

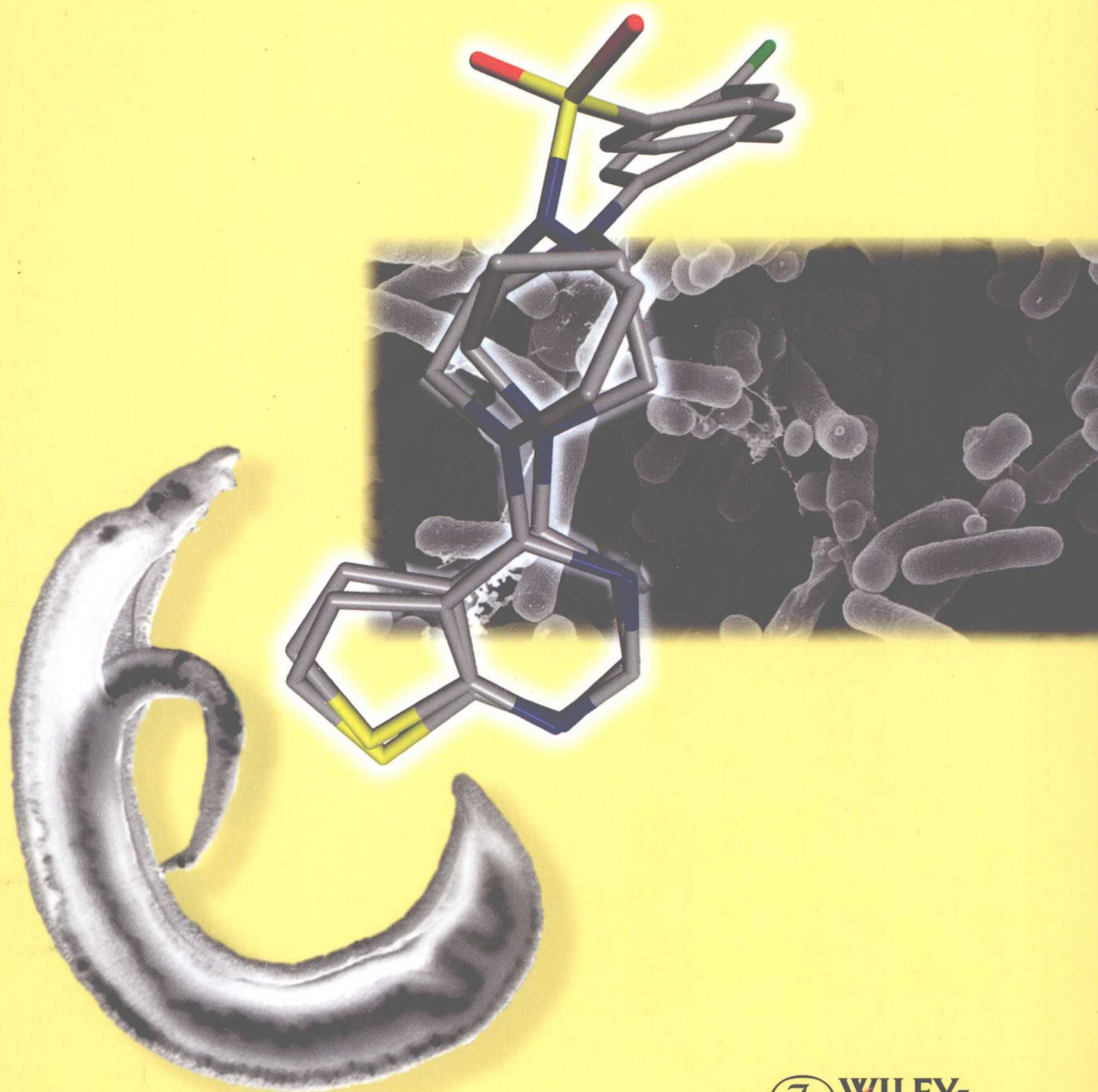



Drug Discovery in Infectious Diseases  
Edited by Paul M. Selzer

# Antiparasitic and Antibacterial Drug Discovery

From Molecular Targets to Drug Candidates

Edited by Paul M. Selzer



 WILEY-  
BLACKWELL

# Antiparasitic and Antibacterial Drug Discovery

From Molecular Targets to Drug Candidates

*Edited by*  
*Paul M. Selzer*



**WILEY-  
BLACKWELL**

WILEY-VCH Verlag GmbH & Co. KGaA

#### The Editor

**Prof. Dr. Paul M. Selzer**

BioChemInformatics  
Intervet Innovation GmbH  
Zur Propstei  
55270 Schwabenheim  
Germany

paul.selzer@sp.intervet.com

#### Cover

Light microscopic image of the helminth *Schistosoma mansoni*—with a male hosting a female in the *canalis gynaecophorus*: courtesy of Dr. Conor R. Caffrey, University of California San Francisco, USA.  
Scanning electron microscopic image of the gram-negative bacteria *Mannheimia haemolytica*: courtesy of Prof. Dr. Lothar H. Wieler, Freie Universität Berlin, Dr. Heike Kaspar, and Dr. Christoph Schaudinn, Robert Koch Institut Berlin, Germany. The chemical structure is taken from chapter 19 authored by Thorsten Meyer *et al.*, figure 19.9.

All books published by Wiley-VCH are carefully produced. Nevertheless, authors, editors, and publisher do not warrant the information contained in these books, including this book, to be free of errors. Readers are advised to keep in mind that statements, data, illustrations, procedural details or other items may inadvertently be inaccurate.

**Library of Congress Card No.:** applied for

#### British Library Cataloguing-in-Publication Data

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

#### Bibliographic information published by the Deutsche Nationalbibliothek

Die Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at <http://dnb.d-nb.de>.

© 2009 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

