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ORIGINAL ARTICLE

The translational dialogue in spinal cord injury research

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Background: Although the emphasis in clinical spinal cord injury (SCI) research has been directed towards the evaluation of clinical assessments (standards in neurological examination) and the appreciation of outcome measures (that is, extent and pattern of clinical recovery from SCI), the underlying neurological mechanisms for recovery from SCI are not well documented in humans. However, to improve the translational research, a meaningful preclinical–clinical dialogue is required, with an appreciation for both fundamental neural mechanisms and what makes human SCI unique. This holds true both for potential interventions in rehabilitation and novel drug or cell-based treatment approaches in acute SCI.

Objectives: The gap in translational research that needs to be approached from both ends not only includes the appreciation of principal neural mechanisms (repair, sprouting, plasticity) and their assumed impact onto outcomes (even though humans and non primate animals may rely on slightly different supraspinal control for some movements), but also includes an understanding of the spatial (location and size of lesion) and temporal (timelines of damage and recovery) factors in spinal cord damage that can vary considerably between the different species being studied.

Conclusion: The preclinical–clinical dialogue should be encouraged as a venue to improve the appreciation of discoveries in basic research, and to power valid discoveries towards a meaningful translation into advanced treatments downstream. Similarly, the upstream identification of appropriate clinical targets that take into account clinical constraints depends on reliable and advanced clinical information being provided to preclinical investigators.

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INTRODUCTION

The introduction of novel treatment approaches and corresponding clinical trials in disorders of the central nervous system (CNS), such as stroke, traumatic brain injury, has been constantly challenged by multiple constraints (for background see: http://www.strokecenter.org). Consequently many phase I/II clinical trials did not achieve internal (expectations of investigators) and external thresholds (approval by corporate backers or regulatory agencies, including appreciation from the clinical community) to advance towards pivotal studies.[1–3] Of even higher concern is the plethora of failed clinical trials, specifically in stroke (>than 50 clinical trials), which have identified some fundamental concerns by pharmaceutical companies for the field of applied clinical CNS research. Several multinational pharmaceutical companies perceive faults in the rigor of the stroke translation process, as well as long and arduous clinical trial programs with insensitive or non-specific clinical endpoints (see http://www.urchpublishing.com (Dawber[4]) and http://www.medicineaustralia.com.au (Paul *et al.*[5])).

Comparably, but to a lesser extent, a review of spinal cord injury (SCI) trials also revealed challenges in the appropriate choice of primary and secondary outcomes, optimized stratification of patients and customized rehabilitation programs required to facilitate the potential beneficial effects of novel therapeutic approaches.[6–8] To overcome some of these constraints, future SCI clinical research might benefit from advancing and tailoring collaborative activities. Collaboration needs to include partners from basic neurobiological research, the pharmaceutical industry, professionals in SCI rehabilitation, rehabilitation engineering and people living with SCI to work towards the establishment of a successful prioritized translational plan. However, indeed truly multidisciplinary scientific conferences and workshops, beyond the token invitation of a complementary keynote speaker (clinician or scientist), are rather exceptional.

The present manuscript provides a personal vision statement that will briefly discuss some of the aspects that might be considered important for this dialogue, whereas the over-arching goal is to identify tangible targets for the next scientific decade in clinical SCI research. The list of issues (Table 1) is incomplete and unranked for their potential importance. By definition, vision statements are, in time, usually falsified or corrected by reality. Accurate predictions of the future in research are the exception rather than the rule and inherently a desperate expression by the author.

