Toxinology

Editor-in-Chief
P. Gopalakrishnakone

In recent years, the field of toxinology has expanded substantially. On the one hand it studies venomous animals, plants and micro organisms in detail to understand their mode of action on targets. While on the other, it explores the biochemical composition, genomics and proteomics of toxins and venoms to understand their three interaction with life forms (especially humans), development of antidotes and exploring their pharmacological potential. Therefore, toxinology has deep linkages with biochemistry, molecular biology, anatomy and pharmacology. In addition, there is a fast-developing applied subfield, clinical toxinology, which deals with understanding and managing medical effects of toxins on human body. Given the huge impact of toxin-based deaths globally, and the potential of venom in generation of drugs for so-far incurable diseases (for example, diabetes, chronic pain), the continued research and growth of the field is imminent. This has led to the growth of research in the area and the consequent scholarly output by way of publications in journals and books. Despite this ever-growing body of literature within biomedical sciences, there is still no all-inclusive reference work available that collects all of the important biochemical, biomedical and clinical insights relating to toxinology.

Composed of 11 volumes, *Toxinology* provides comprehensive and authoritative coverage of the main areas in toxinology, from fundamental concepts to new developments and applications in the field. Each volume comprises a focused and carefully chosen collection of contributions from leading names in the subject.

Series Titles

1. Biological Toxins and Bioterrorism
2. Clinical Toxinology in the Asia Pacific and Africa
3. Spider Venoms
4. Scorpion Venoms
5. Marine and Freshwater Toxins
6. Venom Genomics and Proteomics
7. Snake Venoms
8. Evolution of Venomous Animals and Their Venoms
9. Microbial Toxins
10. Plant Toxins
11. Toxins and Drug Discovery

More information about this series at http://www.springer.com/series/13330

P. Gopalakrishnakone
Editor-in-Chief

Mahdi Balali-Mood • Lyndon Llewellyn
Bal Ram Singh
Editors

Biological Toxins and Bioterrorism

With 123 Figures and 30 Tables

Springer Reference

Editor-in-Chief
P. Gopalakrishnakone
Venom and Toxin Research Programme
Department of Anatomy
Yong Loo Lin School of Medicine
National University of Singapore
Singapore

Editors
Mahdi Balali-Mood
Medical Toxicology Research Centre
Faculty of Medicine
Mashhad University of Medical Sciences
Mashhad, Iran

Bal Ram Singh
Botulinum Research Center
Institute of Advanced Sciences
Dartmouth, MA, USA

Prime Bio, Inc.
Dartmouth, MA, USA

Lyndon Llewellyn
Data and Technology Innovation
Australian Institute of Marine Science
Townsville, QLD, Australia

ISBN 978-94-007-5868-1 ISBN 978-94-007-5869-8 (eBook)
ISBN 978-94-007-5870-4 (print and electronic bundle)
DOI 10.1007/978-94-007-5869-8
Springer New York Heidelberg Dordrecht London

Library of Congress Control Number: 2014950636

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Series Preface

The term TOXIN is derived from the Greek word *Toeikov* and is defined as a substance derived from tissues of a plant, animal, or microorganism that has a deleterious effect on other living organisms. Studying their detailed structure, function, and mechanism of action as well as finding an antidote to these toxins is the field of TOXINOLOGY, and the scientists are called TOXINOLOGISTS.

In recent years, the field of toxinology has expanded substantially. On the one hand, it studies venomous animals, plants, and microorganisms in detail to understand their habitat, distribution, identification, as well as mode of action on targets, while on the other, it explores the biochemical composition, genomics, and proteomics of toxins and venoms to understand their interaction with life forms (especially humans), the development of antidotes, and their pharmacological potential for drug discovery. Therefore, toxinology has deep linkages with biochemistry, molecular biology, anatomy, pharmacology, etc. In addition, there is a fast-developing applied subfield, clinical toxinology, which deals with understanding and managing medical effects of venoms and toxins on the human body following envenomations. Given the huge impact of envenomation-based deaths globally and the potential of venom in the generation of drugs for debilitating diseases (e.g., diabetes, chronic pain, and cancer), the continued research and growth of the field are imminent.

Springer has taken the bold initiative of producing this series, which is not an easy target of producing about 11 volumes, namely, biological toxins and bioterrorism, clinical toxinology, scorpion venoms, spider venoms, snake venoms, marine and freshwater toxins, toxins and drug discovery, venom genomics and proteomics, evolution of venomous animals and their toxins, plant toxins, and microbial toxins.

