## SUMMARY

The nervous system forms specialized neuronal circuitry and organization that are essential for adequate locomotion. The central nervous system (consisting of the brain and spinal cord) effectively receives and relay information which is then delivered by the peripheral nervous system to muscles to achieve locomotion. It is known that while the peripheral nervous system retains its ability to regenerate, the central nervous system has little to no regenerative capacity in adult stages. Therefore, injuries to the central nervous system are critical and often lack cure. One of them is spinal cord injury, which is a devastating, debilitating, and life-altering condition that lacks a cure or effective treatment as of today. An injury results in severing of supraspinal input into the spinal cord, which leads to locomotor dysfunction beneath the injury. Altered excitation inhibition ratio after an injury, with an increase in inhibition, together with limited endogenous regeneration capacity of the affected neuronal tracts further limit locomotor function. As a result, complete paralysis may occur even in patients with anatomically incomplete injuries. In this doctoral thesis, we focus on these major points to devise a combinatory approach as an effective strategy to treat spinal cord injury. We hypothesized that to aid the limited regeneration capacity of the tracts, a peripheral neuronal transplant (dorsal root ganglia, DRG) which retains the intrinsic ability to regenerate can be an effective transplantation strategy. To overcome inhibition, improve survival and integration of the transplant into circuits, the overexpression of bacterial voltage gated NaChBac sodium channel was employed. Finally, to target and improve the axonal regeneration of endogenous and transplanted cells, we use cytoskeleton modulating drugs to enhance axonal length. This doctoral thesis studies the effects of this combinatory approach to treat spinal cord injury.

In Chapter 1, we describe the *in vitro* studies performed to validate our hypothesis. We first study the synergistic effect of cytoskeleton modulating drugs Epothilone B and Blebbistatin on neurite length *in vitro* and find that while individual treatment with Blebbistatin increases neurite length, combination with Epothilone leads to an altered splayed morphology of the growth cone which results in decreased neurite length. Next, we describe the effect of NaChBac expression in DRGs and Neuro-2A cells. In DRGs, NaChBac expression leads to an increase in intrinsic activity and secretion of neurotrophic factors, promoting pro-survival

signaling and anti-apoptotic signaling in Neuro-2A cells. Finally, we describe how the combinatory effect of NaChBac expression and Blebbistatin further improves neurite length *in vitro*.

In Chapter 2, we evaluate the survival, efficacy, and interaction of the DRG transplant with the corticospinal tract, the most important tract involved in locomotion in a short-term *in vivo* study. We report a satisfactory integration and survival of the transplant into the host tissue. Furthermore, we show that NaChBac expression increases the survival of the total number of transplanted cells, as well as improves preservation of the corticospinal tract after the injury.

In Chapter 3, we study the effect of the combinatory treatment in a chronic, severe injury scenario. We find that the combination of the transplant expressing NaChBac and Blebbistatin limits functional recovery, while that of transplant expressing NaChBac significantly improved locomotor function in mice. Therefore, focusing our further research on this group, we report that animals transplanted with NaChBac-expressing DRGs had increased tubulin-positive neuronal fiber and myelin preservation, while serotonergic and corticospinal descending fibers remained unaffected. We found that transplantation of NaChBac-expressing DRGs increased the neuronal excitatory input, as seen by increased number of VGLUT2 contacts and decrease in VGAT contacts immediately caudal to the injuries. Together, the work in this doctoral thesis suggests that the transplantation of NaChBac-expressing dissociated DRGs rescues significant motor function by retaining an excitatory neuronal relay activity immediately caudal to injuries in a chronic, severe spinal cord injury model and highlights the importance of maintenance of activity as an effective therapy for spinal cord injury.