This is the first resource to provide researchers in academia and industry with an urgently needed update on drug intervention against trypanosomatides. As such, it covers every aspect of the topic from basic research findings, via current treatments to translational approaches in drug development and includes both human and livestock diseases. The outstanding editor and contributor team reads like a Who’s Who of the field, thus guaranteeing the outstanding quality of this ready reference.

Leopold Flohé studied philosophy, medicine, and biochemistry and obtained his MD and the venia legendi for Biochemistry from the University of Tübingen, Germany. He served as Scientific Director for Grünenthal GmbH in Aachen, the German Biotechnology Centre (HZI) in Braunschweig and Molisa GmbH in Magdeburg, Germany, while simultaneously teaching at the local universities. His contributions to science were acknowledged with Honorary Degrees from the Universities of Buenos Aires and Montevideo, the Claudius-Galenus Prize, the Klaus Schwarz Commemorative Medal, the Science and Humanity Prize (OCC) and the Trevor Frank Slater Award and Gold Medal (SFRRI).

Paul M. Selzer studied biology, parasitology, and biochemistry at the University of Tübingen, Germany, where he also received his PhD in biochemistry. He spent three years at the Molecular Design Institute and the Parasitology and Tropical Disease Research Laboratory at the University of California, San Francisco. During his career he has worked as a researcher and scientific manager for several pharmaceutical companies, and is currently Director, Molecular Discovery Sciences at MSD Animal Health Innovation GmbH, Germany. He is also a visiting professor and teacher at the Biochemistry Institute of the University of Tübingen, and an honorary professor of the Department of Infection, Immunity, and Inflammation at the University of Glasgow, UK.
Edited by
Timo Jäger, Oliver Koch, and Leopold Flohé

Trypanosomatid Diseases
### Titles of the Series “Drug Discovery in Infectious Diseases”

<table>
<thead>
<tr>
<th>Title</th>
<th>Author/Editor</th>
<th>ISBN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiparasitic and Antibacterial Drug Discovery</td>
<td>Selzer, P. M. (ed.)</td>
<td>978-3-527-32327-2</td>
</tr>
<tr>
<td>From Molecular Targets to Drug Candidates</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2009</td>
</tr>
<tr>
<td>Parasitic Helminths Targets, Screens, Drugs and Vaccines</td>
<td>Conor R. Caffrey (ed.)</td>
<td>978-3-527-33059-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Becker, K. (ed.)</td>
<td>978-3-527-32731-7</td>
</tr>
<tr>
<td>Apicomplexan Parasites Molecular Approaches toward Targeted Drug Development</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2011</td>
</tr>
</tbody>
</table>

### Forthcoming Topics of the Series

- Protein Phosphorylation in Parasites: Novel Targets for Antiparasitic Intervention

### Related Titles

<table>
<thead>
<tr>
<th>Title</th>
<th>Author/Editor</th>
<th>ISBN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zajac, A. M., Conboy, G. A. (eds.)</td>
<td>Veterinary Clinical Parasitology</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ISBN: 978-0-8138-2053-8</td>
</tr>
<tr>
<td>Immunity to Parasitic Infections</td>
<td>Lamb, T.</td>
<td>978-0-470-97247-2</td>
</tr>
<tr>
<td></td>
<td>Scott, I., Sutherland, I.</td>
<td>Gastrointestinal Nematodes of Sheep and Cattle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ISBN: 978-1-4051-8582-0</td>
</tr>
</tbody>
</table>
Trypanosomatid Diseases

Molecular Routes to Drug Discovery
The Editors

Volume Editors:

Dr. Timo Jäger
German Centre for Infection Research
Inhoffenstraße 7
38124 Braunschweig
Germany
timo.jaeger@dzif.de

Dr. Oliver Koch
TU Dortmund University
Faculty of Chemistry
Otto-Hahn-Straße 6
44227 Dortmund
Germany
Oliver.Koch@tu-dortmund.de

Prof. Dr.med. Dr.h.c. Leopold Flohé
Otto-von-Guericke-Universität
Department of Chemistry
Universitätsplatz 2
39106 Magdeburg
Germany
l.flohe@t-online.de

Series Editor:

