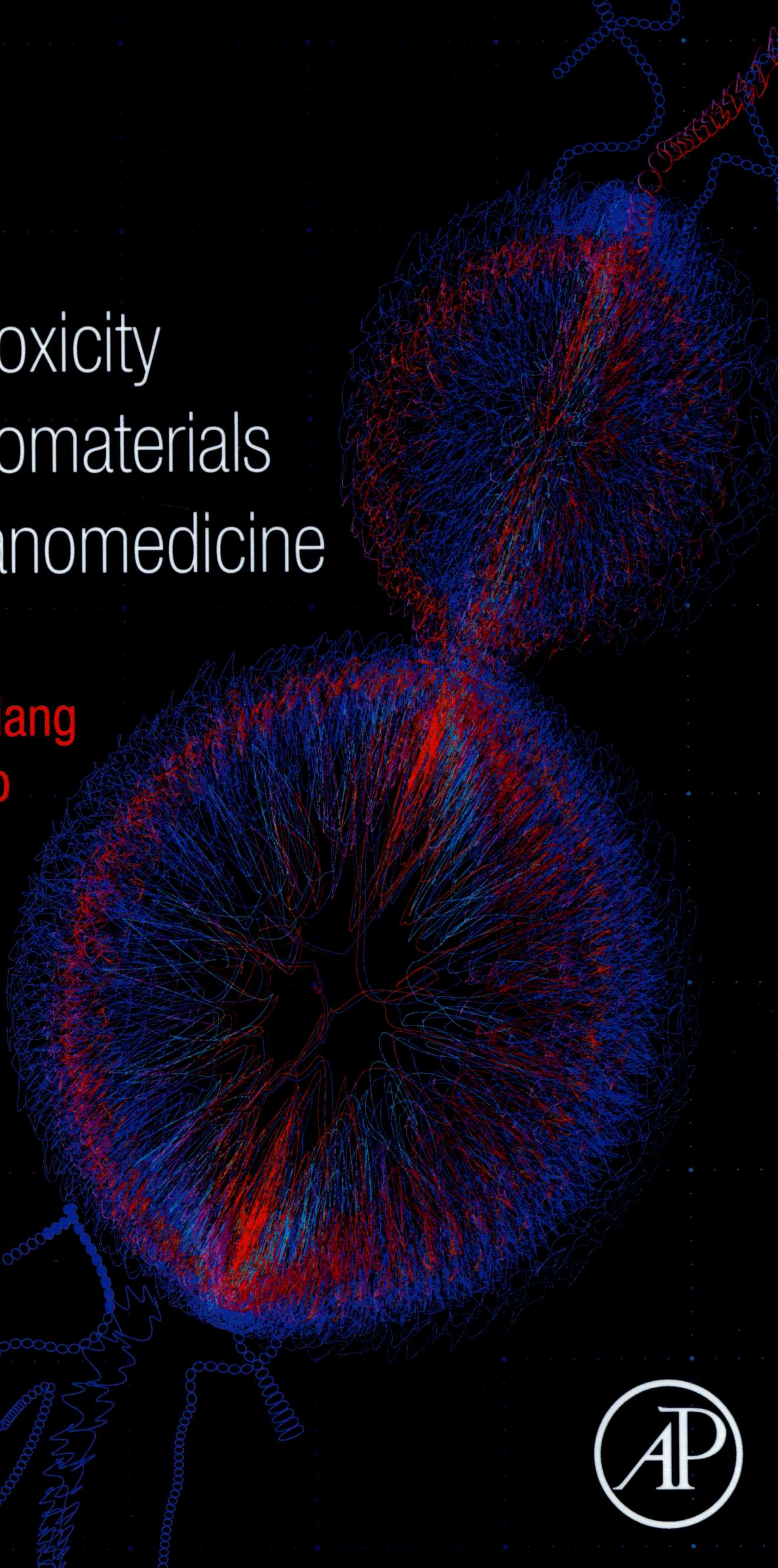
Neurotoxicity of Nanomaterials and Nanomedicine



Edited by
Xinguo Jiang
Huile Gao

Neurotoxicity of Nanomaterials and Nanomedicine

Edited by

Xinguo Jiang
School of Pharmacy, Fudan University, Shanghai, China
Huile Gao
West China School of Pharmacy, Sichuan University, Chengdu, China

ELSEVIER

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
125 London Wall, London EC2Y 5AS, United Kingdom
525 B Street, Suite 1800, San Diego, CA 92101-4495, United States
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

