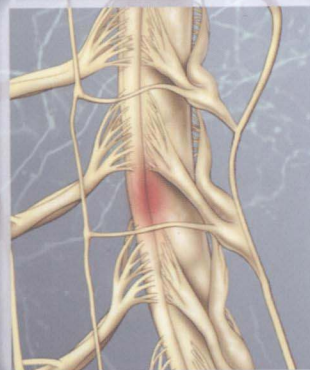


# NEURAL REGENERATION

## 神经再生

KWOK-FAI SO, XIAO-MING XU



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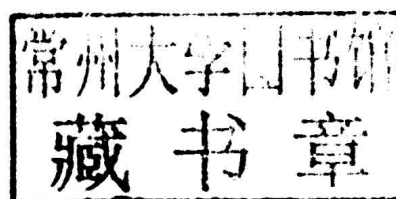
# NEURAL REGENERATION

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*Edited by*

KWOK-FAI SO

XIAO-MING XU



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AMSTERDAM • BOSTON • HEIDELBERG • LONDON  
NEW YORK • OXFORD • PARIS • SAN DIEGO  
SAN FRANCISCO • SINGAPORE • SYDNEY • TOKYO

Academic Press is an imprint of Elsevier



Academic Press is an imprint of Elsevier  
32 Jamestown Road, London NW1 7BY, UK  
525 B Street, Suite 1800, San Diego, CA 92101-4495, USA  
225 Wyman Street, Waltham, MA 02451, USA  
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, UK

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ISBN: 978-7-03-044098-3

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ISBN: 978-0-12-801732-6

### British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library

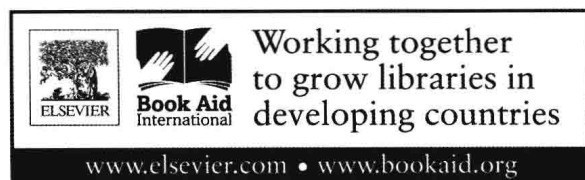
### Library of Congress Cataloging-in-Publication Data

A catalog record for this book is available from the Library of Congress

For information on all Academic Press publications  
visit our website at <http://store.elsevier.com/>

Typeset by TNQ Books and Journals  
[www.tnq.co.in](http://www.tnq.co.in)

Printed and bound in the United States of America



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S E C T I O N I

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INTRODUCTION



# Advances and Challenges for Neural Regeneration Research

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## 1. NERVOUS SYSTEM, NERVE INJURY, AND NEURAL REGENERATION

The nervous system is divided into two parts: the central nervous system (CNS), which consists of the brain and spinal cord, and the peripheral nervous system (PNS), which consists of cranial and spinal nerves along with their associated ganglia. The function of the CNS and PNS is to relay information to and from all parts of the body. This communication is made possible through an extensive network of neurons and supporting cells called glia, including astrocytes, oligodendrocytes, and microglia.

Nerve injury, whether traumatic or degenerative, disrupts the normal flow of information and can, depending on the location and mechanism of injury, lead to deleterious effects. Injury or sudden trauma, such as from automobile accidents, falls, sports-related activities, etc., can cause nerve fibers or axons to be partially or completely severed, crushed, compressed, or stretched. When an axon is damaged, the distal segment undergoes Wallerian degeneration, losing its myelin sheath [1]. The axotomized neurons either die by necrosis or apoptosis or undergo a chromatolytic reaction, which is an attempt to repair. Injury to the nervous system also triggers the responses of glial cells, including oligodendrocytes, astrocytes, and microglia in the CNS; Schwann cells (SCs) in the PNS; and blood-derived macrophages that participate in both CNS and PNS injury processes. The responses of these cells to injury include cell death,

proliferation, migration, and production of inflammatory mediators and growth factors, thus influencing processes of axonal degeneration and regeneration. Thus, nervous system injuries affect not only neurons and their processes but also glial cells.

Neural regeneration refers to the regrowth or repair of nervous tissues, cells, or cell products. Such mechanisms may include generation of new tissues, neurons, glia, axons, myelin, or synapses. Beyond the common knowledge of neurogenesis, a wider concept of neural regeneration may comprise endogenous neuroprotection leading to neuroplasticity and neurorestoration. Neural regeneration can also be promoted by implantation of viable tissues or cells. Neural regeneration differs between the PNS and the CNS owing to different neuronal and glia responses to injury as well as the different environments that the regenerative axons and cells encounter.

## 2. TECHNOLOGICAL ADVANCES IN NEURAL REGENERATION RESEARCH

### 2.1 Models

Preclinical animal models are critical for understanding regenerative neurobiology and for testing treatment strategies prior to implementation in clinical practice. For regeneration research, *in vitro*, *ex vivo*, or *in vivo* models, described below, have been used extensively and complementarily.

