

KEEPING PROMISES: TRANSLATING BASIC RESEARCH INTO
NEW SPINAL CORD INJURY THERAPIES

Naomi Kleitman, PhD

National Institute of Neurologic Disorders and Stroke, National Institutes of Health, Bethesda, Maryland

Received April 6, 2004; accepted May 11, 2004

ABSTRACT

Summary: Centuries of medical wisdom—namely that spinal cord injury (SCI) treatment was limited to caretaking until the patients inevitably succumbed to complications—has given way to tremendous medical and research advancements. The prognosis for survival after SCI improved significantly after World War II, leading to the largest population of people aging with chronic SCI in history. Despite the general lack of optimism for functional recovery after SCI, the spinal cord has proven to be one of the most attractive systems for studying central nervous system plasticity. Predictions of clinical applications derived from basic findings now routinely accompany reports of evidence for spinal axon regeneration. This has led to great debate in the SCI research community about the level and quality of evidence needed to select truly promising candidate therapies. This article reviews the basis for optimism in the new understanding of the processes of degeneration after SCI and the mechanisms of regeneration. The emphasis is on neuroprotective and reparative strategies emerging from the animal literature, and on the steps remaining to be taken to translate these into effective clinical trials of new therapies. Examples of the translational process in related areas of brain injury and stroke are cited, as well as the specific issues relating to the needs of individuals with SCI.

J Spinal Cord Med. 2004;27:311–318

Key Words: Spinal cord injuries; Clinical trials; Animal models; Regeneration; Neuroprotection

INTRODUCTION

At the dawn of the 20th century, Ramón y Cajal and his students studied the inability of central nervous system (CNS) axons to regenerate (1,2), contrasting this failure to the successful repair that they observed in peripheral nerves. Some indications of CNS plasticity and recovery of function were reported mid-century (3–5), but it was the observations of Aguayo and colleagues (6,7) in the early 1980s, who showed that CNS axons regenerate into peripheral nerve bridges and exit short distances back into the spinal cord, that electrified the field of CNS regeneration research. Ironically, despite the general lack of optimism for functional recovery after spinal cord injury (SCI), the outlying regions of the CNS, spinal cord, and optic nerve proved to be among the most attractive systems for studying CNS plasticity (8–10). Since that time, ever-increasing research effort has focused on SCI. Consequently, a number of new strategies for neuroprotection, regeneration, and restoration of function have been described based on animal models. The development of a reliable, quantitative scale to measure locomotor function in rodents (the BBB scale) (11) has enabled researchers to augment their basic regeneration studies with behavioral analysis to an unprecedented extent. Concurrently, recent studies of spinal

cord physiology (12–16) have demonstrated clearly the cord's complexity as an integrator of locomotor and respiratory rhythms as well as the plasticity of reflex circuits in response to experience or injury.

This enthusiasm for spinal regeneration research has evoked stories of promise and hope in popular and scientific publications. Predictions that basic findings could lead to clinical applications routinely accompany studies that report axonal regeneration and statistically significant behavioral recovery in animal studies of novel SCI therapies. To date, that promise has not been fulfilled by improving clinical treatments for SCI. Those hopeful predictions fail to communicate the difficulty and number of unknowns involved in the implementation of successful clinical trials. There is great debate in the SCI research community about the level and quality of evidence needed to select truly promising candidate therapies, as well as debate about the appropriate steps needed to develop decisive clinical tests to assess the efficacy of the proposed therapeutic strategies.

This article reviews the steps that remain to successfully translate therapeutic strategies that promise to restore function to SCI individuals, and the debate about the process. Although not an exhaustive review, it cites some of the many other reviews already available that describe the SCI research literature. The focus is on neuroprotective and reparative strategies emerging from the animal literature; however, this is not meant to minimize the importance of strategies that build on remaining neural connections and functionality, such as

Please address correspondence to Naomi Kleitman, PhD, Neuroscience Center, Room 2204, MSC 9525, 6001 Executive Boulevard, Bethesda, MD 20892-9525; phone: 301.496.1447; fax: 301.480.1080 (e-mail: nk85q@nih.gov).

rehabilitation and neural prosthesis applications, which already are benefiting some patients with SCI.

ALTERING OUTCOMES: IMPROVED MEDICAL CARE AND UNDERSTANDING OF SCI

Throughout the history of medicine to the mid-20th century, medical wisdom dictated that treating severe SCI largely involved caretaking until the patients inevitably succumbed to infections and other complications. During World War II, this hopelessness turned into a focus on survival after SCI. This effort was facilitated by the introduction of antibiotics and long-term medical management at centers for treatment and rehabilitation of patients with SCI, modeled on the center at Stoke Mandeville Hospital in England developed by Sir Ludwig Guttman in 1944. Dr. Guttman's emphasis was on preventing or overcoming systemic complications and helping patients to acquire new skills, engage in sports, and survive long term (17).

Cases of SCI are not tracked comprehensively in the United States; however, the estimated incidence is 12,000 cases per year, with approximately a quarter of a million Americans living with chronic SCI (18,19). The largest proportion still occurs in relatively young men, 16 to 30 years of age, escalating the high social and economic burden of this condition. Medical advances beginning in the 1940s have led to the largest population of people aging with chronic SCI in history. There has been a trend toward more injuries resulting in incomplete motor and sensory loss (now about 55% of injuries), and the injuries diminishing life expectancy to a lesser extent as medical management has improved (20). Improved outcomes can be attributed largely to increased awareness by first responders who immobilize patients after injury, and emergency and hospital care designed to limit secondary injury, all of which help to improve survival and minimize additional loss of function (18). In addition to experiencing losses in motor and sensory function; spasticity; and bowel, bladder, and sexual dysfunctions; persons with chronic SCI continue to face increased risks of urinary and pulmonary infections, pressure ulcers, neurogenic pain, autonomic dysreflexia, bone density loss, and cardiovascular and metabolic diseases (21). Despite progress in basic research, the medical outlook for patients in emergency rooms or rehabilitation units does not include plans for curative therapies. SCI continues to cause permanent impairments, and the hope of reversing these impairments lies with research discoveries.