Translation of outcome measures

The analysis of human data in patients suffering from acute SCI prospectively collected by clinical databases like the US Model Systems (http://www.ED.gov/NIDRR), the European Multicenter Study in SCI (http://www.emsci.org), and the data from large clinical SCI trials (like the control group of the Sygen^{R} trial) revealed rather robust and predictable recovery profiles.[9–11] Most statistical comparisons have been performed in sensorimotor complete (ASIA Impairment Score, AIS-A) patients followed over a one-year period. For many reasons, including safety, AIS-A subjects are often viewed as the most likely patients to be enrolled in early phase acute and sub-acute clinical trials. The independent statistical evaluation of the data regarding neurological scoring (that is, conversion rates, changes in motor and sensory scores) have been shown to be comparable between the data

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Table 1 Issues of translational research in SCI

Problem	*Details of interest*
Sensitivity of clinical trials: (To date, phase I/II trial protocols have been designed like confirmatory phase III trials.)	Phase adjusted trial protocols: • Phase I–II: adequate emphasis on surrogate measures like neurophysiology, imaging, CSF/serum markers • Phase II-III: advanced clinical outcomes with consideration of MCID
Outcome measures: (Do significant changes equal clinical relevance?)	Relevant domains of ICF framework: • body function • activity • performance measures (ADL's)
Stratification of patients: (What patient populations to aim for?)	Phase I/II to include complete and incomplete SCI patients? • AIS-A patients may be too severely injured to reveal subtle beneficial effects of novel interventions? • Appropriately powered trials?
Translational information: (What is the justification to go from animal to human trials?)	Comparative studies: • There should be a clear distinction between physiological and functionally relevant effects? • Is there an adequate injury model? • What species have been tested?
Spatial aspects: (What are the morphological characteristics of the lesion?)	In humans, every lesion is unique: • What kind of damage (contusion, compression, vascular, myelomalacia)? • What is the size of lesion? (Where are the limits?)
Temporal aspects: (What is the time course of the injury?)	Timing of the intervention: • Is earlier better? • What are the sensitive time windows? Duration of intervention: • What are the optimal parameters of the intervention? ○ Duration ○ Dose
Clinical safety: (How can we ensure safety?)	The value of safety assessments: • Safety should be balanced with sufficient sensitivity in complete SCI? • We must first understand the "natural" incidence and time course of complications?

sources when looking at mean changes of upper and lower extremity motor scores (UEMS, LEMS), both in absolute values and in terms of the time course of change, underscored by a more profound spontaneous recovery within the first 12–24 weeks, followed by a stable plateau thereafter.[12,13] This is remarkable considering the separate datasets were collected over relatively long-time periods, with different goals (that is, clinical trials versus registries) and in diverse countries having different standards of care and rehabilitation. More importantly, the similar outcomes provide confidence that the observed natural history of SCI is valid. In addition, data regarding functional outcomes using specialized ADL (activities of daily living) instruments, such as the spinal cord independence measure (SCIM III)[14] and performance measures of walking (walking index spinal cord injury, WISCI II;[15] 6 min walking test, 6 minWT [16]) are now increasingly collected, and relate to the level and completeness (AIS A-D) of the lesion.[17] These measures are not only valid for monitoring the course of recovery, but elements of these tools may also be used as instruments for the appreciation of a clinical trial outcome.[18] Nevertheless, the definition of specific minimal clinically important differences (MCID) needs to be developed for each SCI trial situation (MCID criteria are lacking also in other CNS disorders) to confirm that any achieved outcomes are not only statistically significant but also have a beneficial impact on the life of SCI patients.[19]