### 2.1.1 *In vitro* Model

The flexibility and ease of control offered by the *in vitro* model make it a useful tool for the study of neural regeneration. Glass micropipettes can be used to sever processes from cultured neurons or tissue explants to study axonal and dendritic regrowth *in vitro* [2–4]. Although this method can cut many axon segments simultaneously, it cannot be used to isolate axon and dendritic segments. Fine knife cutting is another localized physical injury, which can precisely cut neurites [5,6]; this method, however, damages the coated substrate and sets up an artificial sulcus, which may prevent the truncated neurite from regrowing. Microdissection of a neurite with a laser beam offers more precise control [7,8] that provides a unique platform for regeneration research [9]. A nanocutting device with a cutting edge of less than 20 nm radius of curvature was developed that enables high-precision microdissection and subcellular isolation of neuronal structures [10]. With these devices, not only can a single-axon transection model be established, but also regeneration-related functional components of neurons, such as segments of axons, dendrites, dendritic spines, and nodes of Ranvier, can be isolated in culture.

### 2.1.2 *Ex vivo* Model

An *ex vivo* model is ethically advantageous, requires no postsurgical animal care, enables more reproducibility between lesions, and provides a tightly controlled artificial environment for regeneration studies. Published *ex vivo* spinal cord models include the culture of several hundred micrometers-thick transverse slices maintained for up to three weeks [11], unfixed longitudinal cryostat sections of spinal cord maintained for one week [12], and a novel *ex vivo* model that enables the culture of intact postnatal spinal cord segments for up to five days and the assessment of peripheral nerve grafting repair [13].

### 2.1.3 *In vivo* Model

Although invertebrates and lower vertebrates, such as *Caenorhabditis elegans* [14–16], lamprey [17–19], zebrafish [20–23], and lizard [24,25], have long been applied for neural regeneration research, the rat sciatic nerve, brain, and spinal cord injury models have been the most commonly used for studies of neural regeneration. Rodent models, such as rats and mice, are economical compared to large-animal models and primates, simple to handle and care for, very resistant to surgical infections, and can be investigated in large groups. Rodent models can be used for electrophysiology, functional recovery, muscle and nerve morphology, and other assessments of nerve regeneration [26,27]. The major value of the mouse model is the ability to answer mechanistic neural

regeneration questions [28,29]. The rabbit, dog, and cat are large-animal species more frequently used for peripheral and central nervous system injury research. Large mammals such as sheep [30,31], pigs [32,33], and monkeys [34–37] have increasingly been employed to study neural regeneration. These large species are limited by extremely high costs related to animal care, the narrow range of assessments available, and the complexity of training for functional testing. Transgenic animals, particularly mice, that express fluorescent proteins in specific neuronal subsets provide potentially powerful tools for the study of neural regeneration. One strategy involves expressing fluorescent proteins under the control of neuron-type-specific promoters [38]. Another approach involves the use of bacterial artificial chromosome (BAC) mice [39,40]. Genetic labels can provide specificity in axonal labeling that is hypothetically independent of tracer transport [41]. Moreover, BAC mice bearing green fluorescent protein-tagged polyribosomes (BAC-TRAP mice) provide an exceptional opportunity to identify potential regeneration-associated transcriptional events in a cell-type-specific manner [40].

A book entitled *Animal Models of Acute Neurological Injuries* [42] has provided a wide array of animal models currently used for assessing acute neurological injuries, providing valuable resource for neural regeneration research.

## 2.2 Labeling and Imaging Technology

How to exquisitely label nerve fibers within the nerve system and their connections to their target continues to be an important concern for neural regeneration research. Transgenic animals that express fluorescent proteins in specific neuronal subsets provide potentially useful tools for the regeneration study of these neurons [38].

Axonal tract tracing technologies are also powerful tools for identifying axonal connections. With appropriate injury models and tracing techniques, the status of axons—sparing, die-back, sprouting, regeneration, or synaptogenesis—can be readily identified [43]. Based on axonal transport, a long series of tracers has been developed as anterograde tracing or retrograde tracing according to the preferential direction of their transport in the axon.

Viruses have been developed for tract-tracing studies. Compared to conventional tracers, viruses have the ability to traverse multisynaptic pathways and replicate to amplify signals at each step in the process [44]. Depending on the species and strain of the virus, viruses can travel preferentially in the anterograde or the retrograde direction or both [45,46]. For example, Wang et al. found that a recombinant adenovirus carrying a green fluorescent protein reporter gene (Adv-GFP) can preferentially, intensely, and bidirectionally label the rat rubrospinal