In the search for novel treatments—either to prevent damaging cellular responses to the initial injury or restore function in chronic injury—researchers are seeking to better understand spinal cord function, the nature of the processes by which injury occurs, and the possibility for regeneration or replacement of neuronal connections that can restore lost functions. There have been a number of excellent reviews of the process of degeneration after SCI (eg, 22–24), which includes acute and ongoing loss of neurons, oligodendrocytes, and other cells (25); vascular damage (26–28); and the deposition of matrix molecules and exposure of myelin proteins that are believed to inhibit successful regeneration (29–34). The lesion cavity itself is a barrier to regeneration, but is not entirely

hostile to axonal sprouting, as indicated by the common phenomenon of Schwannosis (infiltration of aberrant Schwann cell myelinated nerve fibers) (35). This is but one example of the capacity of the adult human spinal cord for endogenous plasticity. Other examples include plasticity in the segments surrounding the site of injury that may be responsible for some neurologic recovery over the first months or years after injury, and may contribute to the development of neurogenic pain, spasticity, and novel reflexes that develop over time (36,37).

Overall, researchers have identified several well-defined targets for development of restorative therapies in SCI. These are “the 5Rs” (6R's):

- **Reduction** of secondary cell death and axon damage (neuroprotection);
- **Replacement** of lost cells, particularly lower motor and/or propriospinal neurons;
- **Repair and regeneration** of damaged axonal systems;
- **Remyelination** of spared, but demyelinated, axons or regenerating fibers;
- **Rehabilitation** to enhance plasticity, modulate reflexes, and improve function.

The rest of this discussion assesses the development of these strategies into viable therapeutic options.

A CASCADE OF NEW POSSIBILITIES

The history of modern CNS regeneration research, which has been described many times (see, eg, 38–40), begins with the major advances made in the 1980s. CNS axon regeneration through peripheral nerve bridges (1,2) was proved to not be an artifact of silver staining (6,7), but to actually have the potential to restore synaptic connections to target cells in distant brain nuclei (41). Grafts of spinal cord tissue enhanced by neurotrophic support were shown to relay signals at the lesion site (42). With the isolation and testing of numerous families of trophic factors, the importance of growth conducive and inhibitory proteins grew (43–45). Concurrently, studies of the pathophysiologic processes, such as detrimental immunologic reactions and membrane disruption by lipid peroxidation (22), led to the development of neuroprotective strategies and clinical testing in the 1980s and 1990s of high-dose methylprednisolone and other promising agents (National Acute Spinal Cord Injury Study trials) (46,47).

Methodologic advances and standardization also have fueled this field. Using standardized rodent models for contusion (48–50) or compression (51) injuries, combined with quantifiable, well-validated, behavioral tests like the 21-point BBB scale (11), researchers have demonstrated remarkably similar differences between treatment groups of 1 to 3 points on this scale. Although it is not known how relevant a change in “the frequency of plantar stepping” or of “forelimb-to-hindlimb coordination” in rats is to clinical outcomes in human trials, these functional results are intriguing. Why do so many dissimilar experimental strategies elicit these small but statistically reliable changes in the midrange of the BBB scale? Is there a common mechanism that can and should

be targeted? Discovery of the mechanisms by which the new strategies cause the observed functional changes would make it possible to better interpret whether these changes could be predictors of clinical importance.

These fundamental leads are developing into numerous avenues being tested for their promise in SCI repair. Although a comprehensive list most likely is unachievable, some of the promising *regenerative strategies* developed so far include (a) introducing complex peripheral and embryonic CNS environments into the site of the lesion (6,42,52,53); (b) isolating particular cell types such as Schwann cells, olfactory ensheathing cells, and, most recently, populations of neural progenitor or stem cells, and their introduction into the injured spinal cord (54–57); (c) introducing trophic factors at the site of lesion or near somas of injured neurons by infusion or via viral or cellular constructs (58–60); (d) disrupting inhibitory molecules or their receptors, including multiple myelin proteins and inhibitory matrix proteoglycans (29–34), or bypassing these inhibitors by modulating intracellular signals (61); and (e) combinations of these, as well as addition of matrix or polymer scaffolds to support implants or guide axons directly (eg, 62). *Neuroprotective strategies* focus on preventing excitotoxicity and destructive cytokine cascades (63), modulating immunologic processes (64,65) or scar formation (66), and inhibiting multiple cellular processes by hypothermia or irradiation (67–70). Finally, *rehabilitative strategies* have received renewed attention as the understanding of the spinal circuitry controlling locomotion, spasticity, and pain has evolved; these therapies include locomotor training and pharmacotherapies (71–73). Although some advocates consider an emphasis on rehabilitation to be antithetical to cure research (the “care versus cure” debate), increasingly, the clinical and research communities are communicating, to the benefit of both (74).

