NEUROMETHODS

Series Editor
Wolfgang Walz
University of Saskatchewan,
Saskatoon, Canada

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Optogenetics: A Roadmap

Edited by

Albrecht Stroh

Focus Program Translational Neurosciences and Institute for Microscopic Anatomy and Neurobiology, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany

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Editor
Albrecht Stroh
Focus Program Translational Neurosciences and Institute
for Microscopic Anatomy and Neurobiology
University Medical Center of the Johannes
Gutenberg-University Mainz
Mainz, Germany

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Preface to the Series

Experimental life sciences have two basic foundations: concepts and tools. The *Neuromethods* series focuses on the tools and techniques unique to the investigation of the nervous system and excitable cells. It will not, however, shortchange the concept side of things as care has been taken to integrate these tools within the context of the concepts and questions under investigation. In this way, the series is unique in that it not only collects protocols but also includes theoretical background information and critiques which led to the methods and their development. Thus it gives the reader a better understanding of the origin of the techniques and their potential future development. The *Neuromethods* publishing program strikes a balance between recent and exciting developments like those concerning new animal models of disease, imaging, in vivo methods, and more established techniques, including, for example, immunocytochemistry and electrophysiological technologies. New trainees in neurosciences still need a sound footing in these older methods in order to apply a critical approach to their results.

Under the guidance of its founders, Alan Boulton and Glen Baker, the *Neuromethods* series has been a success since its first volume published through Humana Press in 1985. The series continues to flourish through many changes over the years. It is now published under the umbrella of Springer Protocols. While methods involving brain research have changed a lot since the series started, the publishing environment and technology have changed even more radically. Neuromethods has the distinct layout and style of the Springer Protocols program, designed specifically for readability and ease of reference in a laboratory setting.

The careful application of methods is potentially the most important step in the process of scientific inquiry. In the past, new methodologies led the way in developing new disciplines in the biological and medical sciences. For example, Physiology emerged out of Anatomy in the nineteenth century by harnessing new methods based on the newly discovered phenomenon of electricity. Nowadays, the relationships between disciplines and methods are more complex. Methods are now widely shared between disciplines and research areas. New developments in electronic publishing make it possible for scientists that encounter new methods to quickly find sources of information electronically. The design of individual volumes and chapters in this series takes this new access technology into account. Springer Protocols makes it possible to download single protocols separately. In addition, Springer makes its print-on-demand technology available globally. A print copy can therefore be acquired quickly and for a competitive price anywhere in the world.

Saskatoon, Canada ***Wolfgang Walz***

Preface

Optogenetics—as the name suggests—coalesces multiple disciplines in Biomedicine, Optics, and Biotechnology, and now, almost 12 years after the publication of the first seminal paper, it may be safe to state that optogenetics truly revolutionized neuroscience.

For the first time, a causal interrogation of neuronal circuitry with millisecond precision, cell-type specificity, and minimal invasiveness became a reality. As a result, optogenetic techniques have pervaded almost all disciplines and fields of neuroscience over the years, from applications in brain slices to in vivo application in rodents, zebrafish, *C. elegans*, and nonhuman primates, and with clinical applications now just on the horizon. What is more, optogenetics allowed for the combination with already well-established readouts, such as single-cell electrophysiology, electric population recordings, functional magnetic resonance imaging, and, more recently, optical methods such as 2-photon calcium imaging.

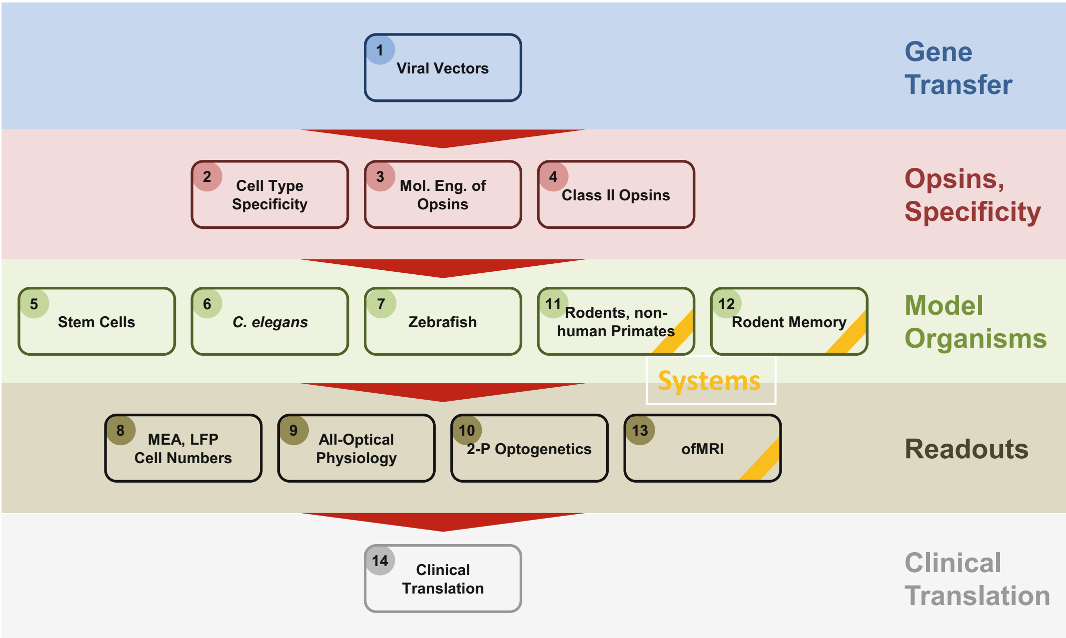
The research questions involving optogenetics are equally diverse, including the modulation of stem cell differentiation in mouse brain, of *C. elegans* behavior, and the causal dissection of sensory processing in nonhuman primates.