All rights reserved (including those of translation into other languages). No part of this book may be reproduced in any form – by photoprinting, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers. Registered names, trademarks, etc. used in this book, even when not specifically marked as such, are not to be considered unprotected by law.

**Typesetting** Thomson Digital, Noida, India

**Printing** Strauss GmbH, Mörlenbach

**Binding** Litges & Dopf GmbH, Heppenheim

**Cover Design** Adam-Design, Weinheim

Printed in the Federal Republic of Germany

Printed on acid-free paper

ISBN: 978-3-527-32327-2

## Foreword

It is ironic that three decades ago infectious diseases were viewed as a problem of the past. Malaria and tuberculosis were going to be eradicated, effective vaccines were available for major childhood infections, and an armamentarium of antibiotics was available for common community and hospital-acquired infections. Young physicians were advised not to enter infectious disease specialties because they were becoming irrelevant. The AIDS epidemic was the first wakeup call that infectious diseases would again become a major global health problem. Drug-resistant malaria and tuberculosis are now almost ubiquitous and new and emerging infectious diseases are almost a weekly staple of the popular press. Indeed the need for new drugs for infectious diseases has never been greater. Global industry and global travel means that formerly exotic diseases can rapidly establish themselves at any port of entry. Effective vaccines against the most prevalent infectious diseases like AIDS and malaria have proven difficult to develop. Multidrug-resistant organisms are an issue in any clinical setting. This publication provides a window on new approaches to drug discovery and development targeting infectious diseases. Fortunately, technology and training in new methodologies of drug discovery have expanded rapidly in the past 10 years. The challenge is how to effectively apply this technology to the thorny problems of global infections and to maintain a drug development pipeline for infectious diseases in light of the immense cost now associated with bringing new drugs to market.