Many of these strategic approaches have been discussed in terms of therapeutic potential from their conception, yet relatively few SCI trials have been initiated. Early tests of neurotrophic factors in neurologic disease encountered problems due to side effects of these powerful compounds (75). Although trophic factors remain some of the most promising compounds for stimulating regeneration in the spinal cord, serious consideration is being given to appropriate delivery systems and the possibility of aberrant growth that could result in neuropathic pain or other side effects (58,76). The effectiveness of even those therapies already in common clinical use, such as methylprednisolone and body-weight-supported treadmill locomotor training, have been called into question by recent observations (eg, 77; Bruce Dobkin, unpublished observations). The situation will become even more complex when therapies combining several novel strategies are tested, which most researchers seem to concur will be necessary.

These obstacles can be overcome, and must be, if the strategies are to truly deliver on the promise of substantial functional recovery to individuals with SCI. Based on the complexities just noted, careful analysis of alterations in not only the locomotor system but also sensory, autonomic, and possibly cognitive function should be assessed in relevant

animal models. This is not just an inconvenient distraction on the way to clinical trials. Sensory and autonomic functions—particularly bowel, bladder, and sexual function—are highly relevant as therapeutic endpoints in themselves, and routinely are ranked by patients as most directly affecting their quality of life (78; Kimberly Anderson, unpublished observations). Thus, it not only is essential to address how a novel therapy augments axonal regeneration, but also how it affects surviving endogenous spinal circuitry.

MOVING AHEAD WITH TRANSLATION

Despite the complexities noted above, the SCI research community is actively interested and appears to be poised to translate its basic observations to human trials. In some cases, this transition is underway (see 74 for a review, 79). Yet overall, since the NASCIS trials examined acute neuroprotective drug therapies, SCI researchers have been slower than their colleagues in brain injury and stroke to initiate new therapeutic trials (80,81). One could argue that the results of the NASCIS trials themselves, and the availability of methylprednisolone therapy, tended to inhibit further incremental trials in SCI while stimulating related fields such as traumatic brain injury to initiate trials search of an effective protective agent.

Recently, however, some agents have been tested clinically [GM-1 ganglioside (82), activated macrophages (79), and the N-methyl-D-aspartate receptor antagonist, gacyclidine (83)]. Initial studies included both complete and incomplete SCI. Trends reported in these early intervention studies suggested that patients with incomplete cervical injuries were more likely to benefit from such interventions than were patients with complete cervical injuries or those with thoracic injuries. In the thoracic region, outcome measures of motor improvement are relatively insensitive, and minor neurologic improvements are less likely to affect functional outcomes. Interventions in chronic SCI have included extensive testing of 4-aminopyridine (73), embryonic cord grafts to diminish cyst expansion in syringomyelia patients (84), and development of various functional neuromuscular stimulation devices (eg, 85,86). As shown by this review of the range of therapeutic possibilities, there are real benefits to discussing experiences and expectations in diverse disciplines such as engineering, basic and clinical sciences. This discussion could help prioritize SCI therapies as they move toward clinical testing (85).

Under the best of circumstances, even failure of a treatment to restore significant function would be informative, if the discrepancies between laboratory and clinical results could be reconciled. Iteration back to animal studies after human trials is essential if we are to develop better preclinical research models that adequately predict clinical outcomes. Unfortunately, this has not yet occurred; trials have not been designed to obtain data to address particular mechanistic assumptions. In brain injury and stroke, post hoc analysis of the trial designs showed that clinical trials often did not faithfully reflect the successful parameters of the animal experiments (80,81). Human testing in SCI also has strayed from the underlying preclinical data. For example, testing of human fetal grafts to arrest cyst expansion is quite different than is the regeneration emphasis in preclinical

studies of transection or contusion injuries (52,84). Similarly, although activated macrophages were tested immediately after injury in transected rat cord, clinical implementation began 1 to 2 weeks after closed SCI (65,79). Nevertheless, these studies showed some evidence of effectiveness in preventing cyst expansion, and intriguing results in some patients after macrophage treatments (79,84). However, the fetal graft trials have not led to further trials or changes in standard treatment, even for syringomyelia. As Dr. Reier pointed out at the 2002 Society for Neurotrauma meeting, evidence that grafted cells survived was not available, making it difficult to draw conclusions about the safety of the cellular therapy itself. Measures that assess the activity of a therapeutic agent would enhance the ability to reconcile either positive or negative clinical results with predictions from animal models.

CONSIDERATIONS IN UNDERTAKING TRANSLATION TO CLINICAL TESTING

Questions of how to safely and ethically develop therapies for a stable, chronic SCI population, and how to run trials large enough to prove efficacy, have been addressed at 2 recent workshops organized by the National Institute of Neurologic Disorders and Stroke (NINDS; 87) in February 2003 and the International Campaign for Cures of Spinal Cord Injury Paralysis in February 2004. These discussions addressed many important questions, but reached few definitive answers.

One of the very difficult questions that the SCI research field is asking is how much preclinical data is enough to justify proceeding to human testing? There is no clear answer. At its essence, this question addresses the value of any of the animal models in predicting clinical outcomes. No animal model is ideal, although contusion/compression injuries often are cited as “clinically relevant.” That does not make them the best choice for every experiment. It is clear that testing of therapies for chronic patients requires assessment in a truly chronic animal setting (60,88). Less universally accepted is the need for large animal or primate models. There is no formula to predict the number of cells or dosing calculation needed to “ramp up” from studies in small rodents to human-sized injuries; thus, larger models are cited as an intermediate step. Cellular testing proposed for dogs (in which naturally occurring injuries can be studied) or primates is not trivial. It also requires developing techniques to acquire and cultivate cells from these species, which do not model human cells directly (89,90) and would not contribute to meeting regulatory requirements for human cell products.