In preclinical research, comparable efforts have been performed to disclose the psychometric properties of the applied functional tests.[20] However, it must be acknowledged that effect sizes, as achieved in animals, cannot be simply extrapolated or easily scaled for humans. Interestingly, locomotor recovery profiles, (time course and pattern) as reported by many independent researchers, show rather comparable scoring outcomes for animal locomotion (locomotor activity evaluation developed by Basso, Beattie and Bresnahan[21] (BBB score) predominantly in rats). However, there is no consensus on how locomotor changes (or other functional domains) in animals should be interpreted both with respect to the potential effect size and specific aspects for human locomotion, such as postural stability, weight bearing, duration and speed.[22] The recent introduction of animal models that address functions beyond locomotion, such as the detailed analysis of voluntary upper limb function after cervical hemisection injuries, will potentially provide novel insights into the fundamental mechanisms of SCI repair and recovery.[23] The assumption[24] is that directed upper limb tasks (like reaching for food), in contrast to locomotor movements, are more closely related to supraspinal control systems that are less reliant on repetitive (that is, less voluntary) central pattern generator-like mechanisms.[25] Increasingly, interventional studies beyond locomotion (like hand function, cardiovascular fitness, bladder and autonomic dysfunction) are consistent with patient expectations, and represents an important area where the preclinical–clinical dialogue needs to be improved.[24,26]

Identifying mechanisms of functional recovery

Parallel research that simultaneously measures preclinical and clinical research outcomes for the same clinical target is rarely undertaken. The common presumption is such combined studies are not advised because of: (a) different outcome measures, and (b) fundamental differences between species. However, a challenge for the next decade (not limited to SCI research) is to overcome this misperception by exploiting the advantages that are actually provided by these differences,[27] and how these differences (real or imagined) may actually uncover a more detailed understanding of SCI pathology, as well as appropriate translational approaches. It is acknowledged that both preclinical and clinical research have their unique advantages and specific limitations.[28,29] However, a complementary approach, where findings that are not (or less) repeatable in animals versus humans (and vice versa), should be specifically emphasized to close some gaps between the research models. There are actually only very few comparative studies following either the natural course (spontaneous) of recovery or resulting from novel interventions in SCI.[30]

Although there are significant differences between humans and non-primate animals in terms of supraspinal motor control of hand and paw (cortical and brainstem connections show different densities and input/output functions), the basic brainstem-spinal control systems for walking are similar. More importantly, cellular mechanisms (activation of microglia, apoptosis, axonal sprouting, inhibitory effects within adult CNS and so on) appear to be very similar. Indeed, similarities in the secondary mechanisms of neuronal death and reactive gliosis provide strong evidence for the direct translation of

experimental discoveries in clinical study.[31] The physiological similarities of these reactions within the CNS, as disclosed by specific outcome measures, should provide confidence to the field that increased translational effort is justified and warranted. The preclinical models may be most informative, with respect to identifying the underlying neuronal mechanisms and appropriate clinical targets; however, the effect size achieved in the preclinical model may be quite different than that after human SCI.[32] No validated algorithm exists that calculates potential functional effects in humans based on animal readouts. The basis for translation is the assumption that comparable cellular mechanisms might be achieved in humans, but the dose, route of administration, and timing of the treatment after SCI may have to be titrated to achieve a functional clinical benefit.[33]

Clinical assessments in humans sometimes rely on complex tasks and voluntary activation (both for upper and lower limbs), but even these can often be achieved in acute SCI patients.[34,35] This enables effects of acute and chronic SCI treatments to be 'mapped' onto a voluntary supraspinal control framework by means of motor planning, dexterity and maximal voluntary muscle strength (including fatigue).[36] Changes in movement strategies due to conscious or involuntary effects of compensation and adjustment of movements can also be revealed. These assessments might be more challenging in animals, but preclinical assessment strategies need to be developed that are sensitive for these domains of neural control. In animal studies, complex sensorimotor function assessments focus on activities that are less dependent on voluntary motor control (spinal pattern generators, propriospinal and brainstem-spinal networks). Thus, the animal models allow for deeper insights into sub-hierarchical (less conscious) neuronal control circuits (like neural recordings of central pattern generator activity in spinalized cats) that are, at best, only indirectly or consciously accessible by patients.[36,37]