Prof. Dr. Paul M. Selzer
MSD Animal Health Innovation GmbH
Zur Propstei
55270 Schwabenheim
Germany
Paul.Selzer@msd.de

Cover Legend

The cover depicts the three-dimensional structure of a trypanothione synthetase model containing ATP, glutathione, and glutathionylspermidine in the active site. The protein is shown in ribbon representation. Glutathionylspermidine, ATP, and glutathione are depicted in ball-and-stick representation. Two magnesium ions are shown as green spheres. The structure visualization was prepared by R. Marhöfer, MSD Animal Health Innovation GmbH, Schwabenheim, Germany on the basis of a structural model, kindly provided by O. Koch et al., Chapter 23. The inset shows an artificially colored scanning electron microscope image of Trypanosoma brucei (blue) surrounded by erythrocytes (red discs) and a single leukocyte (yellow sphere). The original scanning electron microscope image was kindly provided by M. Duszenko, University of Tübingen, Germany.

Limit of Liability/Disclaimer of Warranty: While the publisher and author have used their best efforts in preparing this book, they make no representations or warranties with respect to the accuracy or completeness of the contents of this book and specifically disclaim any implied warranties of merchantability or fitness for a particular purpose. No warranty can be created or extended by sales representatives or written sales materials. The Advice and strategies contained herein may not be suitable for your situation. You should consult with a professional where appropriate. Neither the publisher nor authors shall be liable for any loss of profit or any other commercial damages, including but not limited to special, incidental, consequential, or other damages.

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

© 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Boschstr. 12, 69469 Weinheim, Germany

Wiley-Blackwell is an imprint of John Wiley & Sons, formed by the merger of Wiley's global Scientific, Technical, and Medical business with Blackwell Publishing.

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.

Composition  Thomson Digital, Noida, India
Printing and Binding  betz-druck GmbH, Darmstadt
Cover Design  Adam-Design, Weinheim

Print ISBN: 978-3-527-33255-7
ePDF ISBN: 978-3-527-67039-0
epub ISBN: 978-3-527-67040-6
mobi ISBN: 978-3-527-67041-3
oBook ISBN: 978-3-527-67038-3

Printed in the Federal Republic of Germany
Printed on acid-free paper
Contents

Foreword IX
Acknowledgment XV
Preface XVII
List of Contributors XIX

Part One Disease Burden, Current Treatments, Medical Needs, and Strategic Approaches 1

1 Visceral Leishmaniasis – Current Treatments and Needs 3
Poonam Salotra, Ruchi Singh, and Karin Seifert

2 Chemotherapy of Leishmaniasis: A Veterinary Perspective 17
Maria Jesús Corral-Caridad and José María Alunda

3 Pharmacological Metabolomics in Trypanosomes 37
Darren J. Creek, Isabel M. Vincent, and Michael P. Barrett

4 Drug Design and Screening by In Silico Approaches 57
Mattia Mori and Maurizio Botta

5 Computational Approaches and Collaborative Drug Discovery for Trypanosomal Diseases 81
Sean Ekins and Barry A. Bunin

Part Two Metabolic Peculiarities in the Trypanosomatid Family Guiding Drug Discovery 103

