

**Enhancement of Fiber Growth and Regeneration in the Injured Spinal Cord**  
**Antibody-Mediated Neutralization of the Neurite Growth–Inhibitory Myelin Protein Nogo-**  
**A as a Novel Therapy for CNS Injuries**

**Martin E. Schwab**

A few seconds of inattention on the road or in sports and you can end up wheelchair bound for the rest of your life. Since the early days of neurology, it has been recognized that permanent functional deficits produced by large spinal cord and brain lesions are linked to the absence of regeneration of injured fiber tracts in the CNS. In the late 1980s the presence of specific neurite growth inhibitory factors in the adult CNS, particularly in CNS white matter, was recognized. Ablation of myelin, antisera against CNS myelin, or use of specific function-blocking antibodies against one of the most potent neurite growth inhibitory constituents of CNS myelin, Nogo-A, rapidly showed that regeneration of lesioned fiber tracts in injured rat or chicken spinal cord occurred under these conditions over long distances (Schwab, 2004). The initial anatomical experiments were complemented by the demonstration of functional recovery, as shown in a variety of locomotor and skilled movement tests. Importantly, the results with function-blocking antibodies against the neurite growth inhibitor Nogo-A were confirmed by experiments that utilized other biochemical approaches to block the Nogo–Nogo receptor signaling pathway, including peptides blocking the Nogo receptor (NgR1), truncated receptor fragments that block the NgR1 ligands, and pharmacological blockers of the downstream signaling pathway involving Rho and ROCK (Schwab, 2004). In contrast to these acute interventions, which all produced a similar enhancement of regeneration, compensatory fiber sprouting, and functional recovery, Nogo-A knockout mice had weaker and more variable outcomes, probable due to functional compensation by other inhibitory factors (Dimou et al.,

2006). As an important proof of concept step towards the human situation, macaque monkeys with defined cervical spinal cord lesions producing a unilateral hand paralysis were shown to regain almost full hand and finger dexterity along with regenerative fiber growth of the transected corticospinal tract -following anti-Nogo-A antibody treatment.

In collaboration with an industrial partner, we produced a human IgG-antibody with high binding affinity and function-blocking properties against human Nogo-A. Efficacy for regeneration was shown in macaques, and the absence of neurological as well as general side effects was tested extensively in the required two distant species, i.e., rodents and primates. Due to the impermeability of the blood-brain barrier to antibodies, the application route has to be directly into the CNS compartment. Lumbar intrathecal pumps, such as are in routine clinical use (e.g., for the application of the antispastic drug baclofen) and injections into the lumbar subarachnoid space were used. As this was the first antibody applied directly into the CNS compartment, a very careful in-human dosage and toxicology phase, Phase I of the clinical trial, was required. The trial is currently (2010) being conducted by Novartis in a network of leading spinal cord injury centers in Europe and North America. To show the efficacy of this growth- and regeneration-enhancing antibody, the availability of standardized, sensitive, functionally meaningful read-outs for the recovery of lost functions is crucial. Major efforts are devoted to the improvement of currently available assessment scales for locomotion, hand use, autonomic functions, spasticity, pain and daily life activities (Alexander et al., 2009).

A clinical demonstration of enhanced functional recovery after spinal cord or brain trauma by a novel therapeutic approach based on an understanding of the underlying molecular and cell biological mechanisms would be extremely encouraging. However, the complexity of CNS injuries will probably require combined treatments at least for the repair of the most

extensive lesions. Stimulation of the neuronal growth program, minimizing the barrier function of scars at lesions sites, combined suppression of several growth and inhibitory factors, and, ideally, bridging of large lesions by implants or cell grafts are approaches that are currently tested in animal models. Before they can be applied in combination to patients with spinal cord or brain injuries, however, safety and efficacy of each individual treatment need to be shown. Although the way to these novel therapies for CNS lesions seems still to be long, the door is wide open now, and research is pursued with great effort in many basic science and clinical laboratories worldwide.