San Francisco, USA  
November 2008

*James H. McKerrow*

## Preface

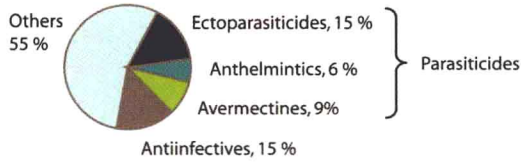
In the age of antibiotics, vaccines, and drugs, we might be lulled into a sense of complacency regarding infectious diseases and that there is “a cure for everything”. This sense of security is maintained at our peril, however. One has only to consider the growing devastation caused by such big-name diseases as influenza, HIV-AIDS, tuberculosis, and malaria to see that the struggle to treat and control infectious diseases is truly titanic and indeed becoming more perilous with the ever-evolving development and spread of drug resistance compounded by the greater freedom and speed of movement of goods, animals, and people. Aside from the recently perceived security threat to the health and business structures of the developed world caused by these and a plethora of other infectious disease, billions living in developing countries must endure the daily struggle of diseases. In contrast to most human health-related pharmaceutical companies, academic institutions, veterinary science, and animal health companies remain very much focused on infectious diseases, including those caused by bacteria and parasites. As illustrated in Figure 1, the animal health sector remains profitable, and thankfully so, as history has shown that therapies produced in this sector often prove invaluable for treatment of similar infectious diseases of humans – the application of anthelmintics being a case in point.

The improved understanding of the resilience of disease-causing agents to therapies, their expanding disease menace in the era of “globalization,” and the balance provided by the opportunities for cross-sector exchange of ideas and applications spurred the preparation of this book. Also, the book serves to highlight the importance and visibility of drug discovery efforts for infectious diseases of both animals and humans.

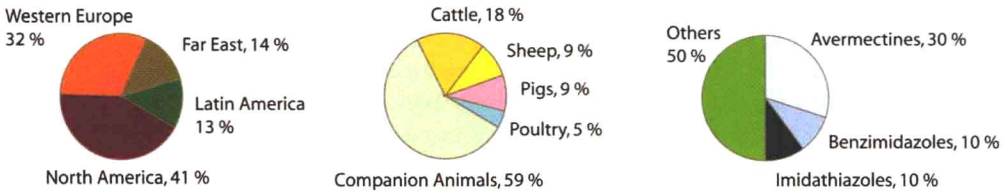
Though it is not possible to address every aspect, disease, or approach within a single volume, this book sets forth a series of case studies and review articles that focus on bacterial and parasitic diseases in order to showcase how scientists in the different disciplines strive to move drug discovery forward. The contributing authors are experts drawn from drug discovery units of the pharmaceutical industry, academia, and nonprofit organizations in an effort to offer a global and balanced insight into the issues and problems at stake and their possible solutions.

Writing this has been a rewarding task for everybody involved. My heartfelt thanks go to the contributing authors for their excellent work performed within a short time-frame. In addition, I am grateful to Intervet/Schering-Plough Animal Health and its Drug Discovery Unit for their unreserved support, inspiration, and motivation

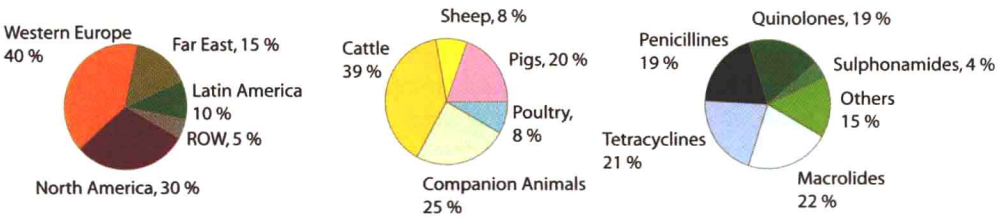
Animal Health Market: 16 Billion USD



Combined Parasiticides Market: 4.8 Billion USD



Antiinfectives Market: 2.4 Billion USD



**Figure 1** The world animal health market based on data from 2006. The first row depicts the proportion of antiparasitics and antiinfectives in the whole animal health market. Rows two and three represent the antiparasitics and antiinfectives market, respectively. From left to right the individual proportions are broken down according to regional sales (ROW = rest of

world), sales per animal species, and sales per chemical class. The area of the individual pie charts is not size-adjusted. Original data were derived by Wood Mackenzie and kindly provided by Linda Franken-Horspool, International Marketing, Intervet/Schering-Plough Animal Health.

during the preparation of this book. I also thank the members of Intervet's Bio-ChemInformatics Unit for their excellent technical backing and team spirit. Finally, I am very grateful to Ms Simone Maus-Gilbert for her outstanding editorial assistance.