6 Interaction of Leishmania Parasites with Host Cells and its Functional Consequences 105
Uta Schurigt, Anita Masic, and Heidrun Moll
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Function of Glycosomes in the Metabolism of Trypanosomatid Parasites</td>
<td>7</td>
</tr>
<tr>
<td>and the Promise of Glycosomal Proteins as Drug Targets</td>
<td></td>
</tr>
<tr>
<td>Melisa Gualdrón-López, Paul A.M. Michels*, Wilfredo Quiñones, Ana J.</td>
<td></td>
</tr>
<tr>
<td>Cáceres, Luisana Avilán, and Juan-Luis Concepción</td>
<td></td>
</tr>
<tr>
<td>Glyoxalase Enzymes in Trypanosomatids</td>
<td>8</td>
</tr>
<tr>
<td>Marta Sousa Silva, António E.N. Ferreira, Ricardo Gomes, Ana M. Tomás,</td>
<td></td>
</tr>
<tr>
<td>Ana Ponces Freire, and Carlos Cordeiro*</td>
<td></td>
</tr>
<tr>
<td>Trypanothione-Based Redox Metabolism of Trypanosomatids</td>
<td>9</td>
</tr>
<tr>
<td>Marcelo A. Comini* and Leopold Flohé</td>
<td></td>
</tr>
<tr>
<td>Thiol Peroxidases of Trypanosomatids</td>
<td>10</td>
</tr>
<tr>
<td>Helena Castro* and Ana M. Tomás</td>
<td></td>
</tr>
<tr>
<td>Peroxynitrite as a Cytotoxic Effector Against Trypanosoma cruzi:</td>
<td>11</td>
</tr>
<tr>
<td>Oxidative Killing and Antioxidant Resistance Mechanisms</td>
<td></td>
</tr>
<tr>
<td>Madia Trujillo, Maria Noel Alvarez, Lucía Piacenza, Martín Hugo,</td>
<td></td>
</tr>
<tr>
<td>Gonzalo Peluffo, and Rafael Radi*</td>
<td></td>
</tr>
<tr>
<td>Selenoproteome of Kinetoplastids</td>
<td>12</td>
</tr>
<tr>
<td>Alexei V. Lobanov and Vadim N. Gladyshev*</td>
<td></td>
</tr>
<tr>
<td>Replication Machinery of Kinetoplast DNA</td>
<td>13</td>
</tr>
<tr>
<td>Rachel Bezalel-Buch, Nurit Yaffe, and Joseph Shlomai*</td>
<td></td>
</tr>
<tr>
<td>Life and Death of Trypanosoma brucei: New Perspectives for Drug</td>
<td>14</td>
</tr>
<tr>
<td>Development</td>
<td></td>
</tr>
<tr>
<td>Torsten Barth, Jasmin Stein, Stefan Mogk, Caroline Schönfeld, Bruno K.</td>
<td></td>
</tr>
<tr>
<td>Kubata, and Michael Duszenko*</td>
<td></td>
</tr>
<tr>
<td>Part Three Validation and Selection of Drug Targets in Kinetoplasts</td>
<td>15</td>
</tr>
<tr>
<td>Rational Selection of Anti-Microbial Drug Targets: Unique or Conserved?</td>
<td>16</td>
</tr>
<tr>
<td>Boris Rodenko and Harry P. de Koning*</td>
<td></td>
</tr>
<tr>
<td>Drug Targets in Trypanosomal and Leishmanial Pentose Phosphate Pathway</td>
<td></td>
</tr>
<tr>
<td>Marcelo A. Comini*, Cecilia Ortíz, and Juan José Cazzulo</td>
<td></td>
</tr>
<tr>
<td>GDP-Mannose: A Key Point for Target Identification and Drug Design</td>
<td>17</td>
</tr>
<tr>
<td>in Kinetoplastids</td>
<td></td>
</tr>
<tr>
<td>Sébastien Pomel* and Philippe M. Loiseau</td>
<td></td>
</tr>
<tr>
<td>Page</td>
<td>Title</td>
</tr>
<tr>
<td>------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>18</td>
<td>Transporters in Anti-Parasitic Drug Development and Resistance</td>
</tr>
<tr>
<td>19</td>
<td>Peptidases in Autophagy are Therapeutic Targets for Leishmaniasis</td>
</tr>
<tr>
<td>20</td>
<td>Proteases of Trypanosoma brucei</td>
</tr>
<tr>
<td></td>
<td><strong>Part Four</strong> Examples of Target-Based Approaches and Compounds Under</td>
</tr>
<tr>
<td>21</td>
<td>Consideration</td>
</tr>
<tr>
<td>22</td>
<td>Screening Approaches Towards Trypanothione Reductase</td>
</tr>
<tr>
<td>23</td>
<td>Redox-Active Agents in Reactions Involving the Trypanothione/Trypanothione</td>
</tr>
<tr>
<td>24</td>
<td>Inhibition of Trypanothione Synthetase as a Therapeutic Concept</td>
</tr>
<tr>
<td>25</td>
<td>Targeting the Trypanosomatidic Enzymes Pteridine Reductase and Dihydrofolate Reductase</td>
</tr>
<tr>
<td>26</td>
<td>Contribution to New Therapies for Chagas Disease</td>
</tr>
<tr>
<td>27</td>
<td>Ergosterol Biosynthesis for the Specific Treatment of Chagas Disease:</td>
</tr>
<tr>
<td></td>
<td>From Basic Science to Clinical Trials</td>
</tr>
<tr>
<td></td>
<td>New Developments in the Treatment of Late-Stage Human African</td>
</tr>
<tr>
<td></td>
<td>Trypanosomiasis</td>
</tr>
<tr>
<td></td>
<td><strong>Index</strong></td>
</tr>
</tbody>
</table>