Given that highly successful clinical strategies based on particular animal models are rare, it seems too conservative to insist on any particular preclinical modeling before human testing is considered—and there is only so much mechanistic information we can and need to determine from animal models. It seems most reasonable to ask that a therapy’s known strengths and weaknesses be calibrated to match experimental and clinical realities as much as possible. The more a strategy’s success relies on use of a particular rodent strain, injury model, or hyperacute therapeutic window, the less likely one would expect it to be in a clinical setting. It would be most informative

to assess new strategies in different models and assess their effects on different components of SCI and its aftermath (80).

Comparing the realities of clinical testing to expectations from animal studies raises the issue of functional outcome assessments in human trials—for example, assessing autonomic functions or incremental functional changes versus “walking.” For trials of regeneration strategies, it also is important to question the usefulness and sensitivity of existing outcome measures, which were developed not for trials but for clinical tracking of patients. Early tests of strategies to promote axonal regeneration may not restore function that is clinically relevant, but will be important scientifically to assess any indication of improvement or deficit attributable to the treatment. Motor and sensory function assessed by the American Spinal Injury Association scale (91) does not take pain or autonomic or sexual function into account, and may not be sensitive enough to detect a few spinal levels of regeneration in thoracic injuries. At least 2 groups have taken on such questions (92,93), which may set new precedents for human SCI trials.

One important consideration that has arisen from discussions between clinicians and basic researchers is that clinical trials place a burden on the patients. Based on its incidence and prevalence, SCI is a relatively rare disorder and the population of eligible participants will be limited. Acute SCI patients are not stable, and the risks of invasive experimental interventions can be significant, which has impacted direct assessment of even neurosurgical treatments. The lack of evidence-based standards for acute surgical or rehabilitation care is another issue to be considered in foreseeing human trials (94,95). If clinical standards are lacking, then controlling for adjunct rehabilitation or surgical therapies will be critical in planning a meaningful trial. However, long-term trials that require extensive rehabilitation time and follow-up may not be practical for patients trying to get back into their work or school environment, especially when long-distance travel is involved. These issues contribute to the need to carefully consider trial design in the testing of complex therapeutic strategies (74).

THE NUTS AND BOLTS OF TRANSLATION

Translation begins with foreseeing clinical use of a strategy. The first burden of proof for advancing a new strategy should be to illustrate that the strategy is robust, and the positive result is repeatable. These qualities could be illustrated by testing in different relevant injury severities, at different spinal levels, across different species, or in independent laboratories. Comparing the various cell types or strategies head to head preclinically also would increase the level of confidence that any particular therapy is ready for translation.

Unlike the oft-used comparison to the moon landing, there is not a basic understanding and agreement on what is needed to reach the goal of spinal cord repair, and numerous strategies are being pursued simultaneously. Although there is no definitive list of considerations that are required and sufficient to predict success in human trials, there are a number of topics that are being considered. For drug studies, the experience of the brain injury community is most informative, and the reader is referred to the excellent suggestions of the Clinical Trials in

Head Injury Study Group (80) and the Stroke Therapy Academic Industry Roundtable (96). Cell-based therapies have other considerations, and some of these have been addressed (97). These considerations include justification of the choice of cell type in comparison with related cells; optimal purity of the population; availability of human source material; manipulation/expansion of the populations before implantation; selection of delivery site and dose (rationale for scaling cell grafts to the size needed for effective human use); assessment of cell survival and migration in vivo; possible need for immune suppression; appropriate time of delivery; potential need to remove scar or reinjure surviving tissue; combinations with factors or scaffolds; and, ultimately, good manufacturing processes, safety/toxicology testing, and so forth.

Other translational considerations include gender and genetic diversity in selecting inclusion/exclusion criteria, possible biomarkers to assess outcomes in short-term trials that may predict long-term functional improvements (ie, success of phase III efficacy testing), and exposing animal models to situations that are like those experienced by patients (eg, adjunct therapies, intensive care, and rehabilitation). The process would be accelerated if the basic scientists who are interested in translation of their models considered these issues early in the process, but generally these are separate from experiments used to establish proof of principle.

In July 2002, the NINDS initiated a series of Program Announcements to support translational research in the neurosciences. One announcement encompasses cooperative agreements for individual investigators, collaborative centers, and meetings (PAR-02-139; see <http://grants1.nih.gov/grants/guide/index.html> for descriptions of any of these announcements). This announcement solicits research that starts only after mechanisms or models for a disorder are established, and ends before clinical testing. PAR-02-138 supports exploratory/development projects, and PAR-02-140 supports career development. The program is intended to catalyze translational research in neuroscience as a cooperative, iterative process leading to new and effective interventions for neurologic disorders. Early-stage projects may lead to the identification and characterization of candidate therapeutics, and late-stage projects—including pharmacology/toxicology and Investigational New Drug or Investigational Device Exemption applications to the Food and Drug Administration—also are within the scope of the program. Funding under this program can cover drug or cell production, sterility, toxicity, pharmacokinetics, dosing, timing; assessing the long-term function of implanted cells, or the diffusion and washout of infused factors; assessing both direct and indirect effects of novel therapeutic strategies, including considering potential side effects; and evaluating combination strategies preclinically. The goal is to facilitate the effective review and research administration of translational research projects.

Clinical testing involves several initial phases before the efficacy of an intervention is tested in a definitive phase III trial. The early stages include safety assessment of the intervention and pilot studies to obtain necessary information to establish the clinical basis for proceeding to an efficacy trial, including early detection of treatment activity and

preliminary data to support the rationale for a phase III clinical trial of an intervention. NINDS has a program (PAR-03-174) to support pilot clinical studies designed to obtain information needed to establish clearly the clinical basis for proceeding to a full-scale trial.