Schwabenheim, Germany  
November 2008

Paul M. Selzer

## List of Contributors

### **Mathias Beig**

Intervet Innovation GmbH  
Zur Propstei  
55270 Schwabenheim  
Germany

### **Michael Berger**

Intervet Innovation GmbH  
Zur Propstei  
55270 Schwabenheim  
Germany

### **Michael J. Blackman**

Division of Parasitology  
National Institute for Medical Research  
The Ridgeway  
Mill Hill  
London  
NW7 1AA  
UK

### **Lothar Brecker**

Institut für Organische Chemie der  
Universität Wien  
Währinger Strasse 38  
1090 Wien  
Austria

### **Heike Bruhn**

University of Würzburg  
Institute for Molecular Infection Biology  
Röntgenring 11  
97070 Würzburg  
Germany

### **Kathryn Bull**

School of Biological Sciences  
University of Southampton  
Bassett Crescent East  
Southampton  
SO16 7PX  
UK

### **Conor R. Caffrey\***

Department of Pathology and  
the Sandler Center for Basic Research  
in Parasitic Diseases  
Byers Hall  
University of California San Francisco  
CA 94158  
USA  
caffrey@cgl.ucsf.edu

### **Christophe Chassaing\***

Intervet Innovation GmbH  
Zur Propstei  
55270 Schwabenheim  
Germany  
christophe.chassaing@sp.intervet.com

\* Corresponding author

**Eric Chatelain**

Drugs for Neglected Diseases Initiative  
(DNDi)  
15 Chemin Louis-Dunant  
1202 Geneva  
Switzerland

**Jörg Cramer**

Intervet Innovation GmbH  
Zur Propstei  
55270 Schwabenheim  
Germany

**Véronique Dartois\***

Novartis Institute for Tropical Diseases  
10 Biopolis Road  
05-01 Chromos  
Singapore 138670  
Singapore  
veronique.dartois@novartis.com

**Thomas Dick**

Novartis Institute for Tropical Diseases  
10 Biopolis Road  
05-01 Chromos  
Singapore 138670  
Singapore

**Ulrich Dobrindt**

University of Würzburg  
Institute for Molecular Infection Biology  
Röntgenring 11  
97070 Würzburg  
Germany

**Rob Don\***

Drugs for Neglected Diseases Initiative  
(DNDi)  
15 Chemin Louis-Dunant  
1202 Geneva  
Switzerland  
rdon@dndi.org

**Patricia Doyle**

Department of Pathology and  
the Sandler Center for Basic Research  
in Parasitic Diseases  
University of California San Francisco  
CA 94158  
USA

**Martin Eckart**

University of Würzburg  
Institute for Molecular Infection  
Biology  
Röntgenring 11  
97070 Würzburg  
Germany

**Kristin Engels**

Intervet Innovation GmbH  
Zur Propstei  
55270 Schwabenheim  
Germany

**Leopold Flohé\***

Molisa GmbH  
Brenneckestraße 20  
39118 Magdeburg  
Germany  
l.flohe@t-online.de

**Michael Gassel**

Intervet Innovation GmbH  
Zur Propstei  
55270 Schwabenheim  
Germany

**Timothy G. Geary\***

Institute of Parasitology  
McGill University  
21111 Lakeshore Road  
Ste-Anne-de-Bellevue  
QC Canada H9X 3V9  
Canada  
timothy.g.geary@mcgill.ca



**Karen M. Grant\***

School of Health & Medicine  
 Division of Medicine  
 Faraday Building, Lancaster University  
 Lancaster  
 LA1 4YB  
 UK  
 k.grant1@lancaster.ac.uk

**Marcus Guest**

School of Biological Sciences  
 University of Southampton  
 Bassett Crescent East  
 Southampton  
 SO16 7PX  
 UK

**Nikolas Gunkel\***

Intervet Innovation GmbH  
 Zur Propstei  
 55270 Schwabenheim  
 Germany  
 nikolas.gunkel@sp.intervet.com