Spatial and temporal aspects

Besides looking at principles in neural repair, there are some spatial and temporal aspects of comparisons between human and animal outcomes after SCI that ask for special consideration. The spatial aspects address issues like the total size of the cord, the magnitude of post-traumatic tissue damage (which may eventually evolve to post-traumatic cyst formation), as well as what is the most frequent pattern of cord damage (contusion) and related SCI syndromes, such as anterior cord, central cord or Brown–Sequard syndrome. The total size of the human cord and regions of damaged cord after SCI are up to $\times 10$ larger (absolute dimensions) than in adult rats. This impacts the necessary morphological requirements after human SCI, and potentially impacts the effective demands (higher vulnerability of longer, unstable projections) for bridging such damaged regions.[38] Although different preclinical models can mimic the contusion like injury mechanism in humans (representing about 80% of the injuries), identifying equivalent animal models of the various human spinal cord syndromes is deficient.[39] These human SCI syndromes are characterized by unique patterns of sensorimotor impairment (specific spatial sensorimotor deficits), which have predictive value in acute traumatic SCI (ranking the cord syndromes from lowest to highest likelihood of recovery: complete cord, anterior cord, central cord, hemi cord[40]). There are now upcoming injury models in animals (rodents and non-human primates) that are attempting to model these human cord syndromes (like lesion models of hemisection and cervical injuries), and will enable comparisons across species.[41]

Temporal aspects also need careful consideration. There is only limited knowledge how recovery timelines in animals can be related to the time course in humans. Looking at recovery profiles it becomes obvious that animals show the steepest mean recovery time within 4–6 weeks compared with about 20 weeks in humans (Figure 1). Several long-term follow-up studies in humans reveal rather comparably long time courses for spontaneous recovery.[42] Only limited human data exists for time estimates of the post traumatic cyst formation from the acute damage to the final definitive cyst formation that gives a more complete picture about the evolving maturation of SCI. Figure 2 illustrates the complex correlations between morphological, neurological and functional changes. Although the morphological maturation (that is, demarcation and consolidation) of the human lesion becomes evident within 3 weeks after injury, changes in neurological deficit (in this example the total ASIA motor score in a C6 AIS-A patient increases from 19 to 23 points) are less evident whereas there is a significant improvement of functional outcomes (total SCIM increased from 4 to 29 points), eventually reaching a plateau at

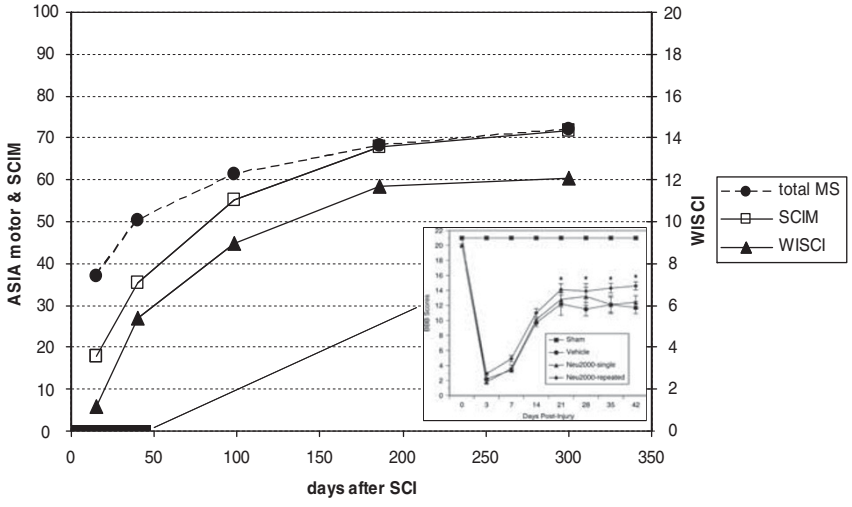

Figure 1 Recovery profiles in patients with incomplete acute cervical SCI (n=116, AIS C-D), followed over the first year after trauma, reveal that neurological (ASIA total motor scores) and functional outcome measures (WISCI, SCIM) reach a plateau of recovery at about 200 days after injury. The inlay represents a typical example of a relatively short time course of recovery (about 40 days) that is described in many preclinical studies.[47]

