

NEUROMETHODS

Series Editor
Wolfgang Walz
University of Saskatchewan
Saskatoon, SK, Canada

For further volumes:
<http://www.springer.com/series/7657>

Neuromethods publishes cutting-edge methods and protocols in all areas of neuroscience as well as translational neurological and mental research. Each volume in the series offers tested laboratory protocols, step-by-step methods for reproducible lab experiments and addresses methodological controversies and pitfalls in order to aid neuroscientists in experimentation. *Neuromethods* focuses on traditional and emerging topics with wide-ranging implications to brain function, such as electrophysiology, neuroimaging, behavioral analysis, genomics, neurodegeneration, translational research and clinical trials. *Neuromethods* provides investigators and trainees with highly useful compendiums of key strategies and approaches for successful research in animal and human brain function including translational “bench to bedside” approaches to mental and neurological diseases.

Nanomedicines for Brain Drug Delivery

Edited by

Javier O. Morales

Department of Pharmaceutical Science and Technology, University of Chile, Santiago, Chile

Pieter J. Gaillard

2-BBB Medicines BV, Leiden, The Netherlands



Editors

Javier O. Morales
Department of Pharmaceutical Science
and Technology
University of Chile
Santiago, Chile

Pieter J. Gaillard
2-BBB Medicines BV
Leiden, The Netherlands

ISSN 0893-2336

ISSN 1940-6045 (electronic)

Neuromethods

ISBN 978-1-0716-0837-1

ISBN 978-1-0716-0838-8 (eBook)

<https://doi.org/10.1007/978-1-0716-0838-8>

© Springer Science+Business Media, LLC, part of Springer Nature 2021

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

The publisher, the authors, and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, expressed or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Cover illustration: Cover image by Ignacio Morales Soto.

This Humana imprint is published by the registered company Springer Science+Business Media, LLC, part of Springer Nature.

The registered company address is: 1 New York Plaza, New York, NY 10004, U.S.A.

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, SK, Canada

Wolfgang Walz

Preface

Nanomedicines have revolutionized research on drug delivery in multiple diseases, and leading strategies have achieved clinical success. Moreover, a significant number of clinical trials are conducted to continue expanding the reach of nanomedicines to new, more effective and with less side effects therapies. The central nervous system (CNS) has similarly been the focus of extended research in the design and evaluation of novel nanocarriers for brain drug delivery. As a target site, the CNS represents a unique challenge given its anatomy and physiology. The blood brain barrier (BBB) is not only a restrictive limitation for systemically administered drugs but also continues to be a largely restrictive barrier to achieve significant CNS nanocarrier bioavailability. While the BBB represents one of the main limitations for significant CNS biodistribution, overcoming it is not the sole reason for limited bioavailability and targeting effects. Successfully targeting the brain microvasculature, distribution through the CNS (after passage through the BBB), and internalization in target brain cells become important challenges once there is a BBB penetration strategy in place.

As such, this book will be a source for finding the latest research in CNS-targeted nanocarriers, methods for their synthesis and thorough characterization. Moreover, a chapter addressing toxicity aspects to be considered in the design and use of brain-targeted nanocarriers will be of interest to the reader. The first two chapters of the book delve into the most widely investigated nanocarriers as brain-targeted delivery systems, i.e., polymeric nanoparticles and liposomes. With a thorough description of the state of the art as well as key aspects of their characterization, the first two chapters also highlight physiological properties relevant to particle design. Chapter 4 depicts the use of self-assembled peptide-based scaffolds for lesions of the nervous system, while Chapter 5 describes not only the use of peptides as CNS drugs but also as potential carriers to optimize brain-targeted delivery. Chapters 6 and 7 describe inorganic and magnetic nanoparticles used for targeting drugs to the CNS as well as their potential in the design of triggerable and aimed systems. Chapter 8 inspects the long-researched nose-to-brain delivery route, highlighting its potential and how the limitations this route presents could be addressed to harness its clinical potential. Chapter 9 is an excellent compilation of characterization methods to model and assess BBB absorption of drugs and drug delivery systems, and as such, this chapter will be of great use to scientists designing brain-targeted delivery systems to predict brain distribution. Finally, Chapter 10 presents the concerns that the use of nanomaterials raises in the context of brain-targeted systems. As such, the last chapter will be a good source to understand the potential neurotoxic effects and the potential role of nanomaterials in neurodegeneration progress.

The editors are immensely grateful to all the individual contributions and authors for sharing their time, effort, and knowledge to create this book. Their outstanding work in the fields covered in this book we hope will be of great interest to the reader and will help guide and move forward the field of nanomedicines to target the brain and the nervous system.

