently conducting clinical trials.^{14,22,25} Stem Cells, Inc. has completed a phase I/II open label multinational study evaluating safety and preliminary efficacy of human fetal neural stem cells (HuCNS-SC) in 12 subjects. This is the first clinical trial in stem cell transplantation to complete enrollment with current data indicating safety as well as some potential benefits. Asterias Biotherapeutics has received FDA approval to initiate clinical testing of oligodendrocyte progenitor cells (AST-OPC1) in chronic SCI. NeuroStem, Inc. also has an active FDA-approved phase I trial for neural stem cell transplantation (NSI-566). Ultimately, this trial will recruit 8 chronic SCI subjects receiving stem cell injections in and around the injury site. Physical therapy and immunosuppression therapy are also used in this trial. The potential negative effects of immunosuppression in human SCI is a potential factor that must be considered in these and future clinical studies.

The Miami Project to Cure Paralysis is actively involved in an FDA-approved trial to test the safety and preliminary efficacy of autologous Schwann cell transplantation in subacute spinal cord-injured subjects. This initial trial is based on a wealth of preclinical data showing that Schwann cell transplantation in various experimental conditions provides benefits in both protection as well as cellular repair.⁹³⁻⁹⁵ Schwann cell transplantation is associated with the release of growth-promoting factors, axonal regeneration, and remyelination. In addition to rodent studies, Schwann cell transplantation protocols have been conducted in larger SCI animal models including minipigs and nonhuman primates with supportive results. Currently, the inclusion criteria for this phase I dose escalation trial is for thoracic SCI between the levels of T3 and T11 with AIS of grade A. A dose escalation protocol is being conducted

with the first 2 subjects receiving 5 million cells, the next 3 subjects 10 million, and the last 3 receiving 15 million. Currently, these studies are progressing satisfactorily with no treatment-related adverse events observed.

In future studies, emphasis will be directed toward targeting chronic SCI with autologous Schwann cell transplantation. Preclinical work is suggesting that delayed transplantation of Schwann cells into the injured spinal cord appears to be safe and associated with some functional improvement. Because most investigators feel that extensive rehabilitation and exercise conditioning may be an important component of providing functional improvement in chronically injured subjects,⁹⁶ a clinical protocol has been developed that will include a Miami Project "boot camp" paradigm where subjects undergo several weeks of intensive conditioning/rehabilitation prior to and following the Schwann cell transplant. The "boot camp" would include exercise conditioning protocols targeting both upper and lower extremity functional training. Body weight-supported locomotive training using either the Lokomat or overground training also be administered, depending upon motor completeness. It is felt that this combination approach of cell therapy plus extensive conditioning/rehabilitation could provide a synergistic effect in terms of promoting repair in the chronic injury setting.

In addition to these ongoing studies, a considerable amount of discovery research is being conducted in the laboratory to uncover the important intrinsic and extrinsic mechanisms facilitating axonal regeneration.^{23,24,30,46,47,97,98} It is now clear from the literature that insufficient growth capacity of the adult neurons may be an important limiting factor in terms of why axonal regeneration does not occur after adult SCI. Strategies that potentially target limitations in the adult nervous system intrinsic growth capacity include cell transplantation, neurotrophic supplementation, the addition of growth-promoting small molecules, genetic manipulation, as well as bioengineered scaffolding materials. In addition to these intrinsic mechanisms, extrinsic factors are also critical in modulating regenerative capacity after trauma by the development of an inhibitory environment that

limits or inhibits axonal regeneration.^{23,30} Various inhibitory molecules including chondroitin sulfate proteoglycans, NOGO, or other myelin inhibitors have been reported to be produced after SCI and associated with lack of regeneration. Glial scar formation around an injury site may be a potential barrier for axonal regeneration. In addition to astrocytic proliferation, fibroblasts may also impede successful axonal regeneration as well as changes in the composition of perineural nets around neurons.⁹⁸ Thus, various strategies have to be considered as the scientific community discusses reparative approaches.