Without agreement on the question of exactly what or how much preclinical evidence of efficacy should be demonstrated before a novel therapeutic approach is tested in human participants, the traditional question of the risk/benefit ratio remains the standard. Like most other translational researchers, the SCI community is addressing questions of adequate informed consent of potential participants, recruiting sufficient numbers of participants to definitively assess efficacy, and deciding on adequate outcome measures to detect effects of incremental therapies (no “cure” is on the horizon yet). Determining realistic and appropriate primary and secondary outcome measures is one of the most important challenges. It is now understood that setting the bar too high can doom a potentially valuable incremental treatment. Risk/benefit calculations vary depending on the purpose and timing of the therapeutic intervention. One group—the International Spinal Research Trust—has stated that for their early tests of novel, presumably invasive therapies, testing will be limited to chronic participants with stable complete thoracic SCI (98). Their goal—to detect as few as 2 segments of partially restored function in the thoracic region—corresponds to setting a rather high bar and is necessitating the development of new outcome assessments (92). This may be prudent for early stages of high-risk clinical testing, but to be significant clinically, later phase trials will need to be more inclusive, and powered to detect incremental, but clinically significant, changes in outcome compared with a control population of individuals with SCI. These trials could be stratified to account for different types of injury (eg, complete/incomplete or cervical/thoracic). Larger trials can be designed to detect changes in subpopulations while testing the relevance of the therapy to all patients that ultimately might benefit from it. Appropriate interim analyses can be incorporated to monitor safety.

In 2002, Dr. Elias Zerhouni, Director of the National Institutes of Health (NIH), initiated a priority-setting process that has resulted in a strategic vision known as the NIH Roadmap (see <http://nihroadmap.nih.gov>). One of the 3 themes of this plan is “Re-Engineering the Clinical Research Enterprise,” a well-defined effort to accelerate translation of basic scientific advances into improved health for the nation. It entails, in part, the standardization of clinical research policies and regulations, the integration of clinical research networks, and enhanced clinical research workforce training. The programs resulting from this effort should facilitate translation of research findings in all areas of neurologic disorders, including SCI. For acute conditions, such as spinal cord and brain injury, stroke, and status epilepticus, clinical research teams may include a unique combination of specialties—involving emergency care specialists and intensivists along with neurosurgeons, neurologists, and ultimately physiatrists and therapists—to assess the effects of acute therapies and adjunct rehabilitation in multicenter trials.

An important consideration in the development of SCI trials—in particular, for invasive or combination therapies—is how to ethically incorporate control groups into the trials. The lack of evidence-based standards for acute or even rehabilitative care will complicate trial design (94,95). The baseline outcomes for SCI have changed to a measurable extent over time [eg, a decline in the relative incidence of complete versus incomplete injuries (18)], bringing historic controls into question. When patients and surgeons cannot be blinded to treatment, placebo effects may be controlled in some cases by blinding outcome assessment. This is yet another area in which experts in the field are seeking agreement as to how best to proceed.

CONCLUSION

The field of SCI research has progressed from hopelessness to an abundance of promise in a relatively short period. There still is no proven path for the successful translation of promising strategies to clinical success, and individuals living with the functional losses imposed by SCI are anxiously awaiting significant improvements in their therapeutic options. Addressing the sometimes dauntingly complex realities of translating basic findings requires committed interactions between basic, translational and clinical scientists. Although debates continue, serious discussion is underway among these groups. This interaction should help to focus the efforts on strategies aimed at the most clinically relevant targets, including not only motor and sensory but also autonomic function.

ACKNOWLEDGMENTS

The author thanks Dr. Joseph Pancrazio, Dr. Mary Ellen Michel, Dr. Thomas Miller, and Ms. Lorraine Fitzsimmons for helpful comments on the manuscript.