*Santiago, Chile
Leiden, The Netherlands*

*Javier O. Morales
Pieter J. Gaillard*

Contents

<i>Preface to the Series</i>	v
<i>Preface</i>	vii
<i>Contributors</i>	xi
1 Biodegradable Polymeric Nanoparticles for Brain-Targeted Drug Delivery	1 <i>Kristian Kempe and Joseph A. Nicolazzo</i>
2 Liposomes as Brain Targeted Delivery Systems	29 <i>Francesco Lai, Michele Schlich, Chiara Sinico, and Anna Maria Fadda</i>
3 Nanofibers and Nanostructured Scaffolds for Nervous System Lesions	61 <i>Jose L. Gerardo Nava, Jonas C. Rose, Haktan Altinova, Paul D. Dalton, Laura De Laporte, and Gary A. Brook</i>
4 Self-Assembling Peptide Nanofibrous Scaffolds in Central Nervous System Lesions	103 <i>Na Zhang, Liumin He, and Wutian Wu</i>
5 The Use of Peptide and Protein Vectors to Cross the Blood-Brain Barrier for the Delivery of Therapeutic Concentration of Biologics	119 <i>Mei Mei Tian and Reinhard Gabathuler</i>
6 Inorganic Nanoparticles and Their Strategies to Enhance Brain Drug Delivery	149 <i>Eduardo Gallardo-Toledo, Carolina Velasco-Aguirre, and Marcelo Javier Kogan</i>
7 Magnetic Nanoparticles as Delivery Systems to Penetrate the Blood-Brain Barrier	173 <i>Joan Estelrich and Maria Antonia Busquets</i>
8 Nose-to-Brain Drug Delivery Enabled by Nanocarriers	209 <i>Zachary Warnken, Yang Lu, Hugh D. C. Smyth, and Robert O. Williams III</i>
9 In Vitro Models of Central Nervous System Barriers for Blood-Brain Barrier Permeation Studies	235 <i>Sounak Bagchi, Behnaz Lahooti, Tanya Chhibber, Sree-pooja Varahachalam, Rahul Mittal, Abhijeet Joshi, and Rahul Dev Jayant</i>
10 Safety and Nanotoxicity Aspects of Nanomedicines for Brain-Targeted Drug Delivery	255 <i>Johanna Catalan-Figueroa and Javier O. Morales</i>
<i>Index</i>	279

Contributors

HAKTAN ALTINOVA • *Department of Neurosurgery, University Hospital RWTH Aachen, Aachen, Germany*

SOUNAK BAGCHI • *Department of Pharmaceutical Sciences, School of Pharmacy, Texas Tech University Health Sciences Center (TTUHSC), Amarillo, TX, USA*

GARY A. BROOK • *Institute of Neuropathology, University Hospital RWTH Aachen, Aachen, Germany*

MARIA ANTÒNIA BUSQUETS • *Pharmacy and Pharmaceutical Technology and Physical Chemistry Department, Faculty of Pharmacy and Food Sciences, University of Barcelona, Barcelona, Catalonia, Spain; Institute of Nanoscience and Nanotechnology, IN2UB, Barcelona, Catalonia, Spain*

JOHANNA CATALAN-FIGUEROA • *Department of Pharmaceutical Science and Technology, School of Chemical and Pharmaceutical Sciences, University of Chile, Santiago, Chile; Department of Biochemistry, School of Chemical and Pharmaceutical Sciences, University of Chile, Santiago, Chile; Experimental Pharmacology Institute, CONICET, National University of Córdoba, Córdoba, Argentina; Advanced Center for Chronic Diseases (ACCDiS), Santiago, Chile*

TANYA CHHIBBER • *Department of Pharmaceutical Sciences, School of Pharmacy, Texas Tech University Health Sciences Center (TTUHSC), Amarillo, TX, USA*

PAUL D. DALTON • *Department for Functional Materials in Medicine and Dentistry and Bavarian Polymer Institute, University of Würzburg, Würzburg, Germany*

LAURA DE LAPORTE • *DWI—Leibniz-Institute for Interactive Materials, Aachen, Germany; Institute of Applied Medical Engineering, RWTH Aachen University, Aachen, Germany; Institute of Technical and Macromolecular Chemistry RWTH Aachen University, Aachen, Germany*

JOAN ESTELRICH • *Pharmacy and Pharmaceutical Technology and Physical Chemistry Department, Faculty of Pharmacy and Food Sciences, University of Barcelona, Barcelona, Catalonia, Spain; Institute of Nanoscience and Nanotechnology, IN2UB, Barcelona, Catalonia, Spain*