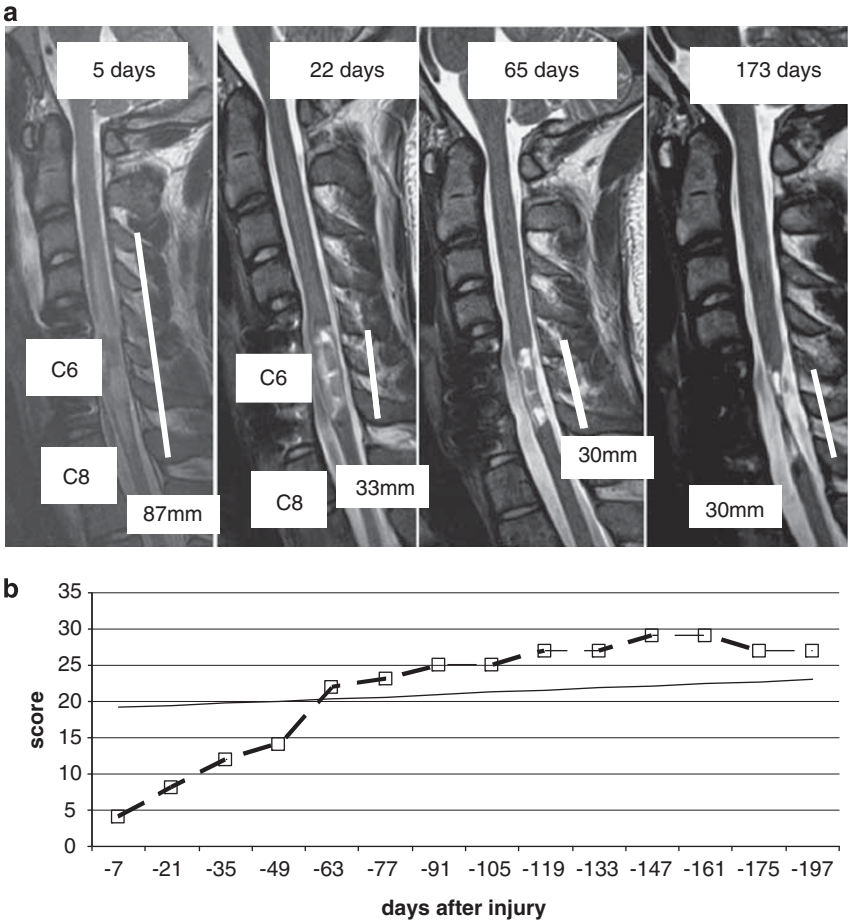

Figure 2 Single case of cervical traumatic SCI (C6 AIS-A) presenting the different time course of changes: (**a**) morphological maturation of the lesion between days 22–65 after injury, and late changes (collapse of post traumatic cyst at 173 days), with final length of cyst of about 30 mm; and (**b**) the increase in independence (SCIM; open squares) reaching a plateau at about 160 days after injury whereas the ASIA motor score (solid trend line) remained relatively stable (total motor score increased from 19 to 23).

about 5 months post-injury. Even later during clinical recovery, a further morphological change of the lesion can be revealed (collapse of post traumatic cyst); however, without an obvious associated change in neurological assessments or ADL.

Lastly, there are very interesting combinations of spatial and temporal aspects that can be witnessed in patients suffering from very slowly developing degenerative spinal cord disorders. In these patients, huge changes in spinal cord morphology (cystic deformations, stenosis leading to cord compression and so on.) can be readily imaged, but with minimal or no obvious clinical deficits. The development of post-traumatic syringomyelia is a well-known example where even extensive changes in spinal cord morphology are detected, either by chance (routine MRI scans) or due to the development of rather minor and less specific symptoms (like increasing pain and spasticity) (Figure 3).[43–46] The common denominator is that these disorders and related changes occur very slowly. This provides evidence that the cord is capable of tremendous plastic changes over a relatively long time. Therefore, the time needed to capitalize on full cord plasticity might be overlooked in some of the interventional studies. It can be argued that interventions lasting about 2–4 weeks (a rather typical treatment duration of pharmacological studies) might be much too short to maximize plasticity within the cord.