531
Foreword
Drug Discovery for Neglected Diseases – Past and Present and Future

The kinetoplastid diseases – sleeping sickness, the leishmaniases, and Chagas disease – are “neglected diseases of poverty,” afflicting millions of people and collectively responsible for over 100,000 deaths per annum. No vaccines are available and current insect vector control methods and other public health measures are insufficient to eliminate them. The currently available drug therapies are far from satisfactory due to issues such as poor efficacy, toxicity, the need for hospitalization, the requirement for prolonged parenteral treatment, and high cost. This book is a timely attempt to address some of these unmet medical needs.

It is somewhat ironic that, at the beginning of the twentieth century, many of the ground-breaking developments in drug discovery were driven by economic and colonial expansion in Africa and Asia. The African trypanosome in particular was an early model for experimental chemotherapy along two main lines of investigation: synthetic dyes, and organic arsenicals and antimonials (for further details, see reviews by Williamson [1] and Steverding [2]). Indeed, the first synthetic compound to cure an infectious disease in an animal model was the dye, Trypan red (Ehrlich, 1904), which was a forerunner of suramin (1916–1920), the first effective trypanocidal drug for human African trypanosomiasis (HAT). The demonstration by Thomas and Breinl in 1905 of the trypanocidal activity in mice of atoxyl (p-aminophenylarsonic acid) formed the basis of Ehrlich’s pioneering work on organic arsenicals that culminated in the development of arsphenamine (606, Salvarsan) for the treatment of syphilis (Ehrlich and Hata, 1910) and tryparsamide for the treatment of HAT (Jacobs and Heidelberger, 1919). Tryparsamide, which caused blindness in 10–20% of patients, was finally replaced by melarsoprol (Friedheim, 1949). Trivalent antimony, in the form of tartar emetic, was shown to be trypanocidal in mice (Plimmer and Thompson, 1908), but lacked efficacy in humans. However, potassium antimony tartrate was found to have some activity in the treatment of leishmaniasis (Vianna, 1912) and was the forerunner of the pentavalent antimonials drugs, sodium stibogluconate (Pentostam®) and meglumine antimonate (Glucantime®), both introduced in the 1940s. Along with the diamidine, pentamidine (1937), all of these drugs are still in use today.

From the 1950s, subsequent drug treatments have largely been discovered by serendipity through repurposing of existing drugs used for other indications. The nitrofuran, nifurtimox, and the nitroimidazole, benznidazole, used for the
treatment of Chagas disease arose from research into nitro-compounds as antibacterial agents. Amphotericin B, isolated in 1953, was originally developed for the treatment of systemic mycoses, but later found use in the treatment of visceral leishmaniasis in the 1990s as the expensive, but highly efficacious liposomal formulation (AmBisome®) or as the cheaper, but more toxic amphotericin B deoxycholate. Both formulations were included in the World Health Organization’s Essential Medicines List in 2009. The off-patent aminoglycoside, paromomycin, originally developed as an oral treatment for intestinal infections in the 1960s, finally gained approval as paromomycin intramuscular injection for the treatment of visceral leishmaniasis in India in 2006. Two anticancer agents, the phospholipid analog, miltefosine, registered as the first oral treatment for visceral leishmaniasis in India in 2002, and efloarthine (now in combination with oral nifurtimox as nifurtimox-efloarthine combination therapy (NECT), 2009) for the treatment of HAT caused by *Trypanosoma brucei gambiense* complete the woefully inadequate treatment options for these diseases. Notably, none of these newer developments have completely displaced their forerunners that were developed prior to the 1950s.