REFERENCES

1. Tello D. La influencia del neurotropismo en la regeneración de los centros nerviosos. *Work of the laboratory of biological studies of the University of Madrid*. 1911;9:123–159.
2. Ramón y Cajal S. *Degeneration and Regeneration of the Nervous System*. May RM, trans. London: Hafner Publishing Co; 1928.
3. Teitelbaum P, Stellar E. Recovery from the failure to eat produced by hypothalamic lesions. *Science*. 1954;120:894–895.
4. Liu CN, Chambers WW. Intrasprouting of dorsal root axons; development of new collaterals and preterminals following partial denervation of the spinal cord in the cat. *AMA Arch Neurol Psychiatry*. 1958;79:46–61.
5. Raisman G. Neuronal plasticity in the septal nuclei of the adult rat. *Brain Res*. 1969;14:25–48.
6. Richardson PM, McGuinness UM, Aguayo AJ. Axons from CNS neurons regenerate into PNS grafts. *Nature*. 1980;284:264–265.
7. David S, Aguayo AJ. Axonal elongation into peripheral nervous system “bridges” after central nervous system injury in adult rats. *Science*. 1981;214:931–933.
8. So KF, Aguayo AJ. Lengthy regrowth of cut axons from ganglion cells after peripheral nerve transplantation into the retina of adult rats. *Brain Res*. 1985;328:349–354.
9. Bray GM, Villegas-Perez MP, Vidal-Sanz M, Aguayo AJ. The use of peripheral nerve grafts to enhance neuronal survival, promote growth and permit terminal reconnections in the central nervous system of adult rats. *J Exp Biol*. 1987;132:5–19.
10. Berry M, Rees L, Hall S, Yiu P, Sievers BT. Optic axons regenerate into sciatic nerve isografts only in the presence of Schwann cells. *Brain Res Bull*. 1988;20:223–231.
11. Basso DM, Beattie MS, Bresnahan JC. A sensitive and reliable locomotor rating scale for open field testing in rats. *J Neurotrauma*. 1995;12:1–21.
12. Chen XY, Wolpaw JR, Jakeman LB, Stokes BT. Operant conditioning of H-reflex increase in spinal cord-injured rats. *J Neurotrauma*. 1999;16:175–186.
13. Wolpaw JR, Tennissen AM. Activity-dependent spinal cord plasticity in health and disease. *Annu Rev Neurosci*. 2001;24:807–843.
14. Edgerton VR, Leon RD, Harkema SJ, et al. Retraining the injured spinal cord. *J Physiol*. 2001;533:15–22.
15. Goshgarian HG. The crossed phrenic phenomenon: a model for plasticity in the respiratory pathways following spinal cord injury. *J Appl Physiol*. 2003;94:795–810.
16. Crown ED, Ferguson AR, Joynes RL, Grau JW. Instrumental learning within the spinal cord. II. Evidence for central mediation. *Physiol Behav*. 2002;77:259–267.
17. McPhee B. Second Sir George Montario Bedbrook Oration—1999. Some milestones in the life of George Bedbrook. Their relationship to management and research of spinal cord injuries. *ANZ J Surg*. 2003;73:650–659.
18. Sekhon LH, Fehlings MG. Epidemiology, demographics, and pathophysiology of acute spinal cord injury. *Spine*. 2001;26:S2–S12.
19. Go BK, DeVivo MJ, Richards JS. The epidemiology of spinal cord injury. In: Stover SL, DeLisa JA, Whiteneck GG, eds. *Spinal Cord Injury Clinical Outcomes From the Model Systems*. Gaithersburg, Md: Aspen Publications; 1995:21–55.
20. DeVivo MJ, Stover SL. Long-term survival and causes of death. In: Stover SL, DeLisa JA, Whiteneck GG, eds. *Spinal Cord Injury: Clinical Outcomes From the Model Systems*. Gaithersburg, Md: Aspen Publications; 1995:289–316.
21. Stover SL, DeLisa JA, Whiteneck GG, eds. *Spinal Cord Injury. Clinical Outcomes From the Model Systems*. Gaithersburg, Md: Aspen Publications; 1995.
22. Schwab ME, Bartholdi D. Degeneration and regeneration of axons in the lesioned spinal cord. *Physiol. Rev*. 1996;76:319–370.
23. Popovich PG. Immunological regulation of neuronal degeneration and regeneration in the injured spinal cord. *Prog Brain Res*. 2000;128:43–58.
24. Carlson GD, Gorden C. Current developments in spinal cord injury research. *Spine J*. 2002;2:116–128.
25. Kim DH, Vaccaro AR, Henderson FC, Benzel EC. Molecular biology of cervical myelopathy and spinal cord injury: role of oligodendrocyte apoptosis. *Spine J*. 2003;3:510–519.
26. Casella GT, Marcillo A, Bunge MB, Wood PM. New vascular tissue rapidly replaces neural parenchyma and vessels destroyed by a contusion injury to the rat spinal cord. *Exp Neurol*. 2002;173:63–76.
27. Loy DN, Crawford CH, Darnall JB, Burke DA, Onifer SM, Whittemore SR. Temporal progression of angiogenesis and basal lamina deposition after contusive spinal cord injury in the adult rat. *J Comp Neurol*. 2002;445:308–324.
28. Noble LJ, Donovan F, Igarashi T, Goussev S, Werb Z. Matrix metalloproteinases limit functional recovery after spinal cord injury by modulation of early vascular events. *J Neurosci*. 2002;22:7526–7535.