Singapore

P. Gopalakrishnakone
MBBS, PhD, FAMS, DSC
Editor-in-Chief

Acknowledgments

I would like to sincerely thank the section editors of this volume, Mahdi Balali-Mood, Lyndon Llewellyn, and Bal Ram Singh, for the invaluable contribution of their expertise and time and the authors who obliged with my request and provided a comprehensive review on the topics.

Springer provided substantial technical and administrative help by many individuals at varying levels, but special mention should go to Mokshika Gaur, Meghna Singh, and Audrey Wong for their tireless effort in bringing these volumes to reality.

Singapore

P. Gopalakrishnakone
MBBS, PhD, FAMS, DSC
Editor-in-Chief

Volume Preface

Biotoxins are an important part of our world, a reality with which we need to cope, so in parallel with understanding their mechanisms of action and thereby improving our fundamental knowledge, there are successful efforts to utilize them as therapeutics against some debilitating human and animal diseases. Over the past several decades, researchers throughout the world have developed techniques and tools to detect these toxins, modify them for specific uses, and develop countermeasures against their effects so that their impacts can be managed.

After the use of chemical warfare agents during World War I, all nations were against any chemical weapon. In spite of the Geneva Protocol in 1925 and further chemical and biological weapon conventions and conferences (the latest one held in 2011) in the last century, both chemical and biological warfare agents were unfortunately applied in war (Iraq-Iran conflict) and terrorism (Matsomoto and Tokyo metro). Due to the application of high technology in biotoxin production, biowar and bioterrorism are now an even bigger threat than chemical war and terrorism. Biotoxins may be abused as bioweapons. As a result, government agencies needed to address it and have developed policies and regulations to allow research on these toxins smoothly.

In view of the complexity of different types of biotoxins and the broad range of toxin structure, physiology, utility, and countermeasures including regulatory issues, it was thus aimed to compile a book on biotoxins and bioweapons.

Some biotoxins are highly potent when administered to victims via a variety of routes and can often be manufactured by means available to even the simplest laboratory, making them ideal candidates for weaponization. But their utility is not solely as weapons. Their exceptional ability to attack physiological mechanisms critical to our survival has allowed us to probe the molecular structures of the enzymes and receptors they attack, improving our understanding of ourselves and the biodiversity important to people everywhere. These natural chemicals can also intrude into our daily lives by contaminating our food and water supplies, being the instrument by which a disease pathogen can sicken us and allowing some animals to defend themselves against predators or subdue their prey.

This volume gathers together knowledge from around the globe about naturally inspired and manufactured bioweapons. The authors describe how they work; how authorities may detect their presence, prevent their use, and diagnose their impacts; and the means by which medical and paramedical professionals may treat victims. Also described are how they have been used to further our knowledge and what insights they have given us into evolutionary and physiological processes. Finally, it is also discussed how these toxins can be used as therapeutics and what the implications of such therapeutics are to their use as biothreat agents.

We have endeavored to provide a reference accessible to scientists, educators, and medical experts alike with an interest in biotoxins, focusing on the major toxins used as bioweapons. Regulatory agencies will also benefit from the information provided in this book. Some in the intended audience may need to understand how they elicit their effects and how we can defend ourselves against them. Others may be interested in the sometimes colorful histories that surround this subset of biotoxins that can be and, in some cases, have been used as weapons.

We are of course deeply grateful to the authors for sharing their expertise with us and contributing to this initiative. We should thank the editor-in-chief, Professor Gopalakrishnakone of the National University of Singapore, whose foresight brought this series to life and allowed us to contribute to the vision. We are also very thankful to Mokshika Gaur, Meghna Singh, and Audrey Wong of Springer who maintained our focus.

We would welcome any comments and feedback from experts in biotoxins and bioweapons to consider for future editions.

January 2015

Mahdi Balali-Mood, Iran
Lyndon Llewellyn, Australia
Bal Ram Singh, USA

Editor-in-Chief

P. Gopalakrishnakone
Venom and Toxin Research Programme
Department of Anatomy
Yong Loo Lin School of Medicine
National University of Singapore
Singapore
antgopal@nus.edu.sg

P. Gopalakrishnakone, MBBS, PhD, FAMS, DSc, is presently professor of anatomy and chairman of the Venom and Toxin Research Programme at the Yong Loo Lin School of Medicine, National University of Singapore. He is also a consultant to the Defence Science Organization in Singapore and adjunct senior research scientist at the Defence Medical Research Institute. Prof. Gopalakrishnakone is an honorary principal fellow at the Australian Venom Research Unit, University of Melbourne, Australia.