While many scholarly articles and books exist on each of these methods and animal models, from viral vectors to electrophysiology and behavior, there are unique requirements for each step of the optogenetic approach. In fMRI, for instance, imaging coils need a lead-through for an optic fiber. Likewise, viral vectors need to accommodate the sequences of promoter, opsin, and fluorophore. Some research questions may not require any sophisticated cellular targeting tools, but rather the implementation of a complicated readout interfering with optical interrogation, while others may center on a novel promoter in combination with fairly standard opsins and analytical tools.

And maybe most importantly, a project involving optogenetics has to entail tailored control experiments addressing both a potential interaction of light with the readout method and the potential effect of light itself on neuronal physiology.

Still, even after more than a decade, a successful implementation of optogenetics requires expertise in multiple fields, and each step of the way poses individual challenges and takes considerable time and efforts.

This book should guide both the optogenetics newbie and the expert through all the steps required for the implementation of optogenetics in neuroscience. It should empower the reader to identify the critical aspects of each methodological step and to decide on the necessary level of complexity to address the respective research question.



This book is structured along the optogenetics work flow, starting with viral vectors, followed by targeting strategies, choice of opsins, animal models, and readouts, and closing with applications in systems neuroscience and an outlook on clinical applications. Due to the unique format of this series, the reader will be able to gain in-depth knowledge of each procedure, yet each chapter only deals with those aspects of the method that are relevant from an optogenetics perspective. For example, the chapter on viral vectors deals exclusively with those viruses that can be used for gene delivery of opsins, and in the chapter on optical readouts, the complex problem of the crosstalk of opsins and optical reporters will be discussed in detail. The chapters comprise a review-like introduction of the current state of the art in the field, followed by a methodological step-by-step manual. Furthermore, a Notes section describes typical roadblocks and offers hands-on advice, and each chapter concludes with an outlook. Clearly, this book cannot cover all procedures and approaches in detail, but it should serve as a guide covering the most relevant aspects. I am very thankful to the series editor Wolfgang Walz and the entire team at Springer for supporting this concept. Lastly, I wish to express my deepest gratitude to all authors, many of whom I had the pleasure of working with since the early days of optogenetics.

May this book be of help and of inspiration particularly to the new generation of neuroscientists.

Mainz, Germany *Albrecht Stroh*

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Contributors

ANTOINE ADAMANTIDIS • *Department of Neurology, Inselspital University Hospital, University of Bern, Bern, Switzerland; Department of Clinical Research, Inselspital University Hospital, University of Bern, Bern, Switzerland*

RAAG D. AIRAN • *Department of Radiology, Neuroimaging and Neurointervention, Stanford University, Stanford, CA, USA*

ALLYSON L. ALEXANDER • *Department of Neurosurgery, Stanford University, Stanford, CA, USA; Department of Neurosurgery, University of Colorado School of Medicine, Aurora, CO, USA*

ISABELLE ARNOUX • *Focus Program Translational Neurosciences and Institute for Microscopic Anatomy and Neurobiology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany*

ANDRÉ BERNDT • *Department of Bioengineering, University of Washington, Seattle, WA, USA*

JOHANNES BOLTZE • *Department of Translational Medicine and Cell Technology, Fraunhofer Research Institution for Marine Biotechnology and Cell Technology, Lübeck, Germany; Institute for Medical and Marine Biotechnology, University of Lübeck, Lübeck, Germany*

KARL EMANUEL BUSCH • *Centre for Discovery Brain Sciences, Edinburgh Medical School: Biomedical Sciences, University of Edinburgh, Edinburgh, Scotland*

I-WEN CHEN • *Wavefront-Engineering Microscopy group, Neurophotonics Laboratory, CNRS UMR8250, Paris Descartes University, Paris Cedex 06, France*