**Jörg Hacker**

Robert-Koch-Institute  
 Nordufer 20  
 13353 Berlin  
 Germany

**Achim Harder\***

Bayer HealthCare AG  
 Animal Health GmbH  
 CRD-Parasitocides  
 Alfred-Nobel-Strasse 50  
 40789 Monheim  
 Germany  
 achim.harder@bayerhealthcare.com

**Chen He**

UCSD Medical Center  
 200 West Arbor Drive  
 San Diego  
 CA 92103-8416  
 USA

**Anja R. Heckeroth**

Intervet Innovation GmbH  
 Zur Propstei  
 55270 Schwabenheim  
 Germany

**Michael Hinz**

Intervet Innovation GmbH  
 Zur Propstei  
 55270 Schwabenheim  
 Germany

**Lindy Holden-Dye**

School of Biological Sciences  
 University of Southampton  
 Bassett Crescent East  
 Southampton  
 SO16 7PX  
 UK

**Thomas Ilg**

Intervet Innovation GmbH  
 Zur Propstei  
 55270 Schwabenheim  
 Germany

**Dayadevi Jirage**

Division of Experimental Therapeutics  
 Walter Reed Army Institute of Research  
 503 Robert Grant Avenue  
 Silver Spring  
 MD 20910  
 USA

**Susan M. Keenan**

School of Biological Sciences  
 University of Northern Colorado  
 501 20th Street  
 Greeley  
 CO 80501  
 USA

**Jennifer Keiser**

Department of Medical Parasitology and  
Infection Biology  
Swiss Tropical Institute  
P.O. Box  
4002 Basel  
Switzerland

**Christopher Kern**

Intervet Innovation GmbH  
Zur Propstei  
55270 Schwabenheim  
Germany

**Marion Kögl (passed away)**

Institut für Organische Chemie der  
Universität Wien  
Währinger Strasse 38  
1090 Wien  
Austria

**Peter Köhler\***

University of Zürich  
Institute of Parasitology  
Switzerland  
peterkoehler@access.uzh.ch

*and*

Niederdorf 833  
8132 Hintereggen  
Switzerland

**Andreas Krasky**

Intervet Innovation GmbH  
Zur Propstei  
55270 Schwabenheim  
Germany

**Franz Joel Leong**

Novartis Institute for Tropical Diseases  
10 Biopolis Road  
05-01 Chromos  
Singapore 138670  
Singapore

**Kirkwood M. Land**

Department of Biological Sciences  
University of the Pacific  
Stockton  
CA 95211  
USA

**Cheryl Lobo**

Lab of Blood-Borne Parasites  
The Lindsley Kimball Research Institute  
New York Blood Center  
310 East 67th Street  
New York  
NY 10021  
USA

**Zachary Mackey**

Department of Pathology and  
the Sandler Center for Basic Research  
in Parasitic Diseases  
Byers Hall  
University of California San Francisco  
CA 94158  
USA

**Richard J. Marhöfer**

Intervet Innovation GmbH  
Zur Propstei  
55270 Schwabenheim  
Germany

**James H. McKerrow\***

Department of Pathology and  
the Sandler Center for Basic Research  
in Parasitic Diseases  
Byers Hall  
University of California San Francisco  
CA 94158  
USA  
jmck@cgl.ucsf.edu

**Christina Mertens**

Intervet International BV  
Wim de Körverstraat 35  
5830 AA Boxmeer  
The Netherlands

**Thorsten Meyer\***

Intervet Innovation GmbH  
Zur Propstei  
55270 Schwabenheim  
Germany  
thorsten.meyer@sp.intervet.com

**Christian Miculka\***

Intervet Innovation GmbH  
Zur Propstei  
55270 Schwabenheim  
Germany

Present address:

Merial Inc.  
3239 Satellite Blvd.  
Duluth, GA 30096  
USA  
christian.miculka@merial.com