29. Silver J, Miller JH. Regeneration beyond the glial scar. *Nat Rev Neurosci.* 2004;5:146–156.
30. Schwab ME. Increasing plasticity and functional recovery of the lesioned spinal cord. *Prog Brain Res.* 2002;137:351–359.
31. Filbin MT. Myelin-associated inhibitors of axonal regeneration in the adult mammalian CNS. *Nat Rev Neurosci.* 2003;4:703–713.
32. Lee DH, Strittmatter SM, Sah DW. Targeting the Nogo receptor to treat central nervous system injuries. *Nat Rev Drug Discov.* 2003;2:872–878.
33. McKerracher L, Winton MJ. Nogo on the go. *Neuron.* 2002;36:345–348.
34. Rhodes KE, Fawcett JW. Chondroitin sulphate proteoglycans: preventing plasticity or protecting the CNS? *J Anat.* 2004;204:33–48.
35. Bruce JH, Norenberg MD, Kraydieh S, Puckett W, Marcill A, Dietrich D. Schwannosis: role of gliosis and proteoglycan in human spinal cord injury. *J Neurotrauma.* 2000;17:781–788.
36. Calancie B, Molano MR, Broton JG. Interlimb reflexes and synaptic plasticity become evident months after human spinal cord injury. *Brain.* 2002;125(pt 5):1150–1161.
37. Weaver LC, Verghese P, Bruce JC, Fehlings MG, Kremz NR, Marsh DR. Autonomic dysreflexia and primary afferent sprouting after clip-compression injury of the rat spinal cord. *J Neurotrauma.* 2001;8:1107–1119.
38. Sagen J, Bunge MB, Kleitman N. Transplantation strategies for treatment of spinal cord dysfunction and injury. In: Lanza RP, Langer RS, Vacanti J, eds. *Principles of Tissue Engineering.* 2nd ed. San Diego, Calif: Academic Press; 2000; 799–820.
39. Reier PJ, Golder FJ, Bolser DC, et al. Gray matter repair in the cervical spinal cord. *Prog Brain Res.* 2002;137:49–70.
40. Murray M. Cellular transplants: steps toward restoration of function in spinal injured animals. *Prog Brain Res.* 2004;143:133–146.
41. Vidal-Sanz M, Bray GM, Villegas-Perez MP, Thangs S, Aguayo AJ. Axonal regeneration and synapse formation in the superior colliculus by retinal ganglion cells in the adult rat. *J Neurosci.* 1987;7:2894–2909.
42. Bregman BS, Coumans JV, Dai HN, et al. Transplants and neurotrophic factors increase regeneration and recovery of function after spinal cord injury. *Prog Brain Res.* 2002;137:257–273.
43. Schnell L, Schwab ME. Axonal regeneration in the rat spinal cord produced by an antibody against myelin-associated neurite growth inhibitors. *Nature.* 1990;343:269–272.
44. Olson L. Grafts and growth factors in CNS. Basic science with clinical promise. *Stereotact Funct Neurosurg.* 1990;54-55:250–267.
45. Lipton SA. Growth factors for neuronal survival and process regeneration. Implications in the mammalian central nervous system. *Arch Neurol.* 1989;46:1241–1248.
46. 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. *N Engl J Med.* 1990;322:1405–1411.
47. Bracken MB, Shepard MJ, Holford TR, et al. Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial. National Acute Spinal Cord Injury Study. *JAMA.* 1997;277:1597–1604.
48. Basso DM, Beattie MS, Bresnahan JC, et al. MASCIS evaluation of open field locomotor scores: effects of experience and teamwork on reliability. Multicenter Animal Spinal Cord Injury Study. *J Neurotrauma.* 1996;13:343–359.
49. Stokes BT, Noyes DH, Behrmann DL. An electromechanical spinal injury technique with dynamic sensitivity. *J Neurotrauma.* 1992;9:187–195.
50. Scheff SW, Rabchevsky AG, Fugaccia I, Main JA, Lumpp JE Jr. Experimental modeling of spinal cord injury: characterization of a force-defined injury device. *J Neurotrauma.* 2003;20:179–193.
51. Dolan EJ, Tator CH. A new method for testing the force of clips for aneurysms or experimental spinal cord compression. *J Neurosurg.* 1979;51:229–233.
52. Anderson DK, Howland DR, Reier PJ. Fetal neural grafts and repair of the injured spinal cord. *Brain Pathol.* 1995;5:451–457.
53. Houle JD. Demonstration of the potential for chronically injured neurons to regenerate axons into intraspinal peripheral nerve grafts. *Exp Neurol.* 1991;113:1–9.
54. Bunge MB. Bridging the transected or contused adult rat spinal cord with Schwann cell and olfactory ensheathing glia transplants. *Prog Brain Res.* 2002;137:275–282.
55. Barnett SC, Riddell JS. Olfactory ensheathing cells (OECs) and the treatment of CNS injury: advantages and possible caveats. *J Anat.* 2004;204:57–67.
56. Roy NS, Nakano T, Keyoung HM, et al. Telomerase immortalization of neuronally restricted progenitor cells derived from the human fetal spinal cord. *Nat Biotechnol.* 2004;22:297–305.
57. Keirstead HS. Stem cell transplantation into the central nervous system and the control of differentiation. *J Neurosci Res.* 2001;63:233–236.
58. Romero MI, Rangappa N, Garry MG, Smith GM. Functional regeneration of chronically injured sensory afferents into adult spinal cord after neurotrophin gene therapy. *J Neurosci.* 2001;21:8408–8416.
59. Tuszynski MH. Gene therapy for neurological disease. *Expert Opin Biol Ther.* 2003;3:815–828.
60. Kwon BK, Liu J, Messerer C, et al. Survival and regeneration of rubrospinal neurons 1 year after spinal cord injury. *Proc Natl Acad Sci USA.* 2002;99:3246–3251.
61. Spencer T, Filbin MT. A role for cAMP in regeneration of the adult mammalian CNS. *J Anat.* 2004;204:49–55.
62. Kapur TA, Shoichet MS. Chemically-bound nerve growth factor for neural tissue engineering applications. *J Biomater Sci Polym Ed.* 2003;14:383–394.
63. Hall ED, Springer JE. Neuroprotection and acute spinal cord injury: a reappraisal. *NeuroRx.* 2004;1:80–100.
64. Popovich PG, Jones TB. Manipulating neuroinflammatory reactions in the injured spinal cord: back to basics. *Trends Pharmacol Sci.* 2003;24:13–17.
65. Schwartz M. Sell Memorial Lecture. Helping the body to cure itself: immune modulation by therapeutic vaccination for spinal cord injury. *J Spinal Cord Med.* 2003;26(suppl 1):S6–S10.
66. Logan A, Berry M. Cellular and molecular determinants of glial scar formation. *Adv Exp Med Biol.* 2002;513:115–158.
67. Bethea JR, Dietrich WD. Targeting the host inflammatory response in traumatic spinal cord injury. *Curr Opin Neurol.* 2002;15:355–360.
68. Kalderon N, Xu S, Koutcher JA, Fuks Z. Fractionated radiation facilitates repair and functional motor recovery after spinal cord transection in rat. *Brain Res.* 2001;904:199–207.
69. Kipnis J, Avidan H, Markovich Y, et al. Low-dose gamma-irradiation promotes survival of injured neurons in the central nervous system