His research studies include structure–function studies, toxin detection, biosensors, antitoxins and neutralization factors, toxinogenomics and expression studies, antimicrobial peptides from venoms and toxins, and PLA2 inhibitors as potential drug candidates for inflammatory diseases. The techniques he employs include quantum dots to toxinology, computational biology, microarrays, and protein chips.

Prof. Gopalakrishnakone has more than 160 international publications, 4 books, about 350 conference presentations, and 10 patent applications.

He has been an active member of the International Society on Toxinology (IST) for 30 years and was president from 2008 to 2012. He is also the founder president of its Asia Pacific Section, a council member, as well as an editorial board member of *Toxicon*, the society's official journal.

His research awards include the Outstanding University Researcher Award from the National University of Singapore (1998); Ministerial Citation, NTSB Year 2000

Award in Singapore; and the Research Excellence Award from the Faculty of Medicine at NUS (2003).

His awards in teaching include the Faculty Teaching Excellence Award 2003/4 and the NUS Teaching Excellence Award 2003/4. Prof. Gopalakrishnakone also received the Annual Teaching Excellence Award in 2010 at both university and faculty levels.

Editors

Mahdi Balali-Mood
Visiting Professor of Newcastle University, UK
Professor of Medicine and Clinical Toxicology
Head of Department of Clinical Toxicology
and
Director, Medical Toxicology Research Centre
Imam Reza Hospital, Faculty of Medicine
Mashhad University of Medical Sciences
Mashhad
Iran
BalalimoodM@mums.ac.ir

Mahdi Balali-Mood, M.D., Ph. D., was a lecturer in clinical pharmacology and toxicology at the University of Edinburgh, UK, in 1981–1982. He returned home during the Iraq-Iran war to assist the chemical casualties. Mahdi was promoted to associate professor in 1984 and full professor of Mashhad University in 1988. His other positions are as follows:

Founding member and president, Iranian Society of Toxicology (1989–2001), Asia-Pacific Association of Medical Toxicology (1994–2001), clinical toxicology adviser to WHO (1989 to date); member of many national and international organizations including Iranian Academy of Medical Sciences (1991 to date), World Academy of Sciences (1997 to date), Scientific Advisory Board and the working groups of the Organization for the Prohibition of Chemical Weapons (2004 to date); editor-in-chief, *Scientific Journal of Birjand University of Medical Sciences* (2002 to date); associate editor, *Emerging Health Threats Journal*, Forum of Emerging Health Threats, London, 2006 to 2012.

His research is in the clinical toxicology of chemical warfare agents, organophosphorous heavy metals, drug abuse/overdosage, epidemiology of poisonings, occupational and environmental toxicology, and natural toxins. He is a winner of the National Gold Medal in Research and international awards in medical toxicology. He is editor and author of 28 books/monographs including *Basic and Clinical*

Toxicology of Organophosphorous Compounds by Springer (2014) and author of 143 original papers and 291 short papers/abstracts in national and international medical journals.

Lyndon Llewellyn
Program Leader, Data and Technology Innovation
Australian Institute of Marine Science
Townsville, Queensland
Australia
L.Llewellyn@aims.gov.au

Lyndon Llewellyn is currently the program leader, data and technology innovation, at the Australian Institute of Marine Science. He has a technical background in marine biology, biochemistry, and molecular pharmacology and has conducted numerous studies on both natural and artificial chemical toxicants on marine organisms using tools ranging from the molecular to mangrove trees as well as on biodiscovery for biotechnology. He has a particular expertise in organic marine toxins including saxitoxin, the only marine toxin declared a chemical weapon, which can contaminate seafood as well as marine and aquatic environments.

Dr. Llewellyn also has extensive experience with very large data sets and their management; database design, interrogation, and visualization; as well as technology development, specifically with biosensors. He has led and managed major projects with industry collaborators ranging in size from start-ups to publicly traded companies. Dr. Llewellyn has authored 76 research publications, 12 major technical reports, and an electronic data atlas and is an inventor on international patents. A regular reviewer for national and international granting agencies, he has also been an invited reviewer for almost 30 scientific journals covering a wide variety of disciplines such as analytical chemistry, biochemistry, toxicology, microbiology, and biomedicine.