After nearly a century of research, only 10 novel chemical entities for three diseases is a singularly unimpressive output by the pharmaceutical industry. The reason for this lamentable performance is not hard to find. Poor economic return on investment by pharma is a major factor, since these are diseases of poverty. The thalidomide disaster of the late 1950s kick-started regulatory demands for greater patient safety resulting in ever-increasing development costs. Blockbuster drugs were “in;” smaller, less profitable markets were “out.” Ninety percent of research and development was aimed at 10% of the world’s unmet medical need – the so-called “10–90 gap.” The drive for greater efficiency and profitability through mergers and acquisitions resulted in the loss of parasitology expertise in most pharma companies. Medicinal chemists were seduced by combinatorial chemistry without due regard for chemical space and drug-likeness. Miniaturization of chemical synthesis restricted the use of animal disease models and shifted emphasis towards target screening. Intellectual property rights were increasingly used as an obstructive, rather than an enabling tool.

At the end of the twentieth century, the situation had become so dire that a radical new approach was required. One of the most encouraging developments was the founding of “public–private partnerships” (PPPs), such as the Drugs for Neglected Diseases initiative (DNDi) and Medicines for Malaria Venture (MMV) – non-profit organizations who strive to forge drug discovery partnerships between multiple academic, biotech, and pharma partners with funding from the governmental and charitable sector [3]. PPPs were initially met with much skepticism, but by 2005, an analysis by Mary Moran and colleagues concluded that PPPs were responsible for three-quarters of an expanded research and development portfolio for neglected diseases [4]. Another important development was the publication of annotated genomes for *T. brucei*, *L. major*, and *T. cruzi* in 2005 [5–7]. As Barry Bloom optimistically prophesized 10 years earlier “Sequencing bacterial and parasitic pathogens . . . could buy the sequence of every virulence determinant, every protein antigen and every drug target . . . for all time” [8]. Certainly, pathogen
genomes are proving to be a valuable resource for target discovery, but without a deeper understanding of parasite biology the full potential of these genomes will not be realized. About the same time as genome sequencing was getting underway, C.C. Wang threw down the gauntlet that academics needed genetic evidence of essentiality to justify their claims of the therapeutic potential of their research field [9]. This dogma has now been refined and extended to include chemical evidence of druggability, driven by a defined therapeutic product profile [10]. These challenges have encouraged some academics to move out of their traditional comfort zones to fill the early-stage drug discovery gap in translational medicine not adequately covered by the PPPs [11]. The concept of “one gene, one target, one drug” has been very much at the forefront of current academic (and industry) thinking, with structure-based design an important adjunct in this strategy. Thus, it is timely that much of this book is devoted to the identification of metabolic peculiarities in the kinetoplastids that can be chemically and genetically validated as drug targets.

However, what of the future? Experience in industry and in academia suggests that the rate of validation of new targets is failing to keep pace with the rate of attrition of currently validated targets. Despite initial promise, the target-based approach has yielded disappointing results in anti-bacterial discovery in pharma [12] and lessons need to be learned from this if we are to avoid making the same mistakes. Rapid and robust methods of genetic target validation are still needed for parasites causing visceral leishmaniasis and Chagas disease, and we need a better understanding of basic biology to understand why targets fail. Certainly, not all targets are equal from a medicinal chemistry point of view. Greater attention needs to be paid to drug likeness [13] and ligand efficiency [14] for lead selection. Screening of fragment libraries using biophysical methods should help to weed out “undruggable” targets without recourse to expensive high-throughput screens [15]. From a pharmacology perspective, cytoidal activity is much preferable to cytostatic, so biologists should address this question early in discovery. Likewise, the potential ease for resistance arising as a result of point mutations in a single-target strategy should be a research priority for biologists. Systems biology suggests that exquisitely selective, single-target compounds may exhibit lower than desired clinical efficacy compared with multitarget drugs due to the robustness of biological networks [16]. Thus, polypharmacology (network pharmacology) is undergoing a resurgence of interest. Given the paucity of validated druggable targets, phenotypic screening is undergoing a revival aided by access to large compound collections held by pharma and the development of suitable miniaturized whole-parasite screens and mammalian counter-screens. This approach has the advantage of addressing the key druggability issues of cell permeability, desirable cytoidal activity, and a suitable parasite–host selectivity window. Phenotypic screening can also identify compounds hitting non-protein targets (e.g., amphotericin B) or compounds that act as prodrugs (e.g., nitroimidazoles). However, the future challenge will be to identify the often complex mode(s) of action of such phenotypic hits (target deconvolution), and to use modern technologies to improve the potency and selectivity of these molecules [17]. Finally, we should ask ourselves whether our compound collections are too “clean” in terms of chemical reactivity. After all, arsenicals, antimonials,
nitro-drugs, and efornithine all undergo reaction with one or more targets, and about one-quarter of all drugs that inhibit enzymes are essentially irreversible reactions [18].