Along these lines, recent studies have tested several combination approaches to promote successful axonal regeneration and the development of new relay circuits after SCI.^{24,31,40,99} For example, a study by Lu and colleagues³¹ reported long-distance growth and connectivity of neural stem cells after severe SCI using fibrin matrices containing growth factor cocktails. In that study, 10 compounds were investigated that added to the benefits of the stem cell treatment after complete SCI. Importantly, large numbers of extended axons over remarkable distances with abundant synapses with host cells was reported. Grafted cells were also shown to differentiate into multiple cell phenotypes including neurons. In terms of the translational potential, this axonal regeneration was associated with improvement in motor function. Another study has provided some degree of replication of these results in terms of long-track regeneration.⁹⁹ However, with any stem cell therapy there can be the potential for abnormal cell proliferation and enhanced tumorigenicity that could be a major risk factor.¹⁰⁰⁻¹⁰² Thus, the potential for novel combination approaches having positive as well as potentially detrimental effects is a consideration as we move reparative therapies into the clinical arena.

Programs in Discovery science are also clarifying new approaches for axonal regeneration using state-of-the-art high content screening approaches. These screening strategies allow large chemical libraries containing FDA-approved compounds or novel molecules to be screened for their ability to enhance neurite growth under injury or inhibitory conditions.^{103,104} Combined with viral vector technology, cultured cells can be transfected with

specific genes, transcriptional factors, or micro-RNAs and then systematically evaluated for their effects on neurite growth in a rigorous manner. Recently, new molecules and genes including those from the KLF family have been reported to be important in regulating axonal regeneration follow corticospinal tract injury.¹⁰⁴ Because this specific spinal cord tract is involved in many skilled motor functions and has been difficult to promote regeneration, these types of studies may be important in future experiments when novel combination approaches are being considered for promoting regeneration. Again, the regeneration field is extremely exciting and there are many approaches and directions that scientists are taking. Hopefully in the future, successful regeneration programs will allow us to concentrate on how best to improve function in our SCI populations.

Rehabilitation/Locomotive Training

The field of rehabilitation has a rich history of providing improvements in functional recovery in people living with the detrimental consequences of SCI.^{5,34-39} Recently, evidence-based medicine supported by experimental and clinical data has provided a strong rationale for the use of new and innovative rehabilitation strategies targeting paralysis.^{39,40,105-108} Body weight support and treadmill training to improve walking has been shown to improve balance, speed of walking, and endurance. Upper limb rehabilitation is also providing improved function in individuals with neurological disorders including stroke, brain trauma, and SCI. The important concept of aging successfully with SCI has been emphasized, and rehabilitation and conditioning protocols play an important part in targeting many quality of life issues.

An evolving area of continued advancement in the rehabilitation field includes robotic and rehabilitation techniques that utilize new technologies that can maximize the benefits of routine rehabilitation approaches. Devices including the Lokomat, exoskeletal devices, Zero G support for walking, as well as robotic arms and wrist devices are showing efficacy in various studies.^{35,37,109-117} Ultimately, a goal would be to move these types of very specialized equipment and technologies into a larger SCI population

to maximize the benefits of rehabilitation both in rehabilitation hospitals as well as in the home environment.

Exciting data using spinal cord stimulation have also been provided in chronically complete paralyzed subjects.^{38,39,107,108} A study by Angeli and colleagues³⁹ reported in 4 individuals voluntary movements occurring with epidural stimulation as part of a stand and step training program. Investigative studies enhancing neuromodulation of spinal cord circuitry with epidural stimulation as well as other approaches may potentially enable paralyzed individuals to process sensory input. Underlying mechanisms for enabling circuits to function in the chronic injury setting are currently being investigated by several laboratories.^{40,105-108} Obviously, the clarification of the biological mechanisms underlying these types of functional results would provide important information on how best to maximize circuit function and plasticity in injured subjects. In parallel to these clinical studies, preclinical researchers using experimental models of SCI are also including rehabilitation strategies in their experimental protocols. Simple as well as innovative robotic rehabilitation strategies have been tested to promote stepping, swimming, and other types of motor function in animals with different types of SCI. It is clear that combining neuroprotective or reparative strategies with rehabilitation has a strong scientific rationale based on the evolving experimental and clinical literature.