**Andrew Morris**

Institute for Science and Technology in  
Medicine  
Huxley Building  
Keele University  
Keele, Newcastle-under-Lyme  
ST5 5BG  
UK

**Johann Mulzer\***

Institut für Organische Chemie der  
Universität Wien  
Währinger Strasse 38  
1090 Wien  
Austria  
johann.mulzer@univie.ac.at

**Momar Ndao**

National Reference Centre for  
Parasitology  
Department of Medicine  
Division of Infectious Diseases  
Research Institute of the McGill  
University Health Centre  
Montreal General, Hospital/Research  
Institute R3-13  
1625 Pine Ave West  
Montreal H3G 1A4  
Quebec Canada

**David L. Nelson**

Departamento de Alimentos  
Faculdade de Farmácia  
Universidade Federal de Minas Gerais  
31270-901 Belo Horizonte  
Minas Gerais  
Brazil

**Trevor Newton**

BASF SE  
GVA/HC – B009  
67056 Ludwigshafen  
Germany

**Sandra Noack**

Intervet Innovation GmbH  
Zur Propstei  
55270 Schwabenheim  
Germany

**Solomon Nwaka**

Special Programme for Research and  
Training in Tropical Diseases (TDR)  
World Health Organization  
20 Avenue Appia  
1211 Geneva 27  
Switzerland

**Frank Oellien**

Intervet Innovation GmbH  
Zur Propstei  
55270 Schwabenheim  
Germany

**Knut Ohlsen\***

University of Würzburg  
Institute for Molecular Infection Biology  
Röntgenring 11  
97070 Würzburg  
Germany  
knut.ohlsen@mail.uni-wuerzburg.de

**Roger K. Prichard**

Institute of Parasitology  
McGill University  
21111 Lakeshore Road  
Sainte Anne-de-Bellevue  
H9X 3V9  
Quebec  
Canada

**Sharon L. Reed**

UCSD Medical Center  
200 West Arbor Drive  
San Diego  
CA 92103-8416  
USA

**Petra Rohrwild**

Intervet Innovation GmbH  
Zur Propstei  
55270 Schwabenheim  
Germany

**Andreas Rohwer**

Intervet Innovation GmbH  
Zur Propstei  
55270 Schwabenheim  
Germany

**Georg von Samson-Himmelstjerna\***

Institute for Parasitology  
University of Veterinary Medicine  
Buenteweg 17  
30559 Hannover  
Germany  
gvsamson@tiho-hannover.de

**Mohammed Sajid\***

Department of Pathology and  
the Sandler Center for Basic Research  
in Parasitic Diseases  
University of California San Francisco  
CA 94158  
USA  
sajid@ucsf.edu

*and*

Leiden University Medical Centre  
Leiden Malaria Research Group, afd.  
Parasitologie  
Albinusdreef 2  
Kamer P4-35  
2333 ZA Leiden  
Netherlands  
m.sajid@lumc.nl

**Jörg Schröder**

Intervet Innovation GmbH  
Zur Propstei  
55270 Schwabenheim  
Germany

**Theo P.M. Schettlers\***

Intervet/Schering-Plough Animal Health  
Körperstraat 35  
5830 AA Boxmeer  
The Netherlands  
theo.schettlers@sp.intervet.com

**Frank Seeber\***

Molecular Parasitology  
 Institute for Biology  
 Humboldt University  
 Philippstraße 13  
 10115 Berlin  
 Germany  
 seeber@staff.hu-berlin.de

**Harald Sekljic**

Intervet Innovation GmbH  
 Zur Propstei  
 55270 Schwabenheim  
 Germany

**Paul M. Selzer\***

Intervet Innovation GmbH  
 Zur Propstei  
 55270 Schwabenheim  
 Germany  
 paul.selzer@sp.intervet.com

**Brian Shiels**

Institute of Comparative Medicine  
 Vet School  
 University of Glasgow  
 Bearsden Road  
 Glasgow  
 G61 1QH  
 UK