Bal Ram Singh
Professor and Director, Botulinum Research Center
President, Institute of Advanced Sciences
President and CEO, Prime Bio, Inc.
Dartmouth, MA
USA
bsingh@inads.org

Bal Ram Singh, a former professor of biophysical chemistry and Henry Dreyfus Teacher-Scholar at the University of Massachusetts Dartmouth, United States,

and currently a professor and director of the Botulinum Research Center, Institute of Advanced Sciences, has been conducting research for 27 years on the molecular mode of action of botulinum and tetanus neurotoxins, cranberry natural products, and Ayurvedic and herbal products.

His research on biodefense and biotechnology is internationally recognized, and he has served on many national and international scientific panels organized by the U.S. Department of Health and Human Services, the Centers for Disease Control and Prevention, the U.S. Department of Homeland Security, and the U.S. Department of Defense. As the founding director of the Botulinum Research Center at the University of Massachusetts Dartmouth (2003–2013), he has been the organizer of the Annual International Botulinum Research Symposium since 2007.

Dr. Singh has published over 175 research articles, has edited/coedited 10 books, and has obtained 8 patents. He is the editor of *The Botulinum Journal* and managing editor of *Ayurveda Journal of Health*.

Dr. Singh joined the faculty at the University of Massachusetts Dartmouth in 1990, was tenured in 1995, and rose through ranks to become full professor in 1999. He has held visiting professorships at Georgetown University School of Medicine and Harvard Medical School. He took retirement in June 2014 to set up the Institute of Advanced Sciences to advance his research and educational interests independently.

Contents

Contributors

Shradha Bagaria Department of Biochemistry, Indian Institute of Science, Bangalore, Karnataka, India

Mahdi Balali-Mood Medical Toxicology Research Centre, Head of Department of Clinical Toxicology, Medical School, Mashhad University of Medical Sciences, Mashhad, Iran

Phillip Beske US Army Medical Research Institute of Chemical Defense (USAMRICD), APG-EA, MD, USA

Shuowei Cai Department of Chemistry and Biochemistry, University of Massachusetts Dartmouth, North Dartmouth, MA, USA

S. Chandranayaka Department of Biotechnology, University of Mysore, Mysore, Karnataka, India

Tzuu-Wang Chang Department of Chemistry and Biochemistry, University of Massachusetts Dartmouth, Dartmouth, MA, USA

Keya Chaudhuri Molecular & Human Genetics Division, CSIR-Indian Institute of Chemical Biology, Kolkata, West Bengal, India

Hsiao Ying Chen Defence Medical and Environmental Research Institute, DSO National Laboratories, Singapore, Singapore

Li-Ting Cheng Graduate Institute of Animal Vaccine Technology, National Pingtung University of Science and Technology (NPUST), Pingtung, Neipu, Taiwan

Chun-Yen Chu Graduate Institute of Animal Vaccine Technology, National Pingtung University of Science and Technology (NPUST), Pingtung, Neipu, Taiwan

Kuo-Pin Chuang Graduate Institute of Animal Vaccine Technology, National Pingtung University of Science and Technology (NPUST), Pingtung, Neipu, Taiwan

Yao-Chi Chung Graduate Institute of Animal Vaccine Technology, National Pingtung University of Science and Technology (NPUST), Pingtung, Neipu, Taiwan

Yap Peng-Huat Eric Defence Medical & Environmental Research Institute (DMERI), DSO National Laboratories (Kent Ridge), Singapore, Singapore

Samira Eslamizad Department of Toxicology and Pharmacology, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Leila Etemad Pharmaceutical Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

Ling Yann Foo Defence Medical and Environmental Research Institute, DSO National Laboratories, Singapore, Singapore

Eric A. E. Garber Office of Regulatory Science, US Food and Drug Administration (FDA), Center for Food Safety and Applied Nutrition, College Park, MD, USA

Biplab Giri Department of Physiology, Experimental Medicine & Stem Cell Research Laboratory, West Bengal State University, Kolkata, West Bengal, India

Sherwood Hall Office of Regulatory Science, US Food and Drug Administration (FDA), Center for Food Safety and Applied Nutrition, College Park, MD, USA

Mengfei Ho Department of Microbiology, University of Illinois at Urbana-Champaign, Urbana, IL, USA

Pavithra Janardhanan Department of Chemistry and Biochemistry, University of Massachusetts Dartmouth, North Dartmouth, MA, USA