More recently, state-of-the-art neurotechnology therapies have been developed where brain-machine interfaces have been directed toward providing subjects with upper extremity function after SCI.^{36,109-117} These types of studies are motivated by the needs of individuals whose fundamental upper extremity functions following SCI have been limited. Restorations of these types of upper extremity functions including arm motions, independence, and control of thumb and index finger movement are highly sought-after functions. The continued development of brain-computer interface systems that will allow for voluntary movement of the upper extremities by using a fully implantable bidirectional interface that can convert motor sensing from the cortex to specific muscle groups by bypassing the injured spinal cord is the ultimate plan.

Quality of Life

Although restoration of motor function is a highly sought-after aim in the area of spinal cord paralysis, other consequences of SCI are equally if not more important to the SCI population.¹¹⁸⁻¹²¹ People living with paralysis can commonly experience different degrees of neuropathic pain, bowel and bladder dysfunction, and autonomic problems including autonomic dysreflexia. All of these consequences of SCI can significantly affect quality of life, more so than motor impairments, and therefore need to be emphasized in both preclinical and clinical research. In the area of neuropathic pain, studies have been conducted to determine the pathomechanisms underlying abnormal sensation. Current hypotheses include aberrant sprouting of injured circuits, upregulation of various receptors, or chronic inflammation. Most recently, researchers have demonstrated that supraspinal areas undergo plastic and metabolic changes that may contribute to some of the mechanisms underlying abnormal sensation after SCI.¹²¹ Hopefully, with a better understanding of these cellular and molecular mechanisms, targeted therapeutic strategies to minimize these effects can be tested.

In addition to pharmacological studies, new approaches including deep-brain stimulation are providing alternative treatment strategies for targeting neuropathic pain and autonomic dysreflexia. Recent findings from preclinical investigations have shown that stimulating brain regions in and around the raphe nucleus appear to release a variety of neurotransmitters and factors that reduce neuropathic pain observed in rats following SCI. This particular study has recently obtained FDA approval, and clinical investigations are underway to determine whether deep-brain stimulation targeting neuropathic pain and other consequences of SCI can be an alternative strategy to pharmacological or cellular interventions.

Summary

As a scientific community, we have accomplished many things regarding the pathophysiology and treatment of SCI. These are exciting times in the field with many disciplines coming together to help target the complicated problem of SCI. It

is encouraging that so much basic, translational, and clinical research is ongoing throughout the world to help provide effective treatments for SCI. Nevertheless, we have many obstacles and challenges to meet before cures are fully realized.

As we move the field forward, critical factors influence the continued successful progress in the treatment of SCI. These include some items that have been discussed in this article, including demonstrating reproducibility and replication of preclinical findings. There is also a continuing need for cross-fertilization between different research areas where ideas can be exchanged and new hypotheses developed to target SCI. As new clinical trials are developed and initiated, ethical and safety considerations continue to remain important. As a scientific community, there is the necessity to consider the SCI community's top wish list in terms of their priorities of restored functions. The continued involvement of rehabilitation and the development of new biotechnologies to compliment biological approaches including cell therapies is an area of extreme interest. Because of the heterogeneity of the SCI population, we also need to better characterize injury severity to help in developing specialized treatments for individuals. The possible increased use of neuroimaging as well as the examination of circulating biomarkers to help clarify injury severity and participant selection for clinical trials is of utmost importance.

As our studies continue to evolve, the need for large multicenter SCI clinical trials is going to be extremely important. Thus, the continued

support of clinical trial networks, nationally and internationally, that allow established clinician groups to participate in trials is a must for the field. Also, funding for these large multicenter trials is going to continue to be difficult as federal budgets for funding are reduced. That will necessitate the continued interaction between academia, industry, and SCI foundations as these treatments are moved forward. As with other scientific areas, there is a great need for precise data collection regarding participant information and the timely distribution of findings to the scientific population for review and publication. Finally, the continued emphasis on multi-organ dysfunction after SCI and ageing effects is a very important area as the SCI population continues to increase in number. Only through multicenter investigations where multiple factors targeting SCI are investigated can we fully promote successful translational investigations with an ultimate goal of providing new treatments for people living with SCI that make a significant difference in their lives.

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