**Volker Spehr**

Intervet Innovation GmbH  
 Zur Propstei  
 55270 Schwabenheim  
 Germany

**Wolfgang Streber\***

Intervet Innovation GmbH  
 Zur Propstei  
 55270 Schwabenheim  
 Germany  
 wolfgang.streber@sp.intervet.com

**Ryan Swenerton**

Department of Pathology and  
 the Sandler Center for Basic Research  
 in Parasitic Diseases  
 University of California San Francisco  
 CA 94158  
 USA

**Matthew H. Todd**

School of Chemistry  
 University of Sydney  
 NSW 2006  
 Australia

**Hon Q. Tran**

Intervet Innovation GmbH  
 Zur Propstei  
 55270 Schwabenheim  
 Germany

**Robert Walker**

School of Biological Sciences  
 University of Southampton  
 Bassett Crescent East  
 Southampton  
 SO16 7PX  
 UK

**Ralf Warrass**

Intervet Innovation GmbH  
 Zur Propstei  
 55270 Schwabenheim  
 Germany

**Norman C. Waters**

Division of Experimental Therapeutics  
 Walter Reed Army Institute of Research  
 503 Robert Grant Avenue  
 Silver Spring  
 MD 20910  
 USA  
 norman.waters@us.army.mil

and

Australian Army Malaria Institute  
WRAIR laboratory  
Gallipoli Barracks  
Weary Dunlop Drive  
Enoggera  
QLD 4051  
Australia

***William Weir***

Institute of Comparative Medicine  
Vet School  
University of Glasgow  
Bearsden Road  
Glasgow  
G61 1QH  
UK

***Martin Wiese***

Strathclyde Institute of Pharmacy and  
Biomedical Sciences (SIPBS)  
John Arbuthnott Building  
27 Taylor Street  
Glasgow  
G4 0NR  
UK

***David L. Williams***

Department of Biological Sciences  
Illinois State University  
Normal  
IL 61790  
USA

***Tracey Williams***

Pfizer Animal Health  
7000 Portage Road  
Kalamazoo  
MI 49001  
USA

***Christian Wolf***

Intervet Innovation GmbH  
Zur Propstei  
55270 Schwabenheim  
Germany

***Adrian J. Wolstenholme***

Department of Biology and  
Biochemistry  
University of Bath  
Claverton Down  
Bath  
BA2 7AY  
UK

*and*

Department of Infectious Diseases  
University of Georgia  
College of Veterinary Medicine  
Athens  
GA 30602  
USA

***Debra J. Woods***

Pfizer Animal Health  
7000 Portage Road  
Kalamazoo  
MI 49001  
USA

***Manfred Uphoff***

Intervet Innovation GmbH  
Zur Propstei  
55270 Schwabenheim  
Germany

***Gottfried Uden***

Institut für Mikrobiologie und  
Weinforschung  
University of Mainz  
Becherweg 15  
55128 Mainz  
Germany

***Jürg Utzinger***

Department of Public Health and  
Epidemiology  
Swiss Tropical Institute  
P.O. Box 4002 Basel  
Switzerland

## Contents

Foreword	V
Preface	XI
List of Contributors	XIII

### Part One Drug Discovery Approaches 1

- 1 **Target Identification and Mechanism-Based Screening for Anthelmintics: Application of Veterinary Antiparasitic Research Programs to Search for New Antiparasitic Drugs for Human Indications** 3  
*Timothy G. Geary\*, Debra J. Woods, Tracey Williams, and Solomon Nwaka*
- 2 **Anthelmintic Resistance as a Guide to the Discovery of New Drugs?** 17  
*Georg v. Samson-Himmelstjerna\*, Roger K. Prichard, and Adrian J. Wolstenholme*
- 3 **Drug Discovery for Neglected Diseases: View of A Public–Private Partnership** 33  
*Rob Don\* and Eric Chatelain*
- 4 **Bioinformatics and Chemoinformatics: Key Technologies in the Drug Discovery Process** 45  
*Andreas Krasky, Andreas Rohwer, Richard J. Marhöfer, and Paul M. Selzer\**
- 5 **Target Identification and Validation in Antiparasitic Drug Discovery** 59  
*Christian Wolf and Nikolas Gunkel\**
- 6 **Selective Drug Targets in Parasites** 75  
*Peter Köhler\* and Richard J. Marhöfer*

- 7      **Lessons Learned from Target-Based Lead Discovery** 99  
*Michael Gassel, Jörg Cramer, Christopher Kern, Sandra Noack,  
and Wolfgang Streber\**
- 8      **Approaches Towards Antiparasitic Drug Candidates for  
Veterinary Use** 117  
*Christophe Chassaing\* and Harald Sekljic*
- 9      **Learning to Relate Structural Space to Property Space** 135  
*Michael Berger, Jörg Cramer, Michael Hinz, Christina Mertens,  
Christian Miculka\*, Trevor Newton, Jörg Schröder, and Harald Sekljic*
- 10     **Recruiting the Host Defense Mechanisms: Roles for Vaccines  
and Chemotherapeutics** 159  
*Theo P.M. Schettlers\**
- Part Two Protozoan Parasites** 175
- 11     **Proteases of Parasitic Protozoa – Current Status and Validation** 177  
*Mohammed Sajid\*, Michael J. Blackman, Patricia Doyle, Chen He,  
Kirkwood M. Land, Cheryl Lobo, Zachary Mackey, Momar Ndao,  
Sharon L. Reed, Brian Shiels, Ryan Swenerton, and William Weir*
- 12     **In Search of Trypanocidal Drugs** 211  
*Leopold Flohé\**
- 13     **Trypanosomatid Protein Kinases As Potential Drug Targets** 227  
*Martin Wiese, Andrew Morris, and Karen M. Grant\**
- 14     **Targeting the Malaria Kinome: Discovering Kinase Inhibitors  
as Novel Antimalarial Agents** 249  
*Dayadevi Jirage, Susan M. Keenan, and Norman C. Waters\**
- 15     **Malaria and Antimalarials – a Focused View** 277  
*Frank Seeber\**
- Part Three Multicellular Parasites** 299
- 16     **Chemotherapeutic Development Strategies for Schistosomiasis** 301  
*Conor R. Caffrey\*, David L. Williams, Matthew H. Todd, David L. Nelson,  
Jennifer Keiser, and Jürg Utzinger*



- 17      **Searching New Antiparasitics in Virtual Space** 323  
*Frank Oellien, Kristin Engels, Jörg Cramer, Richard J. Marhöfer, Christopher Kern, and Paul M. Selzer\**
- 18      **Cyclooctadepsipeptides – an Anthelmintically Active Class of Compounds Exhibiting a Novel Mode of Action** 339  
*Achim Harder\*, Kathryn Bull, Marcus Guest, Lindy Holden-Dye, and Robert Walker*
- 19      **Chemical Optimization of Anthelmintic Compounds – A Case Study** 357  
*Thorsten Meyer\*, Jörg Schröder, Manfred Uphoff, Sandra Noack, Anja R. Heckeröth, Michael Gassel, Petra Rohrwild, and Thomas Ilg*
- Part Four Bacteria** 373
- 20      **Pathogenomics: Identification of Novel Drug Targets and Vaccine Candidates in Bacteria** 375  
*Knut Ohlsen\*, Martin Eckart, Ulrich Dobrindt, Heike Bruhn, and Jörg Hacker*
- 21      **Tuberculosis Drug Discovery: Issues, Gaps and the Way Forward** 415  
*Véronique Dartois\*, Franz Joel Leong, and Thomas Dick*
- 22      **Decreasing the Number of Gaps in the Draft Assembly of the *Mannheimia haemolytica* M7/2 Genome Sequence** 441  
*Hon Q. Tran, Mathias Beig, Volker Spehr, Andreas Rohwer, Gottfried Unden, and Paul M. Selzer\**
- 23      **Total Synthesis and Configurational Assignment of Pasteurestin A and B, a Natural Product with Antimicrobial Activity on Pasteurellaceae** 453  
*Marion Kögl, Lothar Brecker, Ralf Warrass, and Johann Mulzer\**
- Index** 473