Anjali A. Karande Department of Biochemistry, Indian Institute of Science, Bangalore, Karnataka, India

Gholamreza Karimi Medical Toxicology Research Center and Pharmacy School, Mashhad University of Medical Sciences, Mashhad, Iran

Guan-Ming Ke Graduate Institute of Animal Vaccine Technology, National Pingtung University of Science and Technology (NPUST), Pingtung, Neipu, Taiwan

Labanyamoy Kole VINS Bioproducts Limited, Mahaboobnagar, Andhra Pradesh, India

Roshan Kukreja Botulinum Research Center and Department of Chemistry and Biochemistry, University of Massachusetts, North Dartmouth, MA, USA

Raj Kumar Department of Chemistry and Biochemistry, University of Massachusetts Dartmouth, Dartmouth, MA, USA

Gyanendra Kumar Department of Structural Biology, St. Jude Children's Research Hospital, Memphis, TN, USA

Olivier Laczka Plant Functional Biology and Climate Change Cluster (C3), University of Technology, Sydney, NSW, Australia

Chao-Nan Lin Department of Veterinary Medicine, National Pingtung University of Science and Technology, Pingtung, Taiwan, Republic of China

Lyndon E. Llewellyn Australian Institute of Marine Science, Townsville MC, QLD, Australia

Weng Keong Loke Defence Medical and Environmental Research Institute, DSO National Laboratories, Singapore, Singapore

Patrick McNutt US Army Medical Research Institute of Chemical Defense (USAMRICD), APG-EA, MD, USA

Soghra Mehri Pharmaceutical Research Center and School of Pharmacy, Department of Pharmacodynamy and Toxicology, Mashhad University of Medical Sciences, Mashhad, Iran

Shabbir Moochhala Defence Medical & Environmental Research Institute (DMERI), DSO National Laboratories (Kent Ridge), Singapore, Singapore

Mohammad Moshiri Pharmacodynamy and Toxicology Department, Mashhad University of Medical Sciences, Mashhad, Iran

S. R. Niranjana Department of Biotechnology, University of Mysore, Mysore, Karnataka, India

Andy Pickett Toxin Science Limited, Wrexham, UK

Segaran Pillai Science and Technology Directorate, Department of Homeland Security, Washington, DC, USA

H. S. Prakash Department of Biotechnology, University of Mysore, Mysore, Karnataka, India

Maryann C. Principato Office of Food and Veterinary Medicine, Office of Applied Research and Safety Assessment, US Food and Drug Administration (FDA), Center for Food Safety and Applied Nutrition, College Park, MD, USA

Ganapathy Rajaseger Defence Medical & Environmental Research Institute (DMERI), DSO National Laboratories (Kent Ridge), Singapore, Singapore

Jason Ramage Science and Technology Directorate, Department of Homeland Security, Washington, DC, USA

Padmanabhan Saravanan Technology Development, School of Applied Science, Temasek Polytechnic, Singapore, Singapore

Barbara B. Saunders-Price ASA Inc., Kaneohe, HI, USA

Shashi K. Sharma Office of Regulatory Science, US Food and Drug Administration (FDA), Center for Food Safety and Applied Nutrition, College Park, MD, USA

Ajay K. Singh Office of Regulatory Science, US Food and Drug Administration (FDA), Center for Food Safety and Applied Nutrition, College Park, MD, USA

Bal Ram Singh Botulinum Research Center and Department of Chemistry and Biochemistry, University of Massachusetts, North Dartmouth, MA, USA

Nagarajan Thirunavukkarasu Department of Chemistry and Biochemistry, United States Food and Drug Administration, College Park, MD, USA

Baskaran Thyagarajan College of Health Sciences, School of Pharmacy, University of Wyoming, Laramie, WY, USA

Michael J. Tyler School of Earth and Environmental Studies, University of Adelaide, Adelaide, SA, Australia

M. Venkataramana DRDO-BU- Centre for Life Sciences, Bharathiar University Campus, Coimbatore, Tamilnadu, India

Brenda A. Wilson Department of Microbiology, University of Illinois at Urbana-Champaign, Urbana, IL, USA

Chung-Da Yang Graduate Institute of Animal Vaccine Technology, National Pingtung University of Science and Technology (NPUST), Pingtung, Neipu, Taiwan

Hassan Yazdanpanah Department of Toxicology and Pharmacology, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran