Published in final edited form as:
Neurochem Res. 2013 May ; 38(5): 895–905. doi:10.1007/s11064-013-0991-6.

Spinal Cord Injury: A Review of Current Therapy, Future Treatments, and Basic Science Frontiers

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Abstract

The incidence of acute and chronic spinal cord injury (SCI) in the United States is more than 10,000 per year, resulting in 720 cases per million persons enduring permanent disability each year. The economic impact of SCI is estimated to be more than 4 billion dollars annually. Preclinical studies, case reports, and small clinical trials suggest that early treatment may improve neurological recovery. To date, no proven therapeutic modality exists that has demonstrated a positive effect on neurological outcome. Emerging data from recent preclinical and clinical studies offer hope for this devastating condition. This review gives an overview of current basic research and clinical studies for the treatment of SCI.

Keywords

Spinal cord injury; Clinical; Preclinical

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Introduction

Spinal cord injury (SCI) is a serious clinical problem for which only acute methylprednisolone therapy has shown to be protective, its efficacy is limited and it only marginally improves outcomes [1]. SCI is associated with a drastic decrease in quality of life for affected individuals [2]. Thus, there is a need to explore new therapeutic strategies to treat SCI patients and also to expand our knowledge on the cellular and molecular aspects of the pathophysiology of SCI. Although effective treatments for SCI remain limited, there have been many studies in recent years that have promise for the future from a clinical translational perspective. Current basic science, preclinical, and clinical studies are aimed at overcoming the factors that are involved in impeding recovery from SCI. Specifically, current research is aimed at preventing secondary injury, promoting regeneration, and replacing destroyed spinal cord tissue. This review discusses basic research, ongoing clinical trials, and new therapies used for the treatment of SCI.

Current experimental studies and clinical situations provide us with a better understanding of the complex interaction of pathophysiologic events after SCI. Future approaches involve strategies aimed at blocking the multiple mechanisms of progressive pathogenesis in SCI and promoting neuroregeneration. SCI results from primary and secondary injury mechanisms. Primary injury refers to the immediate physical injury to the spinal cord resulting from the laceration, contusion, compression, and contraction of the neural tissue [3]. It is also known that the severity of the SCI determines a given patient's neurologic grade on admission and consequently this is the strongest prognostic marker [4].

Pathological changes resulting from primary injury mechanisms include severed axons, direct mechanical damage to cells, and ruptured blood vessels. Secondary injury is responsible for expansion of the injury site and limiting restorative processes [5]. Secondary injury can also influence long term morbidity due in part to inflammatory and secondary sequelae following primary injury. Specific secondary sequelae include alterations in local ionic concentrations, loss of regulation of local and systemic blood pressure, reduced spinal cord blood flow, breakdown of the blood–brain barrier, penetration of serum proteins into the spinal cord, inflammatory responses (alterations in chemokines and cytokines), apoptosis, excitotoxicity, calpain proteases, neurotransmitter accumulation, production of free radicals/lipid peroxidation, and imbalance of activated metalloproteinases. These changes lead to demyelination, ischemia, necrosis, and apoptosis of spinal cord tissue [5]. Therefore, apart from achieving stabilization of the patient, the immediate post-injury focus must be on reducing further damage and access to specialized care [6].

Methylprednisolone (MP), a glucocorticoid, is the only current pharmacotherapy approved for SCI but MP has not shown clinically significant effects. Clinically, MP when given in very high doses after SCI intravenously (35 mg/kg) has been associated with significant side effects [1, 7– 10]. To overcome these problems, Chvatal and colleagues demonstrated remarkable protective, regenerative, and functional outcome after 1 week of the primary insult when MP was applied topically at the injury site encapsulated in poly-lactic-co-glycolic acid (PLGA) nanoparticle formulations [11]. These studies are the first to successfully indicate a role for nanoparticle drug delivery patterns for SCI.

Preclinical Research

Current strategies in basic research have begun to develop therapies that address changes associated with both the primary and secondary injuries. The approach is to target the cascading mechanism leading to secondary injury. In particular, a variety of therapies have been studied to alter neuro-inflammation [1, 12–14], reduce free radical damage[15–17], reduce excitotoxic damage to neurons [18, 19], improve blood flow [20, 21], and counter the effects of local ionic changes [21–25]. Previous investigations from our laboratories indicated increased intracellular free Ca^{2+} levels, increased proteolytic activity, degradation of myelin and cytoskeletal proteins, granular degeneration of axons, and vesiculation of myelin all of which contribute to secondary injury and propagation of SCI [12, 17, 26– 28].

In addition to MP, much work has been undertaken with a variety of secondary injury inhibitors in hopes of superior protection in SCI. Estrogen and its analogs have been used to improve outcomes in rat models as well as to protect cells in culture. It has been shown to prevent apoptosis in oligodendrocytes [29], microglia, and neurons [30] as well as to decrease activation of cysteine proteases, including calpain [23]. The protective effects of estrogen in SCI have also been linked to its attenuation of VEGF and aquaporin upregulation [31].

Melatonin has also been shown to be protective in SCI. Known as an antioxidant and anti-inflammatory agent, melatonin is thought to provide protection from secondary damage via free oxygen radical scavenging [32, 33]. Like, estrogen, melatonin has also been associated with attenuation of intracellular Ca^{2+} influx, and cysteine protease activation [23, 34]. Many of these treatments have clinical potential, but have yet to be translated into clinical practice.

Advances in therapeutic modalities have recently allowed basic research to focus on mechanisms that target functional restoration and regeneration of the injured sites within the spinal cord, and in particular axonal regeneration. There are many factors found in myelin such as Nogo, myelin-associated glycoprotein (MAG), oligodendrocyte-myelin glycoprotein (OMGP), ephrins, semaphorins, netrins, and repulsive guidance molecule (RGM) that affect the success of neuronal regeneration following SCI [35–41]. These factors also alter the physical and biochemical barriers that are induced or inherent within the injured spinal cord and inhibit neurite formation. In addition, the astrocyte-lined glial scar is also an impediment for neural regeneration. The glial scar releases a number of factors that make the biochemical milieu surrounding the injury site inhospitable for regenerating axons. At the same time, regeneration-associated gene expression plays a role in the synthesis of number of proteins including GAP-43, CAP-23, and neurotrophins; the cellular downstream signaling molecules cAMP and CREB; and integrins that are important in regeneration [42].

Although neurons atrophy and have declining neuroregenerative capability after axotomy in the CNS, pathways important for regeneration can be stimulated with growth factors to partially promote regeneration. It is well established that inhibitors of RhoA GTPase (RhoA) and Rho kinase (ROCK) signaling promote neural regeneration in vitro and in vivo and that brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin-3 (NT-3), and NT-4, are the core neurotrophins known to promote neuron survival [35, 43–

47]. A variety of studies have reported that neurotrophins and neurotrophin receptors improve various aspects of behavioral recovery following SCI [48–50]. In addition, many researchers are involved in trying to replace this lost tissue by transplanting stem cells, olfactory ensheathing glia, Schwann cells, bone marrow, and peripheral blood stem cells into the spinal cord at or near the site of injury in order to replace lost tissue, and, in turn, lost function [49, 51, 52].

Recent advances in SCI research have led to a variety of novel experimental therapeutics. Our laboratory is employing in vivo experiments to use nanoparticles associated with protective drugs in order to attenuate brain and spinal cord pathology. The use of nanoparticles in the treatment of SCI has major advantages for spinal cord repair because of their structural and chemical versatility [53, 54]. Because a major difficulty in treating SCI is to maintain the exact concentration of the active ingredients of the drug within the spinal cord cells and tissues to achieve neuroprotection [55], biomaterial polymers have been tested as guidance channels and delivery systems for neuronal and axonal-protective agents in animal models of SCI [56, 57]. The advantages of nanodrug delivery are three-fold: (1) enhanced drug delivery to the target cells, (2) a reduction in concentration-related toxicity, and (3) an increase in duration of drug exposure [58]. Targeted drug delivery after systemic administration has been explored by several groups [56, 59, 60] in attempt to create a nanoparticulate formulation capable of penetrating blood brain barrier (BBB). It was shown that a number of functionalized nanoparticles such as poly butyl cyanoacrylate) (PBCA) nanoparticles exhibited a capability of penetrating the BBB with little evidence of toxicity and an ability to deliver to the CNS [61, 62]. Our group has shown in vitro neuroprotective efficacy of PBCA nanoparticles coated by the antioxidant enzyme superoxide dismutase. Presumably, these properties increase the therapeutic index of nanodrug delivery systems [63]; however, portion of the drug may be at increased risk of being trapped by mononuclear phagocytes in the liver and spleen [64, 65].

Local delivery can address some of the limitations of systemically delivered drug. Biodegradable nanoparticles, which are loaded with a therapeutic drug, are used to allow for a controllable, region specific treatment regime. Chvatal Kim, Bratt-Leal, Lee, and Bellamkonda all demonstrated remarkable protective, regenerative, and functional outcome after 1 week of the primary insult when MP was applied topically at the injury site encapsulated in polylactic-co-glycolic acid (PLGA) nanoparticle formulations [11]. These studies are the first to successfully indicate a role for nanoparticle drug delivery patterns for treatment of SCI. As the particle degrades, a consistent, tunable amount of drug is released to the injury site. This sustained release of low, effective doses of drug prevents rapid clearance of the drug, which is seen when there is no nanoparticle vehicle, but still provides the needed therapeutic action. Sustained release of drug at therapeutic levels can limit systemic side effects, while providing a more efficient use of drug than the systemic alternative. Other advantages to this method include a tunable nanoparticle size, which can affect their ability to diffuse, and the ability to regulate drug release rate. In another study, fibroblast growth factor 2 (FGF2) incorporated into polylactide-co-glycolide nanoparticles and further embedded in a hydrogel consisting of hyaluronian and methylcellulose was used to reduce vasoconstriction at the site of primary SCI and improve angiogenesis in a rat SCI model. It was found that use of the nanoparticulate formulation of FGF2 resulted in higher

blood vessel density in the dorsal horns 28 days post-injury; it was also noted that nanoparticulate FGF2 did not induce proliferative lesions that had been previously reported for locally administered with free FGF2 [66].

Other successful uses of nanoparticle-based approaches for treatment of SCI have also been associated with local delivery. Cho et al. [67] demonstrated that treatment by polyethylene glycol coated silica nanoparticles restores neuronal membrane integrity and leads to recovery of conduction through the SCI lesion in a guinea pig contusion model. Wu et al. [68] showed that local administration of gold nanoparticle conjugated with human NgR–Fc (hNgR-Fc) fusion protein vaccine promotes and improves the efficacy of the repair in a rat SCI model. Overall, there is considerable enthusiasm about potential of nanoparticle-based drug formulations for treatment of SCI; however, nanoparticles also present their own risks. The makeup of the polymer coatings can result in great variations in nanoparticle-induced blood coagulation, mitochondrial reactive oxygen species (ROS) generation, and/or cellular oxidative burst phenomena [69]. In addition to these potential complications, systemic administration of nanoparticle-born drugs may pose a serious threat to unintended delivery targets, such as the liver and spleen. Finally, should polymer coatings be insufficient to retain drug stability prior to localization within the injury area, a decrease in drug-to-injury-site efficiency may occur. Thus, nanoparticle surface polymers must be carefully developed to avoid these pitfalls while also preserving enhanced drug delivery potentials.

Clinical Trials

In addition to basic research, several clinical trials have been undertaken to explore how SCI therapies may translate to the human host. Like basic science work, clinical trials can be broadly classified into those directed at neuroprotection and those directed at neuroregeneration. Neuroprotective agents act to minimize the secondary injury after spinal cord trauma and may, therefore, be considered acute. Neuroregenerative treatment modalities, on the other hand, are directed at promoting neuronal regeneration and re-establishing axonal pathways to restore neurological function in chronic SCI. The following section reviews both acute neuroprotective and sub-acute to chronic neuroregenerative therapies, which have been employed in a clinical setting.

Methylprednisolone (MP)

MP was originally shown to protect against secondary injury in animal models. Mainly, MP minimized secondary damage by reducing the injury-induced free radical catalyzed lipid peroxidation in spinal cord tissue. Additionally, it was thought to facilitate neuronal excitability and impulse conduction and to improve blood flow through the injured cord [70].

MP was subsequently evaluated in 4 clinical trials [7, 9, 10, 71]. The first of these trials was the National Acute Spinal Cord Injury Study I (NASCIS I). Acute SCI patients with motor or sensory deficits below the level of injury were randomized into high dose MP groups (1,000 mg IV bolus and daily thereafter for 10 days) and standard dose MP groups (100 mg IV bolus and daily thereafter for 10 days). No difference in neurological recovery was

observed at 6 weeks or 6 months after injury, though wound infection was more common in the high dose group.

New data from animal model studies suggested that the dose of MP administered in NASCIS I was below the theoretical therapeutic threshold of about 30 mg/kg of body weight [70, 72]. This initiated the NASCIS II, a multicenter randomized controlled trial (RCT), to investigate the efficacy of high dose MP administered as a 30 mg/kg bolus over the first hour followed by an infusion of 5.4 mg/kg/h over the next 23 h. This study included a placebo group as well as a third group that received the opiate receptor antagonist naloxone as a 5.4 mg/kg bolus followed by 4.0 mg/kg/h infusion for next 23 h. The naloxone arm was added since endorphins were hypothesized to be instrumental in promoting secondary injury by reducing blood pressure and thus spinal cord blood flow, and naloxone was shown to reverse hypotension and improve spinal cord blood flow in animal studies [73]. The study concluded that patients treated with high dose MP within 8 h of injury had a significant improvement in neurological function at 6 months and 1 year post-injury compared to placebo and naloxone group [8]. Naloxone therapy yielded no beneficial effect on neurological outcome.

The outcome of NASCIS II prompted the National Institutes of Health to issue an advisory, on the positive impact of MP in acute SCI, to clinicians in the United States. The initial optimism generated by the results of the trial was not matched by effectiveness of MP in clinical settings. As a result, the study was criticized: 1) for lack of robust statistical analysis and 2) for basing the final conclusion on post hoc analysis of a subset of original cohorts [74, 75]. It was also felt that marginal benefits were offset by increased risk of infections and myopathy [10, 76]. A multicenter randomized trial from Japan compared routine management with NASCIS II regimen (30 mg/kg bolus over the first hour followed by an infusion of 5.4 mg/kg/h over the next 23 h) started within 8 h of injury. The study reported improved sensory function at 6 weeks and 6 months post-injury. This Japanese study suffered from small sample size and conclusions based on post hoc analyses [75].

The NASCIS III was conducted to compare the efficacy of MP administered for 24 h, and 48 h with tirilazad mesylate (TM) administered in patients with acute SCI [71]. TM is an inhibitor of lipid peroxidation without glucocorticoid activity [77]. All patients received an intravenous bolus of 30 mg/kg MP. Patients in the 24 h MP regimen group received 5.4 mg/kg/h for 24 h; patients in 48 h MP regimen group received 5.4 mg/kg/h for 48 h; patients in the TM group received a 2.5 mg/kg bolus infusion of TM every 6 h for 6 weeks. This study concluded that when treatment was initiated within 3 h of injury, equivalent neurological and functional recovery was seen in all 3 groups. Patients in whom treatment was initiated between 3 and 8 h did better with 48 h MP regimen. Critics of this study point to selection bias and higher incidence of infection as major shortcomings of the overall quality of NASCIS III [74, 75]. Based on the literature available it can be stated that the role of high dose MP in the management of acute SCI following non penetrating injury has not been unequivocally established.