- via homeostasis-driven proliferation of T cells. *Eur J Neurosci*. 2004;19:1191–1198.
70. Gilmore SA, Phillips N, Liu KM, Houle JD. Radiation-induced modulation of the microglial population in the normal and injured mature spinal cord. *Exp Neurol*. 2003;182:169–179.
 71. Edgerton VR, Roy RR. Paralysis recovery in humans and model systems. *Curr Opin Neurobiol*. 2002;12:658–667.
 72. Orsal D, Barthe JY, Antri M, et al. Locomotor recovery in chronic spinal rat: long-term pharmacological treatment or transplantation of embryonic neurons? *Prog Brain Res*. 2002;137:213–230.
 73. Potter PJ, Hayes KC, Segal JL, et al. Randomized double-blind crossover trial of fampridine-SR (sustained release 4-aminopyridine) in patients with incomplete spinal cord injury. *J Neurotrauma*. 1998;15:837–849.
 74. Dobkin BH, Havton LA. Basic advances and new avenues in therapy of spinal cord injury. *Annu Rev Med*. 2004;55:255–282.
 75. Apfel SC. Neurotrophic factor therapy—prospects and problems. *Clin Chem Lab Med*. 2001;39:351–355.
 76. Ramer MS, Priestley JV, McMahon SB. Functional regeneration of sensory axons into the adult spinal cord. *Nature*. 2000;403:312–316.
 77. Hurlbert RJ. The role of steroids in acute spinal cord injury: an evidence-based analysis. *Spine*. 2001;26(suppl 24):S39–S46.
 78. Widerstrom-Noga EG, Felipe-Cuervo E, Broton JG, Duncan RC, Yezierski RP. Perceived difficulty in dealing with consequences of spinal cord injury. *Arch Phys Med Rehabil*. 1999;80(5):580–586.
 79. Lammertse DP. Clinical trials in spinal cord injury: The Proneuron activated macrophage trial. *J Spinal Cord Med*. 2003;26:279.
 80. Narayan RK, Michel ME, Ansell B, et al. Clinical trials in head injury. *J Neurotrauma*. 2002;19:503–557.
 81. Gladstone DJ, Black SE, Hakim AM. Heart and Stroke Foundation of Ontario Center of Excellence in Stroke Recovery. Toward wisdom from failure: lessons from neuroprotective stroke trials and new therapeutic directions. *Stroke*. 2002;33:2123–2136.
 82. Geisler FH, Coleman WP, Grieco G, Poonian D, Sygen Study Group. Recruitment and early treatment in a multicenter study of acute spinal cord injury. *Spine*. 2001;26(suppl 24):S58–S67.
 83. Tadie M, Gaviria M, Mathe J-F, et al. Early care and treatment with a neuroprotective drug, gacyclidine, in patients with acute spinal cord injury.
 84. Wirth ED 3rd, Reier PJ, Fessler RC, et al. Feasibility and safety of neural tissue transplantation in patients with syringomyelia. *J Neurotrauma*. 2001;18:911–929.
 85. Grill WM, McDonald JW, Peckham PH, Heetderks W, Kocsis J, Weinrich M. At the interface: convergence of neural regeneration and neural prostheses for restoration of function. *J Rehabil Res Dev*. 2001;38:633–639.
 86. Jacobs PL, Nash MS. Modes, benefits, and risks of voluntary and electrically induced exercise in persons with spinal cord injury. *J Spinal Cord Med*. 2001;24:10–18.
 87. National Institute of Neurological Disorders and Stroke. *Translating Promising Strategies for Spinal Cord Injury Therapy*. Feb. 3–4, 2003. Available at: http://www.ninds.nih.gov/news_and_events/sci_translation_workshop.htm. Accessed March 31, 2004.
 88. Houle JD, Tessler A. Repair of chronic spinal cord injury. *Exp Neurol*. 2003;182(2):247–260.
 89. Smith PM, Lakatos A, Barnett SC, Jeffery ND, Franklin RJ. Cryopreserved cells isolated from the adult canine olfactory bulb are capable of extensive remyelination following transplantation into the adult rat CNS. *Exp Neurol*. 2002;176:402–406.
 90. Morrissey TK, Bunge RP, Kleitman N. Human Schwann cells in vitro. I. Failure to differentiate and support neuronal health under co-culture conditions that promote full function of rodent cells. *J Neurobiol*. 1995;28:171–189.
 91. American Spinal Injury Association. *International Standards for the Neurological Classification of Spinal Cord Injury*. *J Spinal Cord Med*. 2003(26 suppl.):550–556.
 92. Ellaway PH, Anand P, Bergstrom EM, et al. Towards improved clinical and physiological assessments of recovery in spinal cord injury: a clinical initiative. *Spinal Cord*. 2004.
 93. Curt A, Schwab ME, Dietz V. Providing the clinical basis for new interventional therapies: refined diagnosis and assessment of recovery after spinal cord injury. *Spinal Cord*. 2004;42:325–327.
 94. Guidelines for the management of acute cervical spine and spinal cord injuries. *Neurosurgery*. 2002;50(suppl 3):S1–S199.
 95. Whyte J, Hart T. It's more than a black box; it's a Russian doll. Defining rehabilitation treatments. *Am J Phys Med Rehabil*. 2003; 82:639–652.
 96. Stroke Therapy Academic Industry Roundtable (STAIR). Recommendations for standards regarding preclinical neuroprotective and restorative drug development. *Stroke*. 1999; 30:2752–2758.
 97. The American Society for Neural Transplantation and Repair. Considerations and guidelines for studies of human subjects. *Cell Transplant*. 2001;10:661–664.
 98. Fawcett JW. Spinal cord repair: from experimental models to human application. *Spinal Cord*. 1998;36:811–817.