Preface

After spinal cord injury in humans severed axons do not regrow. This causes permanent functional deficits, such as loss of sensation and paralysis. These devastating consequences of spinal cord injury have long been thought to be incurable, but this pessimistic view is changing. Over the last decade we have gained a much better insight into the environmental and neuron-intrinsic factors that prevent axon regrowth in the central nervous system (CNS) of mammals. Progress in experimentally eliciting some axon regrowth in mammals is currently leading to therapeutic strategies. In the light of these encouraging findings, it is important to address further challenges for *functional* regeneration. Namely, we may ask how axon regrowth can be made even more robust, what the targets are that regrowing axons have to contact, how axons manage to grow there and how reconnections can lead to functional recovery. These aspects of spinal cord regeneration are difficult to study in mammals that do not normally regenerate their spinal cord and in vitro analyses cannot mimic the complex spinal network. There are, however, other vertebrate model systems that share many basic features of connectivity in the spinal cord with mammals and show robust axon regrowth and functional recovery, such as fish and amphibians. By comparing the mammalian situation, in which enhancement of axon growth seems to be feasible now, with that in functionally regenerating vertebrates, we may learn which mechanisms are important for functional recovery. For these reasons, this volume aims in its first part to give a comprehensive view over the state of the art in research into spinal cord injury in mammals in 2006. The second part is to increase our understanding of the spinal-intrinsic circuitry, the target of regenerating axons. The third part demonstrates how diverse non-mammalian regenerating model systems contribute to our understanding of spinal cord regeneration. Finally, in the fourth part non-mammalian models of optic nerve regeneration are discussed, because this popular and accessible system is likely to yield insights into CNS regeneration that is also relevant for the spinal cord.

In the first part of the book Pat Anderson, *Jez Fabes* and *David Hunt* (Chapter 1) are illuminating recent findings on the array of molecules in the environment of the lesioned CNS of mammals that are inhibitory to axon regrowth. In a complementary review *Ferdinando Rossi* (Chapter 2) gives a current account of the factors intrinsic to neurons that prevent vigorous axon regrowth. *Bhavna Ylera* and *Frank*

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Bradke (Chapter 3) show us how the neuron-intrinsic response of axotomized neurons can be enhanced in mammals. Richard Benton and *Scott Whittemore* (Chapter 4) report how the inhibitory environment in the CNS can be replaced by more conducive and growth promoting cellular substrates including promising stem cell approaches. They finish the part on mammalian regeneration research by critically discussing the latest clinical trials.

Stan Grillner and *Peter Wallén* (Chapter 5) begin the second part by describing the spinal-intrinsic neuronal network that produces locomotion-related patterns of activity, the so-called central pattern generator of locomotion, in the lamprey. This jawless vertebrate possesses a simple, yet typical vertebrate spinal network and the authors show us how mathematical modeling increases our understanding of the activity in this network. *Anna Vallstedt* and *Klas Kullander* (Chapter 6) then describe genetic techniques in mice that are currently being used to improve our surprisingly small knowledge of the central pattern generator in mammals. The spinal central pattern generator is a target for regenerating descending axons. *Agustin Gonzáles* and *Hans ten Donkelaar* (Chapter 7) point out how major descending tracts are evolutionarily conserved between non-mammalian vertebrates and mammals. This adds to the significance of findings from non-mammalian vertebrates for regeneration research.

In the third part *Michael Shifman, Li-Quing* and *Michael Selzer* (Chapter 8) demonstrate the power of the lamprey system to understand spinal cord regeneration at the level of individually identifiable neurons. The zebrafish is an important model organisms for developmental biology. *Joe Fetcho, Dimple Bhatt* and *Steven Zottoli* (Chapter 9) continue to show that regeneration can be experimentally augmented in larval zebrafish and the process of axon regrowth can be visualized in the living larva. We show in our own contribution (Chapter 10) that specific genes expressed during spinal cord regeneration in adult zebrafish can be directly manipulated, which leads to alterations in behavioural recovery. Thus the importance of individual molecules for the regenerative outcome can be tested in fish model systems.

In the third part we compiled contributions on regeneration in the optic system of non-mammalian vertebrates, which provides the researcher with a relatively homogeneous population of neurons, i.e. retinal ganglion cells, that is readily accessible and easily lesioned by an optic nerve crush. *Sarah Dunlop* (Chapter 11) shows how regenerative capacity for this cell type varies across vertebrate classes from full functional regeneration in fish via axon regrowth without recovery of function in reptiles to no axon regrowth in mammals. *Saturo Kato, Yoshiki Koriyama, Tori Matsukawa* and *Kayo Sugitani* (Chapter 12) demonstrate how the optic system in goldfish can be used to find new regeneration-associated genes and how the function of these genes can be tested in vivo and in vitro. Finally, *Marie-Claude Senut, Blake Fausett, Matthew Veldman* and *Daniel Goldman* (Chapter 13) show how promoter analysis of regeneration-associated genes can be performed in transgenic zebrafish and new regeneration-associated genes can be discovered by gene array analysis. Many of the genes activated in regenerating retinal ganglion cells in fish are also upregulated in regenerating mammalian neurons. Therefore, there is a justified hope that some of the regeneration-associated genes discovered in gold- and zebrafish are part of a general regeneration program in vertebrates.

Secondary neuron loss around a spinal lesion site in mammals is significant and thought to exacerbate the condition. These neurons are usually not replaced. Transgenic fish used by *Senut* et al. also shed light on gene activation during lesion-induced stem cell proliferation in the CNS of zebrafish, indicating a mechanism by which damaged neurons may be replaced. Salamanders are even able to regenerate the entire spinal cord during tail regeneration. Thus, the analysis of stem cell proliferation and functional integration of newly generated neurons in fish and amphibians may lead to ways to activate similar mechanisms in mammals.

Overall, there is an enormous increase in the number of findings on spinal cord regeneration both from mammalian and non-mammalian systems. Bringing together insights from different vertebrate classes from the molecular to systems level offers an opportunity to identify the critical steps necessary for successful regeneration of highly complex spinal functions. We hope that this book gives an up to date introduction into the many facets of CNS regeneration research for students and provides specialists in the field with a useful entry point to comparative analysis.

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