Nimodipine

Calcium channel blockers were shown to improve blood flow to the injured spinal cord in the laboratory setting [25, 78–80]. Nimodipine was used in a French RCT to evaluate the safety and efficacy of nimodipine, MP or both compared to no medical treatment [81]. Patients with acute SCI were randomized into 4 groups to receive MP (30 mg/kg over 1 h, followed by 5.4 mg/kg/h for next 23 h) or nimodipine (0.015 mg/kg/h for 2 h followed by 0.03 mg/kg/h for 7 days), or both drugs or no medication. Patients who sustained injury within the preceding 8 h were enrolled. Neurological assessment was performed by a blinded neurologist before treatment and at 1 year follow up. The study failed to demonstrate any benefit from either or both agents. Similar to the NASCIS studies, infections were seen more often in the MP group.

Gacyclidine

Gacyclidine is a *N*-methyl-D-Aspartate antagonist. It minimizes secondary injury following blunt trauma to the spinal cord in a rat model by blocking glutamate induced Ca^{2+} influx [82, 83]. A multicenter RCT was conducted in France to evaluate the clinical efficacy of this drug. There were 4 groups: three different doses of the drug (0.005 mg/kg, 0.01 mg/kg, and 0.02 mg/kg) and the placebo group. Gacyclidine was administered to patients with acute SCI within 2 h of injury, followed by a second dose 4 h later. The outcome measures were American Spinal Injury Association (ASIA) motor and sensory scores and the Functional Independence Measure (FIM) score. The trial failed to show any clinical benefit of Gacyclidine in acute SCI at 1 year follow up [10, 84].

Thyrotropin Releasing Hormone (TRH)

TRH is a tripeptide, which apart from its well established role in regulating pituitary-thyroid axis, also influences an array of neurological functions [85]. TRH has shown a neuroprotective effect in animal SCI models through anti-oxidant and membrane stabilizing properties in addition to enhancement of spinal cord blood flow [86, 87]. These laboratory findings formed the basis for a double blind RCT [88]. A total of 20 patients were randomized to receive TRH (0.2 mg/kg IV bolus followed by 0.2 mg/kg/h infusion over 6 h) or placebo within 12 h of injury. Neurological recovery was followed with motor and sensory testing and Sunnybrook functional scores. At 4 months patients with incomplete injury and treatment with TRH had a noticeable neurological recovery compared to placebo treated patients. Patients with complete SCI demonstrated no benefit with TRH therapy. Despite encouraging results with this initial study, a higher powered follow up study was not conducted.

GM1 Ganglioside

Gangliosides, which are glycolipids found in the cell membrane, are in high concentrations in CNS cells [89]. Gangliosides induce neuronal sprouting in vitro [36] and they promote neuronal regeneration and restoration of neuronal function after CNS trauma in animal studies [38, 90–92]. Based on these laboratory results, a double blind RCT was conducted in 1991 to evaluate the efficacy of monosialotetrahexosylganglioside sodium (GM-1) in 34 human subjects with acute SCI (Maryland GM-1 study) [93]. All patients received 250 mg

of MP intravenous (IV) on admission followed by 125 mg MP by IV every 6–72 h. Patients were randomly assigned to receive GM-1 100 mg IV per day for 18–32 doses (first dose administered within 72 h of injury), or to a placebo control group. Neurological recovery was assessed with ASIA and Frankel scale up to 1 year following injury. At 1 year there was significant improvement in Frankel grades and ASIA motor score in the GM-1 treated group.

These promising findings led to a larger, multicenter double blind RCT of 797 patients with ASCI (Sygen GM-1 Study) [94–96]. All patients received NASCIS II MP regimen within 8 h of injury. Patients were then randomized into low dose group (300 mg IV GM-1 followed by 100 mg IV GM-1/day for 56 days), high dose group (600 mg IV GM-1 followed by 200 mg IV GM-1/day for 56 days), and placebo group. Modified Benzel Classification and ASIA scores were used to assess neurological recovery. The study failed to establish efficacy of GM-1 in a clinical setting but ASIA motor, light touch and pin prick scores, bladder function, bowel function, anal contraction and sacral sensation did demonstrate a trend in favor of using GM-1. However, a Cochrane review of GM-1 therapy in ASCI did not show improved neurological recovery or quality of life [97].

Rho Antagonist (Cethrin®)

Rho is a GTPase associated signaling protein that inhibits neuronal regeneration, and promotes neuronal, astrocytic and oligodendroglial apoptosis [44, 45, 47]. C3 transferase, an enzyme from *Clostridium botulinum*, blocks Rho signaling by blocking RhoA (a type of Rho protein), and promotes neuronal growth [35, 43, 46]. A recombinant engineered variant of C3 transferase (Cethrin®) has been evaluated in a clinical trial for safety in SCI [98]. A total of 48 complete SCI patients were enrolled. Patients were scheduled to undergo surgery within 7 days of injury, wherein a single dose of Cethrin was applied extradurally. Five doses of Cethrin (0.3 mg, 1 mg, 3 mg, 6 mg and 9 mg) were evaluated. No serious adverse events attributable to the drug were reported. Patients were followed neurologically for 1 year after treatment. Approximately 6 % of the thoracic spine injury patients and 66 % of cervical spine injury improved from ASIA scale A to ASIA scale C or D. Currently, further clinical trials to test efficacy of Cethrin in SCI patients are planned.

Anti-Nogo Antibodies

Axonal regeneration in the injured CNS is impeded by inhibitory molecules in myelin [37, 39, 41]. The most potent inhibitor is the myelin associated protein Nogo-A. Neutralization of Nogo-A, after CNS injury, promotes axonal regeneration in the injured tract and compensatory sprouting of uninjured tracts in animal studies [37, 40, 41, 99, 100]. Anti-Nogo A IgG antibody enhances axonal regeneration in CNS injury and has undergone a Phase I safety trial in human subjects with acute SCI [101]. Fifty-two patients with ASIA A to C cervical or thoracic injuries were enrolled in the study. Human anti human-Nogo-A antibody was administered intrathecally into the lumbar spine within 4–14 days of injury for periods ranging from 24 h to 4 weeks. No adverse effects ascribable to anti Nogo-A antibody have been reported, but efficacy trials are still ongoing (www.clinicaltrials.gov, NCT00406016).

Acidic Fibrobast Growth Factor

Acidic fibroblast growth factor (aFGF) applied with bridging nerve grafts results in regeneration of spinal tracts in transected spinal cord in a rodent model [102]. Clinical use of aFGF without nerve grafts has also shown promising results in patients with SCI [103]. A study to evaluate safety and feasibility of directly applying aFGF on injured spinal cord in human subjects was conducted in Taiwan [104]. Sixty patients with cervical or thoracic spinal cord injury were enrolled. The injury was more than 10 weeks old. Laminectomy was performed at the injured segment(s), dura was opened, neurolysis of injured cord was done and a mixture of aFGF and fibrin glue was applied to the injured cord. Two additional doses of aFGF and fibrin glue were administered through lumbar puncture at 3 and 6 months post-surgery. Fortynine patients completed 24 month follow up. There were no reports of adverse events related to therapy. The ASIA motor scores, ASIA sensory scores, and ASIA impairment scale demonstrated significant improvement.

