Clinical spinal cord injury (SCI) research has thus far focused much effort into the evaluation of clinical assessments (standards in neurological examination) and understanding the outcome measures, ie the extent and pattern of clinical recovery from SCI. Less is known about the mechanisms underlying neurological recovery from human SCI and how this is comparable to preclinical animal models.

Translational research beyond formal statements
The gap in translational research needs to be approached from both sides, requiring close cooperation between basic scientists from many disciplines, eg neurobiology, rehabilitation engineering, neuroimaging physicists, with clinicians experienced in clinical trials. This exchange should not be limited to scientific meetings to discuss important neural mechanisms, such as repair, sprouting, plasticity, rehabilitation, but also involve interactive research programmes where findings from preclinical models or clinical observations are studied.

Success in translational research
In the following, we detail three research projects that exemplify the successful transfer of preclinical findings into current clinical interventions and/or investigations.

Project 1: getting rid of the inhibitors in the central nervous system
One reason for the restricted recovery following SCI is the fact that myelin, the insulation material that surrounds central nervous system (CNS) axons, is highly inhibitory to growth due to the presence of various proteins, such as Nogo-A.1 A significant step forward in the field of SCI research came when it was shown that rats treated with an antibody that neutralised the inhibitory properties of Nogo-A showed enhanced regeneration of injured axons2 and significant improvements in locomotor ability.3 These findings were subsequently reproduced by several other laboratories using different injuries, treatment paradigms4 and species, including primates.5 Anti-Nogo-A treatments in rodents were also shown to enhance sprouting and growth of intact fibres post-injury6 and, importantly, this growth was associated with recovery of function and sensation in the impaired body parts (Fig. 1A).7

Currently, a clinical Phase I trial of a human function blocking anti-Nogo-A antibody (ATI355) has been successfully accomplished (http://clinicaltrials.gov/ct2/show/NCT00406016). The Phase I study, which investigated safety, dosing, tolerance and pharmacokinetics has been completed and reported no safety concerns, while the route of application and dosing could be optimised (Fig. 1B).

Project 2: use it or lose it!
Optimising rehabilitation outcome and motivation
Training is a powerful modifier of CNS anatomy and function, for example enhancing activity in nerve fibres spared from the injury increases fibre growth and functional recovery.8-10 Locomotor and rehabilitation training have been shown to lead to functional recovery in animals11 and humans.12 Self-training, ie activity outside the specific training programme, is thought to be important but little is known about its exact influence on recovery. In unpublished findings the Laboratory of Professor Martin Schwab, University of Zurich and Federal Institute of Technology (ETH) Zurich, developed RatTrack, an animal tracking system, to investigate the influence of self-training on functional recovery following SCI in rats (Fig. 2A). It was found that enhanced self-training led to good and in some cases even complete functional recovery (Starkey et al, unpublished findings).

In SCI humans precise and accurate measures of the amount and intensity of activity correlated with the extent and quality of recovery are lacking, both for rehabilitation training sessions and in normal everyday life. Currently, the Laboratory of Professor Armin Curt, Balgrist University Hospital and the Laboratory of Professor Roger Gassert, ETH Zurich, are introducing a novel, long-term personal monitoring...
device, REACT\textsuperscript{13} into clinical SCI rehabilitation (Fig. 2B). The REACT device allows the measurement of a patient’s arm activity outside the standard training sessions in order to investigate the influence of self-training on functional and anatomical recovery.

Project 3: what limping tells about the nervous system

Individual walking patterns can vary considerably between healthy subjects, and can depend on many biological factors, such as age, gender, mood and the environment. Animal studies (Laboratory of Professor Martin Schwab) demonstrated that different locomotor behaviours, such as over-ground walking, climbing and swimming, show differences in motor pattern, sensory input and, most importantly, the CNS anatomical networks that participate in the movements (Fig. 3A).\textsuperscript{14} Subsequently, these features of the locomotor pattern were differentially affected by a given CNS injury, eg stroke, SCI, neurological disorder. Hence, a comprehensive analysis of gait should always include different types of ambulation in order to link neuroanatomical changes to functional outcome.

Comparably gait disorders are one of the most common symptoms in neurology and have serious consequences, including isolation, economic disadvantages and increased risk of death due to falls. As observed in rodents, walking deficits in humans are variable and unspecific, which hinders the correct diagnosis and optimal treatment. The most commonly used scores and clinical outcome measures to evaluate walking function are often subjective or have a low sensitivity, especially with regards to improvements or compensatory strategies. For the assessment of walking ability in humans, 3D gait analysis combined with selected clinical tests is considered the gold standard.

However, comparative studies using a multimodal gait analysis approach in neurological diseases are rare. Therefore, the Laboratory of Professor Curt, Balgrist University Hospital and the Department of Neurology (Drs Zörner and Linnebank), University Hospital Zürich, have developed a comprehensive gait analysis approach (GaitPortfolio, Fig. 3B) for humans in order to systematically examine neurological syndromes in which single and multiple neuroanatomical systems are affected.

Accepting the challenge

Although SCI is a rare disorder (with an annual incidence of about 15-30 million per year) it might herald the beginning of successful translational research. SCI is not only seen as a very drastic and devastating disorder affecting young and elderly people, but also as one of the most significant and central ‘challenges’ in the field of neuroscience research and for the planning of rehabilitation. There is a reasonable assumption that if you can repair an SCI other disorders inducing damage to the CNS will benefit. The high expectations set in the beginning of successful translational research pathway.

1 Schwab M E, Functions of Nogo proteins and their receptors in the nervous system. Nat Rev Neurosci, 2010. 11(12): pp. 799-811
7 Ibid
9 Stanley M L et al, Rehabilitative training following unilateral pyramidalotomy in adult rats improves forelimb function in a non-task specific way. Experimental neurology, 2011
14 Zörner B et al, Profiling locomotor recovery: comprehensive quantification of impairments after CNS damage in rodents. Nat Methods, 2010. 7(9): pp. 701-708