ISBN: 978-0-12-804598-5

For information on all Academic Press publications visit our website at https://www.elsevier.com/

Publisher: Mica Haley
Acquisition Editor: Erin Hill-Parks
Editorial Project Manager: Tracy Tufaga
Production Project Manager: Chris Wortley
Designer: Matthew Limbert

Typeset by TNQ Books and Journals

Neurotoxicity of Nanomaterials and Nanomedicine

List of Contributors

F. Brandão Portuguese National Institute of Health, Porto, Portugal; University of Porto, Porto, Portugal

H. Chen Shanghai Jiao Tong University School of Medicine, Shanghai, China

C. Costa Portuguese National Institute of Health, Porto, Portugal; University of Porto, Porto, Portugal

N. Fernández-Bertólez Universidade da Coruña, A Coruña, Spain

S.J.S. Flora Defence Research and Developmental Establishment, Gwalior, India

F. Gao East China University of Science and Technology, Shanghai, China

H. Gao Sichuan University, Chengdu, China

X. Gao Shanghai Jiao Tong University School of Medicine, Shanghai, China

X. Gu Shanghai Jiao Tong University School of Medicine, Shanghai, China

M. He East China University of Science and Technology, Shanghai, China

Q. He Sichuan University, Chengdu, China

K. Ikeda The Jikei University School of Medicine, Tokyo, Japan

X. Jiang Fudan University, Shanghai, China

D. Ju Fudan University, Shanghai, China

G. Kiliç Karolinska Institutet, Stockholm, Sweden

B. Laffon Universidade da Coruña, A Coruña, Spain

J. Li Lancaster University, Lancaster, United Kingdom

Y. Liu Sichuan University, Chengdu, China

Y. Li Fudan University, Shanghai, China; University of Pennsylvania, Philadelphia, PA, United States

K. Lou East China University of Science and Technology, Shanghai, China

Y. Manome The Jikei University School of Medicine, Tokyo, Japan

F.L. Martin Lancaster University, Lancaster, United Kingdom; University of Central Lancashire, Preston, United Kingdom

G. Mi Northeastern University, Boston, MA, United States

E. Pásaro Universidade da Coruña, A Coruña, Spain

L.Q. Shao Southern Medical University, Guangzhou, China

D. Shi Northeastern University, Boston, MA, United States

B. Song Southern Medical University, Guangzhou, China; Guizhou Provincial People's Hospital, Guiyang, China

L. Strużyńska Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland

T. Tachibana The Jikei University School of Medicine, Tokyo, Japan

J.P. Teixeira Portuguese National Institute of Health, Porto, Portugal; University of Porto, Porto, Portugal

V. Valdiglesias Universidade da Coruña, A Coruña, Spain

T.J. Webster Northeastern University, Boston, MA, United States; King Abdulaziz University, Jeddah, Saudi Arabia

C. Zhong East China University of Science and Technology, Shanghai, China

Biography

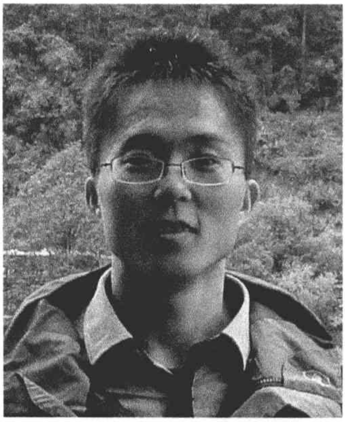
Xinguo Jiang, BS

Professor, Key Laboratory of Smart Drug Delivery (Ministry of Education), School of Pharmacy, Fudan University, Shanghai, China.

Prof. Xinguo Jiang obtained BS in Pharmacy from Shanghai First Medical College in July 1982. Then he worked in the Department of Pharmaceutics in Fudan University (originally Shanghai First Medical College) since October 1986. Between January and July 1996, he was a guest professor in the Department of Pharmacy in Nagasaki University (Japan). He also served as the vice editor for *Chinese Journal of Clinical Pharmacy* and as editorial board member for eight other journals including *Acta Pharmaceutica Sinica* and *Chinese Pharmaceutical Journal*. Prof. Jiang's research interests focus on the development of novel drug delivery systems especially for brain-targeting drug delivery. Having served as the Principal Scientist, Prof. Jiang received a research grant from the State Plan for Development of Basic Research in Key Areas. He also has won eight research grants from National Natural Science Foundation of China and five research grants from Shanghai government. He has accomplished over 70 R&D projects on novel drug delivery systems under cooperation with pharmaceutical companies. Prof. Jiang has published over 120 research papers in peer-reviewed journals and has 15 patents. He has developed three marked formulations. He served as guest editor and edited two theme issues for *Pharmaceutical Research* and *Current Pharmaceutical Biotechnology*. He also wrote several book chapters and edited three books (in Chinese).