Autologous Activated Macrophages

A local immune response develops after SCI that is inimical to neuronal survival and regeneration. In rat model of SCI, local injection of autologous macrophages incubated with autologous skin at the site of injury was shown to promote neurological recovery [105]. Skin co-incubation increases the tolerance of macrophages to neural tissue and elevates secretion of interleukin-1β, increases brain derived neurotrophic factor (BDNF) expression, and reduces secretion of tumor necrosis factor alpha (TNFα). This bolsters immune protection of neurons and makes the environment congenial for axonal regeneration. In a Phase I study involving 14 patients with ASIA Grade A SCI, autologous monocytes from the patient's blood were incubated with autologous dermis. The resulting macrophages were injected into patient's spinal cord immediately caudal to the lesion within 14 days of injury. Five patients improved on the ASIA impairment scale, and no adverse events attributable to the therapy were reported during a 3 year follow up [106, 107]. A Phase II trial is underway [10, 107].

Autologous Mesenchymal Stem Cells

Mesenchymal stem cells (MSC) have the ability to differentiate into mature cell types and also secrete bioactive macromolecules that lay down an environment conducive to regeneration at the site of injury [108]. MSC have been used in pilot studies to evaluate their roles in chronic SCI. The methodology used was different in most studies and the results have been variable. In a study in Czech republic, 20 patients with complete SCI received MSC transplants into the spinal cord at the site of injury 10–467 days after injury [109]. The cells were delivered through intra-arterial or an intra-venous route. Improvement in neurological function was observed in five of six patients after intra arterial administration and five of seven patients who received MSC within 30 days of injury. No adverse reactions were observed during a 2 year follow up period.

In another study, MSC were injected into the spinal cord at the site of injury [110]. Nine patients with ASIA Grade A SCI sustained 6 months ago or longer received the treatment. At a 1 year follow up, all patients had improved to ASIA grade B or C. No adverse effects were reported. Kumar and colleagues conducted a Phase I/II non-randomized, open-label study on 297 patients with SCI [111]. Autologous bone marrow derived mononuclear cells

were administered through a lumber puncture. Neurological improvement was recorded in one-third of patients. No adverse events were reported. The time elapsed between injury and therapy and the number of CD34+/− cells injected correlated with improvement. In a study in Egypt, 44 patients received monthly intra-thecal autologous MSC for 6 months, at a mean of 3.6 years after SCI [112]. Twenty subjects who refused therapy served as control. Spasticity and neuropathic pain were observed in some patients receiving the therapy. No significant motor improvement was reported in this study.

Olfactory Mucosa Autograft

In the olfactory mucosa, the sensory neurons are replaced throughout adult life, and the newly formed axons continually reenter the CNS. The entry point of the olfactory axons into the olfactory bulb is associated with special glial cells, known as olfactory ensheathing cells (OECs). Additionally, olfactory mucosa contains progenitor cells that can mature into supporting cells or neurons [113]. Removing part of the olfactory mucosa does not cause permanent loss of olfaction because of the regenerative capacity of the mucosa (Table 1).

In animal experiments, OECs formed a bridge across damaged myelinated fiber tracts of the spinal cord, conveying axons across the lesion and promoting their remyelination [114]. Therefore, olfactory mucosa offers the advantage of autologous neural tissue that is capable of differentiating into mature neurons, promoting axonal growth and remyelination, and is easy to harvest without causing long term problems. In a safety study, 20 patients with SCI (ASIA grade A or B) sustained 18–189 months (>15 years) ago were treated with autologous olfactory mucosa grafts at the site of injury [115]. Pre- and postoperative assessment was performed using ASIA scores and classification, electromyography (EMG) of attempted muscular contractions, somatosensory evoked potentials (SSEP), urodynamic studies, magnetic resonance imaging (MRI) of spinal cord and otolaryngology evaluations. The functional independence measure (FIM), and walking index for SCI (WISCI) were obtained in 13 patients. Mean follow up was 27.7 months. Olfaction recovered in every patient. One patient developed aseptic meningitis 2 weeks after surgery. Atrophy and cavitation was partially reversed on the MRI scan. ASIA grades improved in 11 patients and declined in 1, EMG responses improved in 15 patients, SSEP improved in 5 patients, and urodynamic responses improved in 5 patients. FIM and WISCI scores improved in all 13 patients tested.

Conclusion

Although the emphasis in clinical SCI research has been directed towards the evaluation of clinical assessments and the appreciation of outcome measures (that is, extent and pattern of clinical recovery from SCI), the underlying pathophysiology of SCI is not well understood. To improve translational research, a meaningful preclinical–clinical dialogue is required, with an appreciation of fundamental neural mechanisms of SCI and their relationship to the clinical features of SCI. Multiple therapeutic modalities have been evaluated in the preclinical and clinical trials without unequivocal success. It will likely take multimodal approaches to find a cure for SCI.

Use of nanotechnology, cellular therapy, and tissue engineering offers promising future therapies for SCI. There are now many investigators examining combinations and permutations of multimodal therapies. Given the complexity of the factors that are involved, research into multi-modal therapies will require rigorous preclinical research before it can be translated to clinical trials.

Acknowledgments

Completion of this project was made possible by funding from the National Institutes of Neurological Disorders and Stroke (NS-31622, NS-38146, and NS-41088), the South Carolina Spinal Cord Injury Research Fund (SCSCIRF), and Department of Neurosciences (Neurosurgery). Authors thank Casey Holmes for help with the preparation of this manuscript.

References

1. Bracken MB. Steroids for acute spinal cord injury. Cochrane Database Syst Rev. 2012; 1:CD001046. [PubMed: 22258943]
2. Budh CN, Osteraker AL. Life satisfaction in individuals with a spinal cord injury and pain. Clin Rehabil. 2007; 21(1):89–96. [PubMed: 17213246]
3. Farooqui. Neurochemical aspects of spinal cord injury. In: Farooqui, AA., editor. Neurochemical aspects of neurotraumatic and neurodegenerative diseases. Springer; Berlin: 2010. p. 107-142.
4. Kiser, TS. Comission ASC. , editor. Predicting outcome (prognosis) in spinal cord injury. 2010. http://www.spinalcord.ar.gov/Resources/Prognosis%20Fact%20Sheet.pdf
5. Dumont RJ, Okonkwo DO, Verma S, et al. Acute spinal cord injury, part I: pathophysiologic mechanisms. Clin Neuropharmacol. 2001; 24(5):254–264. [PubMed: 11586110]
6. Guly HR, Bouamra O, Lecky FE. The incidence of neurogenic shock in patients with isolated spinal cord injury in the emergency department. Resuscitation. 2008; 76(1):57–62. [PubMed: 17688997]
7. Bracken MB, Collins WF, Freeman DF, et al. Efficacy of methylprednisolone in acute spinal cord injury. JAMA J Am Med Assoc. 1984; 251(1):45–52.
8. Bracken MB, Shepard MJ, Collins WF Jr, et al. Methylprednisolone or naloxone treatment after acute spinal cord injury: 1-year follow-up data. Results of the second national acute spinal cord injury study. J Neurosurg. 1992; 76(1):23–31. [PubMed: 1727165]
9. Bracken MB, Shepard MJ, Collins WF, et al. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. Results of the second national acute spinal cord injury study. New Engl J Med. 1990; 322(20):1405–1411. [PubMed: 2278545]
10. Tator CH. Review of treatment trials in human spinal cord injury: issues, difficulties, and recommendations. Neurosurgery. 2006; 59(5):957–982. discussion 982–957. [PubMed: 17143232]
11. Chvatal SA, Kim YT, Bratt-Leal AM, Lee H, Bellamkonda RV. Spatial distribution and acute anti-inflammatory effects of methylprednisolone after sustained local delivery to the contused spinal cord. Biomaterials. 2008; 29(12):1967–1975. [PubMed: 18255138]
12. Das A, Smith JA, Gibson C, Varma AK, Ray SK, Banik NL. Estrogen receptor agonists and estrogen attenuate TNF-alpha-induced apoptosis in VSC4.1 motoneurons. J Endocrinol. 2011; 208(2):171–182. [PubMed: 21068071]
13. Sribnick EA, Wingrave JM, Matzelle DD, Wilford GG, Ray SK, Banik NL. Estrogen attenuated markers of inflammation and decreased lesion volume in acute spinal cord injury in rats. J Neurosci Res. 2005; 82(2):283–293. [PubMed: 16130149]
14. Wingrave JM, Schaecher KE, Sribnick EA, et al. Early induction of secondary injury factors causing activation of calpain and mitochondria-mediated neuronal apoptosis following spinal cord injury in rats. J Neurosci Res. 2003; 73(1):95–104. [PubMed: 12815713]
15. Bains M, Hall ED. Antioxidant therapies in traumatic brain and spinal cord injury. Biochim Biophys Acta. 2012; 1822(5):675–684. [PubMed: 22080976]