ANNA MARIA FADDA • *Department of Life and Environmental Sciences, University of Cagliari, Cagliari, Italy*

REINHARD GABATHULER • *Faculty of Life Sciences and Medicine, Blood-Brain Barrier Group, Kings College London, London, UK*

EDUARDO GALLARDO-TOLEDO • *Departamento de Química Farmacológica y Toxicológica, Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile, Santiago, Chile; Advanced Center for Chronic Diseases (ACCDiS), Santiago, Chile*

JOSE L. GERARDO NAVA • *Institute of Neuropathology, University Hospital RWTH Aachen, Aachen, Germany; DWI—Leibniz-Institute for Interactive Materials, Aachen, Germany*

LIUMIN HE • *Guangdong-Hong Kong-Macau Institute of CNS Regeneration, Jinan University, Guangzhou, People's Republic of China*

RAHUL DEV JAYANT • *Department of Pharmaceutical Sciences, School of Pharmacy, Texas Tech University Health Sciences Center (TTUHSC), Amarillo, TX, USA*

ABHIJEET JOSHI • *Centre for Biosciences and Bio-medical Engineering, Indian Institute of Technology Indore (IIT-I), Indore, Madhya Pradesh, India*

- KRISTIAN KEMPE • *ARC Centre of Excellence in Convergent Bio-Nano Science & Technology, and Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, VIC, Australia*
- MARCELO JAVIER KOGAN • *Departamento de Química Farmacológica y Toxicológica, Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile, Santiago, Chile; Advanced Center for Chronic Diseases (ACCDiS), Santiago, Chile*
- BEHNAZ LAHOOTI • *Department of Pharmaceutical Sciences, School of Pharmacy, Texas Tech University Health Sciences Center (TTUHSC), Amarillo, TX, USA*
- FRANCESCO LAI • *Department of Life and Environmental Sciences, University of Cagliari, Cagliari, Italy*
- YANG LU • *Department of TCM Pharmaceutical, School of Chinese Material Materia, Beijing University of Chinese Medicine, Beijing, People's Republic of China*
- RAHUL MITTAL • *Laboratory of Human Molecular Genetics, Department of Otolaryngology, Miller School of Medicine, University of Miami (UM), Miami, FL, USA*
- JAVIER O. MORALES • *Department of Pharmaceutical Science and Technology, School of Chemical and Pharmaceutical Sciences, University of Chile, Santiago, Chile; Advanced Center for Chronic Diseases (ACCDiS), Santiago, Chile; Center of New Drugs for Hypertension (CENDHY), Santiago, Chile; Pharmaceutical and Biomaterial Research Group, Department of Health Sciences, Luleå University of Technology, Luleå, Sweden*
- JOSEPH A. NICOLAZZO • *Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, VIC, Australia*
- JONAS C. ROSE • *DWI—Leibniz-Institute for Interactive Materials, Aachen, Germany*
- MICHELE SCHLICH • *Department of Life and Environmental Sciences, University of Cagliari, Cagliari, Italy*
- CHIARA SINICO • *Department of Life and Environmental Sciences, University of Cagliari, Cagliari, Italy*
- HUGH D. C. SMYTH • *Molecular Pharmaceutics and Drug Delivery Division, College of Pharmacy, The University of Texas at Austin, Austin, TX, USA*
- MEI MEI TIAN • *Bioaxis Technologies Inc., Guilford, CT, USA*
- SREE-POOJA VARAHACHALAM • *Department of Pharmaceutical Sciences, School of Pharmacy, Texas Tech University Health Sciences Center (TTUHSC), Amarillo, TX, USA*
- CAROLINA VELASCO-AGUIRRE • *Departamento de Química Farmacológica y Toxicológica, Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile, Santiago, Chile; Advanced Center for Chronic Diseases (ACCDiS), Santiago, Chile*
- ZACHARY WARNEKEN • *Molecular Pharmaceutics and Drug Delivery Division, College of Pharmacy, The University of Texas at Austin, Austin, TX, USA*
- ROBERT O. WILLIAMS III • *Molecular Pharmaceutics and Drug Delivery Division, College of Pharmacy, The University of Texas at Austin, Austin, TX, USA*
- WUTIAN WU • *Guangdong-Hong Kong-Macau Institute of CNS Regeneration, Jinan University, Guangzhou, People's Republic of China; Re-Stem Biotech, Suzhou, People's Republic of China*
- NA ZHANG • *Guangdong-Hong Kong-Macau Institute of CNS Regeneration, Jinan University, Guangzhou, People's Republic of China*