Huile Gao, PhD

Associate Professor, Key Laboratory of Drug Targeting and Drug Delivery Systems, West China School of Pharmacy, Sichuan University, Chengdu, Sichuan, China.



Dr. Huile Gao received his PhD in Pharmaceutics from School of Pharmacy, Fudan University, in 2013 under the supervision of Prof. Xinguo Jiang. Then he joined the West China School of Pharmacy, Sichuan University, as Instructor in July 2013 and was promoted to Associate Professor in July 2014. Dr. Gao's research interests focus on the design, synthesis, characterization, and evaluation of stimuli-responsive nanomaterials for drug and imaging probe delivery to improve treatment and diagnosis of human diseases especially tumor and brain diseases. He has published over 50 peer-reviewed articles. His research is supported by the National Natural Science Foundation of China (81373337, 81402866), Excellent Young Scientist Foundation of Sichuan University (2015SCU04A14), and four other grants. He has been given the Excellent Doctoral Dissertation of Shanghai award and the Young Excellent Pharmaceutics Scientist award, both in 2015.

Preface

Development of nanomaterials and nanomedicines is an impressive endeavor by researchers from chemistry, physics, engineering, biology, and medicine to improve the quality of our life. Many kinds of nanomaterials and nanomedicines are approved for human use or are under evaluation. The extensive application considerably elevates the exposure of nanomaterials and toxicity potential to human beings. Even as we enjoy the benefit from nanomaterials and nanomedicines, the toxicity potential should not be ignored.

The central nervous system (CNS) is the most important part of the human body, and should be paid serious attention when we talk about toxicity. The blood–brain barrier (BBB) has contributed to the protection of the CNS from harm by toxicants. Knowledge about BBB and the interaction between BBB and compounds has greatly expanded in the past several decades especially the past few years. The depth of knowledge about BBB enables researchers to develop nanomaterials and nanomedicines for delivering drugs or imaging probes to brain that display engaging potential for CNS disorders. However, neurotoxicity is emerging as a critical concern. The knowledge about neurotoxicity urgently needs to expand.

The chapters in this book were written by active researchers who dedicate their effort to enlarge the brain application of nanomaterials, develop brain nanomedicines, and improve the understanding of interaction of nanomaterials and the CNS. We appreciate these authors for sharing their knowledge and insights about this topic, which provide all of us, especially who work toward nanomaterials and nanomedicines, with an overview of the field and spark to think more about our research.

The early chapters provide an overview of the application of nanomaterials and nanomedicines in brain. The main routes by which nanomaterials enter brain are described. Then the excretion routes are discussed, although there are few studies related to this important topic.

A general review about neurotoxicity is provided in Chapter 4, with emphasis on the neurotoxicity mechanism. Then contributors describe in detail the application and neurotoxicity of many kinds of nanomaterials (Chapters 5–12) that are widely used, including titanium dioxide nanoparticles, iron oxide nanoparticles, silver nanoparticles, gold nanoparticles, manganese-containing nanoparticles, silica nanoparticles, carbon nanotubes, and cationic polymers. These kinds of nanoparticles represent the most commonly used nanomaterials in this field. Finally, an overview about neurotoxicity is provided with discussion of potential strategies to reduce the neurotoxicity of nanomaterials and nanomedicines. Researchers will benefit from this knowledge to design novel nanomaterials and nanomedicines with minimum neurotoxicity.

The editors greatly thank the individual chapter contributors for kindly sharing their knowledge and ideas. It is a great pleasure to collaborate with them to develop this book. We admire the outstanding work they contributed so that researchers from nanomaterials and nanomedicines can benefit from this book and make greater success in their own work.

Xinguo Jiang
Huile Gao
April 2016

Introduction and Overview

H. Gao[1], X. Jiang[2]
[1]*Sichuan University, Chengdu, China;* [2]*Fudan University, Shanghai, China*

Nanoparticles (NPs) are generally described as particles of size about 0.1–100nm, but particles that are several hundred nanometers in size are also called NPs. Thus in this book, we expand the definition of NPs to all particles around 0.1–1000nm. The materials of NPs are called nanomaterials. One of the most important applications of NPs is delivering drugs and imaging probes to human body for disease diagnosis and treatment. These NPs are called nanomedicines.