16. Robert AA, Zamzami M, Sam AE. Al Jadid M, Al Mubarak S. The efficacy of antioxidants in functional recovery of spinal cord injured rats: an experimental study. Neurol Sci. 2012; 33(4): 785–791. [PubMed: 22068217]

17. Samantaray S, Sribnick EA, Das A, et al. Melatonin attenuates calpain upregulation, axonal damage and neuronal death in spinal cord injury in rats. J Pineal Res. 2008; 44(4):348–357. [PubMed: 18086148]

18. Mazzone GL, Nistri A. Delayed neuroprotection by riluzole against excitotoxic damage evoked by kainate on rat organotypic spinal cord cultures. Neuroscience. 2011; 190:318–327. [PubMed: 21689734]

19. Rong W, Wang J, Liu X, et al. 17beta-estradiol attenuates neural cell apoptosis through inhibition of JNK phosphorylation in SCI rats and excitotoxicity induced by glutamate in vitro. Int J Neurosci. 2012; 122(7):381–387. [PubMed: 22409452]

20. Lutton C, Young YW, Williams R, Meedeniya AC, Mackay-Sim A, Goss B. Combined VEGF and PDGF treatment reduces secondary degeneration after spinal cord injury. J Neurotrauma. 2012; 29(5):957–970. [PubMed: 21568693]

21. Ritz MF, Graumann U, Gutierrez B, Hausmann O. Traumatic spinal cord injury alters angiogenic factors and TGF-beta1 that may affect vascular recovery. Curr Neurovasc Res. 2010; 7(4):301–310. [PubMed: 20860549]

22. Ray SK, Matzelle DD, Sribnick EA, Guyton MK, Wingrave JM, Banik NL. Calpain inhibitor prevented apoptosis and maintained transcription of proteolipid protein and myelin basic protein genes in rat spinal cord injury. J Chem Neuroanat. 2003; 26(2):119–124. [PubMed: 14599661]

23. Ray SK, Samantaray S, Smith JA, Matzelle DD, Das A, Banik NL. Inhibition of cysteine proteases in acute and chronic spinal cord injury. Neurotherapeutics. 2011; 8(2):180–186. [PubMed: 21373949]

24. Sribnick EA, Matzelle DD, Banik NL, Ray SK. Direct evidence for calpain involvement in apoptotic death of neurons in spinal cord injury in rats and neuroprotection with calpain inhibitor. Neurochem Res. 2007; 32(12):2210–2216. [PubMed: 17676387]

25. Guha A, Tator CH, Piper I. Effect of a calcium channel blocker on posttraumatic spinal cord blood flow. J Neurosurg. 1987; 66(3):423–430. [PubMed: 3819838]

26. Das A, McDowell M, Pava MJ, Smith JA, Reiter RJ, Woodward JJ, Varma AK, Ray SK, Banik NL. The inhibition of apoptosis by melatonin in VSC4.1 motoneurons exposed to oxidative stress, glutamate excitotoxicity, or TNF-alpha toxicity involves membrane melatonin receptors. J Pineal Res. 2010; 48(2):157–169. [PubMed: 20082663]

27. Ray SK, Hogan EL, Banik NL. Calpain in the pathophysiology of spinal cord injury: neuroprotection with calpain inhibitors. Brain Res Rev. 2003; 42(2):169–185. [PubMed: 12738057]

28. Samantaray S, Sribnick EA, Das A, et al. Neuroprotective efficacy of estrogen in experimental spinal cord injury in rats. Ann N Y Acad Sci. 2010; 1199:90–94. [PubMed: 20633113]

29. Lee JY, Choi SY, Oh TH, Yune TY. 17beta-estradiol inhibits apoptotic cell death of oligodendrocytes by inhibiting rhoA-JNK3 activation after spinal cord injury. Endocrinology. 2012; 153(8):3815–3827. [PubMed: 22700771]

30. Samantaray S, Smith JA, Das A, et al. Low dose estrogen prevents neuronal degeneration and microglial reactivity in an acute model of spinal cord injury: effect of dosing, route of administration, and therapy delay. Neurochem Res. 2011; 36(10):1809–1816. [PubMed: 21611834]

31. Wang YF, Fan ZK, Cao Y, Yu DS, Zhang YQ, Wang YS. 2-Methoxyestradiol inhibits the up-regulation of AQP4 and AQP1 expression after spinal cord injury. Brain Res. 2011; 1370:220–226. [PubMed: 21092735]

32. Bonnefont-Rousselot D, Collin F, Jore D, Gardes-Albert M. Reaction mechanism of melatonin oxidation by reactive oxygen species in vitro. J Pineal Res. 2011; 50(3):328–335. [PubMed: 21244479]

33. Wu UI, Mai FD, Sheu JN, et al. Melatonin inhibits microglial activation, reduces pro-inflammatory cytokine levels, and rescues hippocampal neurons of adult rats with acute *Klebsiella pneumoniae* meningitis. J Pineal Res. 2011; 50(2):159–170. [PubMed: 21062353]