ILKA DIESTER • *Faculty of Biology, Albert Ludwig University of Freiburg, Freiburg, Germany; Bernstein Center for Computational Neuroscience Freiburg, Albert Ludwig University of Freiburg, Freiburg, Germany; BrainLinks-BrainTools, Albert Ludwig University of Freiburg, Freiburg, Germany*

JAN DOERING • *Focus Program Translational Neurosciences and Institute for Microscopic Anatomy and Neurobiology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany*

ERIK ELLWARDT • *Focus Program Translational Neurosciences (FTN) and Immunology (FZI), Rhine Main Neuroscience Network (rmn^2), Department of Neurology, University Medical Center of the Johannes Gutenberg University of Mainz, Mainz, Germany*

VALENTINA EMILIANI • *Wavefront-Engineering Microscopy group, Neurophotonics Laboratory, CNRS UMR8250, Paris Descartes University, Paris Cedex 06, France*

KATHARINA ELISABETH FISCHER • *Centre for Discovery Brain Sciences, Edinburgh Medical School: Biomedical Sciences, University of Edinburgh, Edinburgh, Scotland*

TING FU • *Focus Program Translational Neurosciences and Institute for Microscopic Anatomy and Neurobiology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany*

MARTA GAJOWA • *Wavefront-Engineering Microscopy group, Neurophotonics Laboratory, CNRS UMR8250, Paris Descartes University, Paris Cedex 06, France*

INBAL GOSHEN • *Edmond and Lily Safra Center for Brain Sciences (ELSC), The Hebrew University, Jerusalem, Israel*

GOLAN KARVAT • *Faculty of Biology, Albert Ludwig University of Freiburg, Freiburg, Germany; Bernstein Center for Computational Neuroscience Freiburg, Albert Ludwig University of Freiburg, Freiburg, Germany*
HANNAH K. KIM • *Department of Neurosurgery, Stanford University, Stanford, CA, USA*
HEIKO J. LUHMANN • *Institute of Physiology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany*
RODRIGO J. DE MARCO • *German Resilience Center, University Medical Center, Johannes Gutenberg University Mainz, Mainz, Germany; Developmental Genetics of the Nervous System, Max Planck Institute for Medical Research, Heidelberg, Germany*
EIRINI PAPAGIAKOUMOU • *Wavefront-Engineering Microscopy group, Neurophotonics Laboratory, CNRS UMR8250, Paris Descartes University, Paris Cedex 06, France; Institut national de la santé et de la recherche médicale–Inserm, Paris, France*
ALEXIS PICOT • *Wavefront-Engineering Microscopy group, Neurophotonics Laboratory, CNRS UMR8250, Paris Descartes University, Paris Cedex 06, France*
PIERRE-HUGUES PROUVOT • *Focus Program Translational Neurosciences and Institute for Microscopic Anatomy and Neurobiology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany*
LIMOR REGEV • *Edmond and Lily Safra Center for Brain Sciences (ELSC), The Hebrew University, Jerusalem, Israel*
EMILIANO RONZITTI • *Wavefront-Engineering Microscopy group, Neurophotonics Laboratory, CNRS UMR8250, Paris Descartes University, Paris Cedex 06, France*
EDUARDO ROSALES JUBAL • *Focus Program Translational Neurosciences and Institute for Microscopic Anatomy and Neurobiology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany; Institute of Biomedical Sciences, Universidad Autónoma de Chile, Santiago, Chile*
SOOJIN RYU • *German Resilience Center, University Medical Center, Johannes Gutenberg University Mainz, Mainz, Germany*
MIRIAM SCHWALM • *Focus Program Translational Neurosciences and Institute for Microscopic Anatomy and Neurobiology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany; GRADE Brain, Goethe Graduate Academy, Goethe University Frankfurt, Frankfurt am Main, Germany*
IVAN SOLTESZ • *Department of Neurosurgery, Stanford University, Stanford, CA, USA*
ALBRECHT STROH • *Focus Program Translational Neurosciences and Institute for Microscopic Anatomy and Neurobiology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany*
KIMBERLY R. THOMPSON • *Drug Discovery, Circuit Therapeutics, Menlo Park, CA, USA*
CHRIS TOWNE • *Gene Therapy, Circuit Therapeutics, Menlo Park, CA, USA*
NATHALIE ALEXANDRA VLADIS • *Centre for Discovery Brain Sciences, Edinburgh Medical School: Biomedical Sciences, University of Edinburgh, Edinburgh, Scotland*
JENQ-WEI YANG • *Institute of Physiology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany*
OFER YIZHAR • *Department of Neurobiology, Weizmann Institute of Science, Rehovot, Israel*