Accompanied with the development of chemistry, biology, and materials science, many kinds of nanomaterials are synthesized with impressive characteristics. Nanomedicines are also extensively designed for both peripheral diseases and central nervous system (CNS) disorders. Despite great achievements, the toxicity of nanomaterials has been emerging as an increasingly important concern. The CNS is the most important part of human being, thus the toxicity to CNS, named neurotoxicity, should be paid particular attention.

In this book, the application and neurotoxicity of nanomaterials and nanomedicines are reviewed and discussed. The book includes the following:

- The application of nanomaterials and nanomedicines in brain targeting drug delivery
- The routes by which nanomaterials and nanomedicines enter into brain
- The excretion of nanomaterials and nanomedicines from brain
- The neurotoxicity of many kinds of nanomaterials, including titanium dioxide nanoparticles, iron oxide nanoparticles, silver nanoparticles, gold nanoparticles, manganese-containing nanoparticles, silica nanoparticles, carbon nanotubes, and cationic polymers
- The general mechanism of neurotoxicity and strategies to reduce the neurotoxicity.

HOW DO NANOMATERIALS AND NANOMEDICINES ENTER INTO AND GET EXCRETED FROM BRAIN?

In the CNS, the blood–brain barrier (BBB) considerably restricts the brain distribution of nanomaterials and nanomedicines. In healthy condition, the BBB protects the CNS from harm by toxicants in blood. But in CNS disorders, the

BBB also restricts the brain access of drugs, making CNS disorders the most difficult diseases to treat. Many researchers dedicate their efforts to enhance brain drug delivery using various methods. In these methods, nanomaterials play a critical role. In Chapter 1, we discuss the general application of nanomaterials and nanomedicines in brain targeting drug delivery and then in Chapter 2, Dr. Liu and Dr. He further summarize the routes that the nanomaterials enter brain, including penetrating the BBB through receptor-mediated endocytosis, transporter-mediated endocytosis, adsorptive-mediated endocytosis, bypassing BBB through intranasal delivery, inhibiting the function of BBB by inhibition of efflux pumps, and disturbing the structure of BBB. The distribution of nanomaterials and nanomedicines in brain is influenced by many factors, such as size, shape, surface charge, and ligand modification of NPs; administration routes; chronobiology; and disease condition, which is reviewed by Dr. Gao in Chapter 3. After entering into brain, the nanomaterials could be degraded or excreted from brain, which is affected by the deformability, biodegradability, size, shape, and ligand modification of the nanomaterials and nanomedicines. The conscious state and disease condition also affect this procedure, which is discussed in Chapter 3.

WHAT IS THE NEUROTOXICITY OF NANOMATERIALS?

Because nanomaterials could enter into brain through various routes, the contact of nanomaterials and nanomedicines with CNS may cause some neurotoxicity. The common neurotoxicity includes oxidative stress, inducing cell apoptosis and autophagy, immune response and inflammation, activating specific signaling pathway, affecting BBB function, and so on, which are reviewed in Chapter 4. Many kinds of nanomaterials have been developed with potential for CNS exposure, among which the widely used nanomaterials are selected for detailed description, such as metal NPs, carbon nanotubes, and cationic polymers. The application and neurotoxicity of these nanomaterials are reviewed in Chapters 5–12. The potential mechanism and influence factors are also reviewed, such as size, shape, crystal type, charge, surface property, release of ions, and administration route. Because neurotoxicity is a critical concern in the application of nanomaterials and nanomedicines, strategies to reduce neurotoxicity are important for researchers. Based on the reasons involved in the neurotoxicity, we conclude several strategies in Chapter 13, including reducing brain exposure and decreasing inherent toxicity of nanomaterials and nanomedicines.

CONCLUSION

This book is prepared with the purpose of benefiting nanomaterial and nanomedicine researchers in the following areas:

- Fundamental knowledge about nanomaterials and nanomedicines application in CNS disorders

- Routes by which nanomaterials and nanomedicines enter into and get excreted from brain
- Common neurotoxicity of nanomaterials and the influence factors
- Mechanism of neurotoxicity and strategies to reduce neurotoxicity.

The valuable insights shared by chapter authors are intended to expand the fundamental knowledge about brain application of nanomaterials and nanomedicines and the corresponding neurotoxicity. Researchers from all related fields may further develop nanomaterials and nanomedicines with lower neurotoxicity for more satisfying application in humans.

Contents