34. Das A, Wallace G IV, Reiter RJ, et al. Overexpression of melatonin membrane receptors increases calcium-binding proteins and protects VSC4.1 motoneurons from glutamate toxicity through multiple mechanisms. J Pineal Res. 2013; 54:58–68. [PubMed: 22823500]
35. Borisoff JF, Chan CC, Hiebert GW, et al. Suppression of Rho-kinase activity promotes axonal growth on inhibitory CNS substrates. Mol Cell Neurosci. 2003; 22(3):405–416. [PubMed: 12691741]
36. Ferrari G, Fabris M, Gorio A. Gangliosides enhance neurite outgrowth in PC12 cells. Brain Res. 1983; 284(2–3):215–221. [PubMed: 6307486]
37. Gonzenbach RR, Schwab ME. Disinhibition of neurite growth to repair the injured adult CNS: focusing on Nogo. Cell Mol Life Sci. 2008; 65(1):161–176. [PubMed: 17975707]
38. Gorio A, Ferrari G, Fusco M, Janigro D, Zanoni R, Jonsson G. Gangliosides and their effects on rearranging peripheral and central neural pathways. Cent Nerv Syst Trauma. 1984; 1(1):29–37. [PubMed: 6400197]
39. Liu BP, Cafferty WB, Budel SO, Strittmatter SM. Extracellular regulators of axonal growth in the adult central nervous system. Philos Trans R Soc Lond B Biol Sci. 2006; 361(1473):1593–1610. [PubMed: 16939977]
40. Schwab ME. Nogo and axon regeneration. Curr Opin Neurobiol. 2004; 14(1):118–124. [PubMed: 15018947]
41. Yiu G, He Z. Glial inhibition of CNS axon regeneration. Nat Rev Neurosci. 2006; 7(8):617–627. [PubMed: 16858390]
42. Karimi-Abdolrezaee S, Billakanti R. Reactive astrogliosis after spinal cord injury-beneficial and detrimental effects. Mol Neurobiol. 2012; 46(2):251–264. [PubMed: 22684804]
43. Dergham P, Ellezam B, Essagian C, Avedissian H, Lubell WD, McKerracher L. Rho signaling pathway targeted to promote spinal cord repair. J Neurosci. 2002; 22(15):6570–6577. [PubMed: 12151536]
44. Dubreuil CI, Winton MJ, McKerracher L. Rho activation patterns after spinal cord injury and the role of activated Rho in apoptosis in the central nervous system. J Cell Biol. 2003; 162(2):233–243. [PubMed: 12860969]
45. Jalink K, van Corven EJ, Hengeveld T, Morii N, Narumiya S, Moolenaar WH. Inhibition of lysophosphatidate- and thrombin-induced neurite retraction and neuronal cell rounding by ADP ribosylation of the small GTP-binding protein Rho. J Cell Biol. 1994; 126(3):801–810. [PubMed: 8045941]
46. Lord-Fontaine S, Yang F, Diep Q, et al. Local inhibition of Rho signaling by cell-permeable recombinant protein BA-210 prevents secondary damage and promotes functional recovery following acute spinal cord injury. J Neurotrauma. 2008; 25(11):1309–1322. [PubMed: 19061375]
47. Sung JK, Miao L, Calvert JW, Huang L, Louis Harkey H, Zhang JH. A possible role of RhoA/Rho-kinase in experimental spinal cord injury in rat. Brain Res. 2003; 959(1):29–38. [PubMed: 12480155]
48. Gu YL, Yin LW, Zhang Z, et al. Neurotrophin expressions in neural stem cells grafted acutely to transected spinal cord of adult rats linked to functional improvement. Cell Mol Neurobiol. 2012; 32(7):1089–1097. [PubMed: 22573254]
49. Quertainmont R, Cantinieaux D, Botman O, Sid S, Schoenen J, Franzen R. Mesenchymal stem cell graft improves recovery after spinal cord injury in adult rats through neurotrophic and pro-angiogenic actions. PLoS One. 2012; 7(6):e39500. [PubMed: 22745769]
50. Uchida K, Nakajima H, Hirai T, et al. The retrograde delivery of adenovirus vector carrying the gene for brain-derived neurotrophic factor protects neurons and oligodendrocytes from apoptosis in the chronically compressed spinal cord of twy/twy mice. Spine. 2012; 37(26):2125–2135. [PubMed: 22648027]
51. Donnelly EM, Lamanna J, Boulis NM. Stem cell therapy for the spinal cord. Stem Cell Res Ther. 2012; 3(4):24. [PubMed: 22776143]
52. Wang H, Fang H, Dai J, Liu G, Xu ZJ. Induced pluripotent stem cells for spinal cord injury therapy: current status and perspective. Neurol Sci. 2013; 34(1):11–17. [PubMed: 22797773]

53. Reddy MK, Wu L, Kou W, Ghorpade A, Labhasetwar V. Superoxide dismutase-loaded PLGA nanoparticles protect cultured human neurons under oxidative stress. Appl Biochem Biotechnol. 2008; 151(2–3):565–577. [PubMed: 18509606]
54. Vertegel AA, Reukov V, Maximov V. Enzyme-nanoparticle conjugates for biomedical applications. Methods Mol Biol. 2011; 679:165–182. [PubMed: 20865396]
55. Sharma HS. New perspectives for the treatment options in spinal cord injury. Expert Opin Pharmacother. 2008; 9(16):2773–2800. [PubMed: 18937612]
56. Begley DJ. Delivery of therapeutic agents to the central nervous system: the problems and the possibilities. Pharmacol Ther. 2004; 104(1):29–45. [PubMed: 15500907]
57. Schroeder U, Sommerfeld P, Ulrich S, Sabel BA. Nanoparticle technology for delivery of drugs across the blood-brain barrier. J Pharm Sci. 1998; 87(11):1305–1307. [PubMed: 9811481]
58. Torchilin VP. Drug targeting. Eur J Pharm Sci. 2000; 11(Suppl 2):S81–91. [PubMed: 11033430]
59. Kreuter J. Nanoparticulate systems for brain delivery of drugs. Adv Drug Deliv Rev. 2001; 47(1): 65–81. [PubMed: 11251246]
60. Lin Y, Pan Y, Shi Y, Huang X, Jia N, Jiang JY. Delivery of large molecules via poly(butyl cyanoacrylate) nanoparticles into the injured rat brain. Nanotechnology. 2012; 23(16):165101. [PubMed: 22460562]
61. Kreuter J, Ramge P, Petrov V, et al. Direct evidence that polysorbate-80-coated poly(butylcyanoacrylate) nanoparticles deliver drugs to the CNS via specific mechanisms requiring prior binding of drug to the nanoparticles. Pharm Res. 2003; 20(3):409–416. [PubMed: 12669961]
62. Kurakhmaeva KB, Djindjikhashvili IA, Petrov VE, et al. Brain targeting of nerve growth factor using poly(butyl cyanoacrylate) nanoparticles. J Drug Target. 2009; 17(8):564–574. [PubMed: 19694610]
63. Sharma HS, Ali S, Tian ZR, et al. Nano-drug delivery and neuroprotection in spinal cord injury. J Nanosci Nanotechnol. 2009; 9(8):5014–5037. [PubMed: 19928182]
64. Gibaud S, Demoy M, Andreux JP, Weingarten C, Gouritin B, Couvreur P. Cells involved in the capture of nanoparticles in hematopoietic organs. J Pharm Sci. 1996; 85(9):944–950. [PubMed: 8877884]
65. Moghimi SM, Hunter AC. Capture of stealth nanoparticles by the body's defences. Crit Rev Ther Drug Carrier Syst. 2001; 18(6):527–550. [PubMed: 11789674]
66. Kang CE, Baumann MD, Tator CH, Shoichet MS. Localized and sustained delivery of fibroblast growth factor-2 from a nanoparticle-hydrogel composite for treatment of spinal cord injury. Cells Tissues Organs. Jul 13.2012
67. Cho Y, Shi R, Ivanisevic A, Borgens RB. Functional silica nanoparticle-mediated neuronal membrane sealing following traumatic spinal cord injury. J Neurosci Res. 2010; 88(7):1433–1444. [PubMed: 19998478]
68. Wang YT, Lu XM, Zhu F, et al. The use of a gold nanoparticle-based adjuvant to improve the therapeutic efficacy of hNgR-Fc protein immunization in spinal cord-injured rats. Biomaterials. 2011; 32(31):7988–7998. [PubMed: 21784510]
69. Xia T, Kovochich M, Brant J, et al. Comparison of the abilities of ambient and manufactured nanoparticles to induce cellular toxicity according to an oxidative stress paradigm. Nano Lett. 2006; 6(8):1794–1807. [PubMed: 16895376]
70. Hall ED, Braughler JM. Glucocorticoid mechanisms in acute spinal cord injury: a review and therapeutic rationale. Surg Neurol. 1982; 18(5):320–327. [PubMed: 7179094]
71. Bracken MB, Shepard MJ, Holford TR, et al. Methylprednisolone or tirilazad mesylate administration after acute spinal cord injury: 1-year follow up. Results of the third national acute spinal cord injury randomized controlled trial. J Neurosurg. 1998; 89(5):699–706. [PubMed: 9817404]
72. Braughler JM, Hall ED. Lactate and pyruvate metabolism in injured cat spinal cord before and after a single large intravenous dose of methylprednisolone. J Neurosurg. 1983; 59(2):256–261. [PubMed: 6864292]
73. Faden AI, Jacobs TP, Mougey E, Holaday JW. Endorphins in experimental spinal injury: therapeutic effect of naloxone. Ann Neurol. 1981; 10(4):326–332. [PubMed: 6274252]