Translational dialogue: what for?

The value for improving the translational dialogue is the creation of bi-directional communication between preclinical and clinical research. The eventual improvement in translating preclinical research discoveries into clinical applications will also be dependent upon the timely and appropriate development of clinical trial protocols. It becomes increasingly obvious that clinical assessments of unique interventions need specific and sensitive tools (clinical endpoints) beyond the currently available functional outcome measures. Most of the currently utilized outcome measures are restricted to assessment of neurological deficits, the functional accomplishment of ADLs and specific performance measures. Novel and advanced assessments beyond immediate clinical value are needed to allow for comparisons with animal models (that is, measures of spinal conductivity, spinal and supraspinal reorganization of neural circuits).

Table 1 presents a list of problems and details that need to be jointly answered between the various research groups, as they are fundamental to successful translation. Obviously a meaningful, open and engaged dialogue is a prerequisite to achieving meaningful progress. Finally, the combination and relative weighting of the many aspects of these discussion will depend on the phase (I-III) of the clinical trial being considered. It is of common interest to the field to not disregard a novel

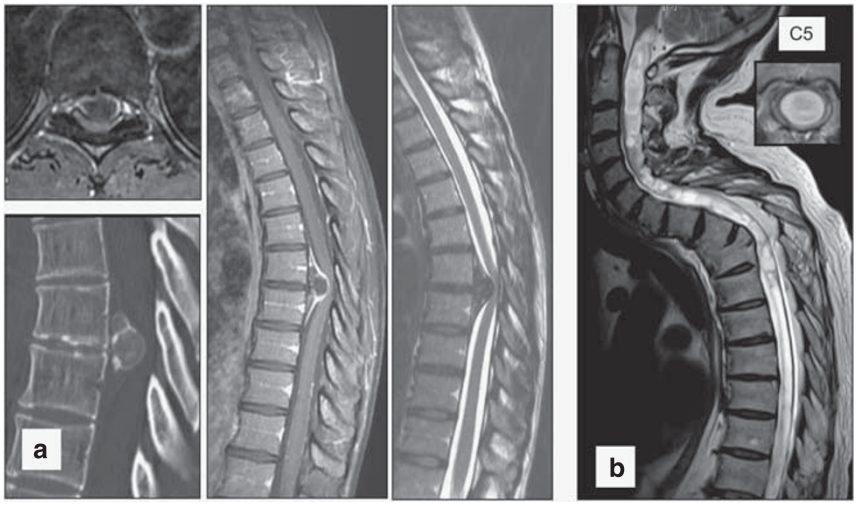

Figure 3 Inset **a** depicts MRI scans (severe spinal cord compression due to disc herniation T7/8) from a 36-year-old female patient with complaints of lower back pain and dysaesthesia in the left leg. Her lower limb reflexes were mildly increased despite unlimited walking capacity and voluntary bladder control. Inset **b** represent MRI scans from a 48-year-old male patient with a T3/4 fracture sustained 26 years previously. The patient, referred due to tingling of the left hand, is clinically diagnosed as an incomplete (AIS B), T3 paraplegia, with full upper limb function. The MRIs, reflects the importance of temporal aspects of spinal cord damage, and reveals extensive changes in spinal cord morphometry that occurred very slowly while inducing only minor symptoms.

intervention due to the lack of an appropriate (sensitive) outcome assessment tool. It is also important to continue the development and translation of therapies having detectable but subtle effects, as they may be resolved by refinements of such aspects as the dose and timing of the intervention.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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