74. Coleman WP, Benzel D, Cahill DW, et al. A critical appraisal of the reporting of the national acute spinal cord injury studies (II and III) of methylprednisolone in acute spinal cord injury. J Spinal Disord. 2000; 13(3):185–199. [PubMed: 10872756]
75. Hurlbert RJ. The role of steroids in acute spinal cord injury: an evidence-based analysis. Spine. 2001; 26(24 Suppl):S39–46. [PubMed: 11805608]
76. Qian T, Guo X, Levi AD, Vanni S, Shebert RT, Sipski ML. High-dose methylprednisolone may cause myopathy in acute spinal cord injury patients. Spinal Cord. 2005; 43(4):199–203. [PubMed: 15534623]
77. Anderson DK, Braughler JM, Hall ED, Waters TR, McCall JM, Means ED. Effects of treatment with U-74006F on neurological outcome following experimental spinal cord injury. J Neurosurg. 1988; 69(4):562–567. [PubMed: 3418389]
78. Fehlings MG, Tator CH, Linden RD. The effect of nimodipine and dextran on axonal function and blood flow following experimental spinal cord injury. J Neurosurg. 1989; 71(3):403–416. [PubMed: 2475595]
79. Haghighi SS, Stiens T, Oro JJ, Madsen R. Evaluation of the calcium channel antagonist nimodipine after experimental spinal cord injury. Surg Neurol. 1993; 39(5):403–408. [PubMed: 8493602]
80. Ross IB, Tator CH. Further studies of nimodipine in experimental spinal cord injury in the rat. J Neurotrauma. 1991; 8(4):229–238. [PubMed: 1803031]
81. Pointillart V, Petitjean ME, Wiart L, et al. Pharmacological therapy of spinal cord injury during the acute phase. Spinal Cord. 2000; 38(2):71–76. [PubMed: 10762178]
82. Gaviria M, Privat A, d'Arbigny P, Kamenka J, Haton H, Ohanna F. Neuroprotective effects of a novel NMDA antagonist, Gacyclidine, after experimental contusive spinal cord injury in adult rats. Brain Res. 2000; 874(2):200–209. [PubMed: 10960605]
83. Gaviria M, Privat A, d'Arbigny P, Kamenka JM, Haton H, Ohanna F. Neuroprotective effects of gacyclidine after experimental photochemical spinal cord lesion in adult rats: dose-window and time-window effects. J Neurotrauma. 2000; 17(1):19–30. [PubMed: 10674755]
84. Fehlings MG, Baptiste DC. Current status of clinical trials for acute spinal cord injury. Injury. 2005; 36(Suppl 2):B113–122. [PubMed: 15993112]
85. Monga V, Meena CL, Kaur N, Jain R. Chemistry and biology of thyrotropin-releasing hormone (TRH) and its analogs. Curr Med Chem. 2008; 15(26):2718–2733. [PubMed: 18991632]
86. Naftchi NE. Prevention of damage in acute spinal cord injury by peptides and pharmacologic agents. Peptides. 1982; 3(3):235–247. [PubMed: 6181489]
87. Faden AI, Jacobs TP, Smith MT. Thyrotropin-releasing hormone in experimental spinal injury: dose response and late treatment. Neurology. 1984; 34(10):1280–1284. [PubMed: 6435011]
88. Pitts LH, Ross A, Chase GA, Faden AI. Treatment with thyrotropin-releasing hormone (TRH) in patients with traumatic spinal cord injuries. J Neurotrauma. 1995; 12(3):235–243. [PubMed: 7473798]
89. Ledeen RW. Ganglioside structures and distribution: are they localized at the nerve ending? J Supramol Struct. 1978; 8(1):1–17. [PubMed: 366282]
90. Sabel BA, Slavin MD, Stein DG. GM1 ganglioside treatment facilitates behavioral recovery from bilateral brain damage. Science. 1984; 225(4659):340–342. [PubMed: 6740316]
91. Sabel BA, DelMastro R, Dunbar GL, Stein DG. Reduction of anterograde degeneration in brain damaged rats by GM1-gangliosides. Neurosci Lett. 1987; 77(3):360–366. [PubMed: 3614768]
92. Cuello AC, Stephens PH, Tagari PC, Sofroniew MV, Pearson RC. Retrograde changes in the nucleus basalis of the rat, caused by cortical damage, are prevented by exogenous ganglioside GM1. Brain Res. 1986; 376(2):373–377. [PubMed: 3730841]
93. Geisler FH, Dorsey FC, Coleman WP. Recovery of motor function after spinal-cord injury–a randomized, placebo-controlled trial with GM-1 ganglioside. New Engl J Med. 1991; 324(26): 1829–1838. [PubMed: 2041549]
94. Geisler FH, Coleman WP, Grieco G, Poonian D. The Sygen multicenter acute spinal cord injury study. Spine. 2001; 26(24 Suppl):S87–98. [PubMed: 11805614]

95. Geisler FH, Coleman WP, Grieco G, Poonian D. Measurements and recovery patterns in a multicenter study of acute spinal cord injury. Spine. 2001; 26(24 Suppl):S68–86. [PubMed: 11805613]
96. Geisler FH, Coleman WP, Grieco G, Poonian D. Recruitment and early treatment in a multicenter study of acute spinal cord injury. Spine. 2001; 26(24 Suppl):S58–67. [PubMed: 11805612]
97. Chinnock P, Roberts I. Gangliosides for acute spinal cord injury. Cochrane Database Syst Rev. 2005; 2:CD004444. [PubMed: 15846715]
98. Fehlings MG, Theodore N, Harrop J, et al. A phase I/IIa clinical trial of a recombinant Rho protein antagonist in acute spinal cord injury. J Neurotrauma. 2011; 28(5):787–796. [PubMed: 21381984]
99. Liebscher T, Schnell L, Schnell D, et al. Nogo-A antibody improves regeneration and locomotion of spinal cord-injured rats. Ann Neurol. 2005; 58(5):706–719. [PubMed: 16173073]
100. Freund P, Schmidlin E, Wannier T, et al. Nogo-A-specific antibody treatment enhances sprouting and functional recovery after cervical lesion in adult primates. Nat Med. 2006; 12(7):790–792. [PubMed: 16819551]
101. Zorner B, Schwab ME. Anti-Nogo on the go: from animal models to a clinical trial. Ann N Y Acad Sci. 2010; 1198(Suppl 1):E22–34. [PubMed: 20590535]
102. Cheng H, Cao Y, Olson L. Spinal cord repair in adult paraplegic rats: partial restoration of hind limb function. Science. 1996; 273(5274):510–513. [PubMed: 8662542]
103. Cheng H, Liao KK, Liao SF, Chuang TY, Shih YH. Spinal cord repair with acidic fibroblast growth factor as a treatment for a patient with chronic paraplegia. Spine. 2004; 29(14):E284–288. [PubMed: 15247588]
104. Wu JC, Huang WC, Chen YC, et al. Acidic fibroblast growth factor for repair of human spinal cord injury: a clinical trial. J Neurosurg Spine. 2011; 15(3):216–227. [PubMed: 21663406]
105. Bomstein Y, Marder JB, Vitner K, et al. Features of skin-coincubated macrophages that promote recovery from spinal cord injury. J Neuroimmunol. 2003; 142(1–2):10–16. [PubMed: 14512160]
106. Knoller N, Auerbach G, Fulga V, et al. Clinical experience using incubated autologous macrophages as a treatment for complete spinal cord injury: phase I study results. J Neurosurg Spine. 2005; 3(3):173–181. [PubMed: 16235699]
107. Schwartz M, Yoles E. Macrophages and dendritic cells treatment of spinal cord injury: from the bench to the clinic. Acta Neurochir. 2005; 93:147–150.
108. Caplan AI. Adult mesenchymal stem cells for tissue engineering versus regenerative medicine. J Cell Physiol. 2007; 213(2):341–347. [PubMed: 17620285]
109. Sykova E, Homola A, Mazanec R, et al. Autologous bone marrow transplantation in patients with subacute and chronic spinal cord injury. Cell Transplant. 2006; 15(8–9):675–687. [PubMed: 17269439]
110. Deda H, Inci MC, Kurekci AE, et al. Treatment of chronic spinal cord injured patients with autologous bone marrow-derived hematopoietic stem cell transplantation: 1-year follow-up. Cytotherapy. 2008; 10(6):565–574. [PubMed: 18615345]
111. Kumar AA, Kumar SR, Narayanan R, Arul K, Baskaran M. Autologous bone marrow derived mononuclear cell therapy for spinal cord injury: a Phase I/II clinical safety and primary efficacy data. Exp Clin Transplant. 2009; 7(4):241–248. [PubMed: 20353375]
112. Kishk NA, Gabr H, Hamdy S, et al. Case control series of intrathecal autologous bone marrow mesenchymal stem cell therapy for chronic spinal cord injury. Neurorehabil Neural Repair. 2010; 24(8):702–708. [PubMed: 20660620]
113. Huard JM, Youngentob SL, Goldstein BJ, Luskin MB, Schwob JE. Adult olfactory epithelium contains multipotent progenitors that give rise to neurons and non-neural cells. J Comp Neurol. 1998; 400(4):469–486. [PubMed: 9786409]
114. Li Y, Field PM, Raisman G. Regeneration of adult rat corticospinal axons induced by transplanted olfactory ensheathing cells. J Neurosci. 1998; 18(24):10514–10524. [PubMed: 9852589]
115. Lima C, Escada P, Pratas-Vital J, et al. Olfactory mucosal autografts and rehabilitation for chronic traumatic spinal cord injury. Neurorehabil Neural repair. 2010; 24(1):10–22. [PubMed: 19794133]

116. Das A, Sribnick EA, Wingrave JM, et al. Calpain activation in apoptosis of ventral spinal cord 4.1 (VSC4.1) motoneurons exposed to glutamate: calpain inhibition provides functional neuroprotection. J Neurosci Res. 2005; 81(4):551–562. [PubMed: 15968645]

117. Ray SK, Wilford GG, Matzelle DC, Hogan EL, Banik NL. Calpeptin and methylprednisolone inhibit apoptosis in rat spinal cord injury. Ann N Y Acad Sci. 1999; 890:261–269. [PubMed: 10668431]

118. Teng YD, Choi H, Onario RC, et al. Minocycline inhibits contusion-triggered mitochondrial cytochrome c release and mitigates functional deficits after spinal cord injury. Proc Natl Acad Sci USA. 2004; 101(9):3071–3076. [PubMed: 14981254]

119. Wu KL, Hsu C, Chan JY. Nitric oxide and superoxide anion differentially activate poly(ADP-ribose) polymerase-1 and Bax to induce nuclear translocation of apoptosis-inducing factor and mitochondrial release of cytochrome c after spinal cord injury. J Neurotrauma. 2009; 26(7):965–977. [PubMed: 19473058]

120. Gensel JC, Tovar CA, Bresnahan JC, Beattie MS. Topiramate treatment is neuroprotective and reduces oligodendrocyte loss after cervical spinal cord injury. PLoS ONE. 2012; 7(3):e33519. [PubMed: 22428066]

121. Kumru H, Kofler M. Effect of spinal cord injury and of intrathecal baclofen on brainstem reflexes. Clin Neurophysiol. 2012; 123(1):45–53. [PubMed: 22030139]

122. Rong W, Wang J, Liu X, et al. 17beta-estradiol attenuates neural cell apoptosis through inhibition of JNK phosphorylation in SCI rats and excitotoxicity induced by glutamate in vitro. Int J Neurosci. 2012; 122(7):381–387. [PubMed: 22409452]

123. Garcia-Zozaya IA. Adrenal insufficiency in acute spinal cord injury. J Spinal Cord Med. 2006; 29(1):67–69. [PubMed: 16572567]

124. Samantaray S, Matzelle DD, Ray SK, Banik NL. Physiological low dose of estrogen-protected neurons in experimental spinal cord injury. Ann N Y Acad Sci. 2010; 1199:86–89. [PubMed: 20633112]

125. Ji B, Li M, Wu WT, Yick LW, et al. LINGO-1 antagonist promotes functional recovery and axonal sprouting after spinal cord injury. Mol Cell Neurosci. 2006; 33(3):311–320. [PubMed: 17011208]

Table 1

Mechanistic targets for SCI therapy

Strategy	General target	Potential agents	Expected outcome
Neuroprotection	Apoptotic regulators	Calpeptin, SNJ1945, Ca^{2+} channel blockers, Bcl-2 activators, cytochrome c blockers, minocycline	Prevent secondary apoptotic induction [116–119]
	Excitotoxic regulators	GluR inhibitors (Agmantine, MK801), GABA agonists (pregnenolone, glutamine synthetase, baclofen, benzodiazepines)	Increase synaptic activation threshold [120, 121]
	Trophic regulators	Adhesion modifiers, hormone therapy (ACTH, estrogen, testosterone, malanotropin, GH), monosialic ganglioside, growth factors (NGF, BDNF, NT-3, NT-4, FGF, GDNF)	Restore general homeostasis, neural growth stimulator, enhance pro-survival glial activation, promotes intracellular survival cascades [122–124]
	Anti-inflammatories	COX-2 inhibitors, MP, selective lymphocyte/macrophage activation, reduces prostaglandin production	Reduce natural killer/macrophage related toxicity,
Axonal regeneration [35–42]	Axonal trophism	Neurotransmitter treatment (Seratonin, clonidine, tizanidine, CPG stimulation, FES/FNS), protein kinase modulation, Chondrotinase, Nogo inhibitors, Nogo receptor blocker, soluble LINGO-1 (LINGO-1-Fc) [125]	Promotes axonal extension and synaptic reconnection
	Glial trophism	FGF, GDNF, VEGF, estrogen, GH	Promotes glial survival/proliferation and thus neuronal/neurite survival
	Glial inhibitors	Nogo inhibitors, Nogo receptor antagonists, anti-inflammatory med's (for microglia)	Prevents inhibitory scar formation, allows axonal regrowth through injury area
	Forced-use training	Constraint-induce therapy, Forced-use training	Potentiates axonal activation by mechanically reducing activation threshold of synapses
Stem cell therapy [49–51]	Adult	BMSCs, fat cells, dermal cells, olfactory ensheathing cells	Potentiates remyelination of axons, glial repopulation, growth factor production
	Embryonic	Human (from in vitro fertilization), cloned	Glial and neuronal repopulation possible (with directed growth factor administration prior to/ immediately following transplantation
	Allografts	Schwann cell autografts, allografts	Axonal recapitulation; glial cell repopulation
Other	Tetracycline	Unclear	Possible anti-inflammatory activities