I believe that there is every cause for optimism in the battle against neglected diseases. As long as “donor fatigue” does not set in, and industry continues to engage in a positive and productive manner with academia, future prospects look better than at any time in history. However, we should all remember the dictum by Sir James Black “to first purge your project of wishful thinking” if we are to succeed!

Dundee, UK

Alan Fairlamb

References


Acknowledgment

This publication is supported by COST.

COST – the acronym for European Cooperation in Science and Technology – is the oldest and widest European intergovernmental network for cooperation in research. Established by the Ministerial Conference in November 1971, COST is presently used by the scientific communities of 36 European countries to cooperate in common research projects supported by national funds.

The funds provided by COST – less than 1% of the total value of the projects – support the COST cooperation networks (COST Actions) through which, with EUR 30 million per year, more than 30 000 European scientists are involved in research having a total value which exceeds EUR 2 billion per year. This is the financial worth of the European added value which COST achieves.

A “bottom-up approach” (the initiative of launching a COST Action comes from the European scientists themselves), “à la carte participation” (only countries interested in the Action participate), “equality of access” (participation is open also to the scientific communities of countries not belonging to the European Union), and “flexible structure” (easy implementation and light management of the research initiatives) are the main characteristics of COST.

As precursor of advanced multidisciplinary research COST has a very important role for the realization of the European Research Area (ERA) anticipating and complementing the activities of the Framework Programmes, constituting a “bridge” towards the scientific communities of emerging countries, increasing the mobility of researchers across Europe, and fostering the establishment of “Networks of Excellence” in many key scientific domains such as: Biomedicine and Molecular Biosciences; Food and Agriculture; Forests, their Products and Services; Materials, Physical, and Nanosciences; Chemistry and Molecular Sciences and Technologies; Earth System Science and Environmental Management; Information and Communication Technologies; Transport and Urban Development; Individuals, Societies, Cultures, and Health. It covers basic and more applied research and also addresses issues of a prenormative nature or of societal importance.

Web: http://www.cost.eu
Legal Notice by COST Office

Neither the COST Office nor any person acting on its behalf is responsible for the use which might be made of the information contained in this publication. The COST Office is not responsible for the external websites referred to in this publication.
Infections caused by parasites of the trypanosomatid family are considered to belong to the most neglected diseases. They comprise the African sleeping sickness (Trypanosoma brucei rhodesiense, T. brucei gambiense), the Chagas’ disease in Latin America (T. cruzi), the black fever or Kala-Azar (Leishmania donovani) and other forms of Leishmaniasis (various Leishmania species). They affect about 30 million of people and account for half a million of fatalities per year. Trypanosomatids also cause substantial economic losses by affecting livestock (T. brucei brucei, T. congolense, T. evansi). Available treatments of the diseases are unsatisfactory in terms of safety and efficacy. Industrial commitments to meet the therapeutic needs remain limited because of unfavourable economic perspectives for drugs acting on diseases that prevail in countries with poor socio-economic conditions. In fact, currently used drugs are overwhelmingly those developed many decades ago when the ‘Western World’ had still to be concerned about the health of administrators and soldiers in their tropical colonies.

The present book originates from an interdisciplinary network of academic and industrial researchers devoted to the development of “new drugs for neglected diseases”. The initiative was sponsored by the European Union (COST Action CM0801) and in the beginnings was largely restricted to Europe. Over the four years of its operation, however, the exchange of experience and cooperative projects expanded far beyond its geographical basis, particularly by integrating countries in Latin America, Africa and Asia where the diseases are endemic. The progress achieved by this network is reflected in many of the contributions to the book. The editors, however, took care not just to present a ‘progress report’ but the state-of-the-art in the entire field of drug discovery for trypanosomatid diseases, as reviewed by leading scientists from all over the world. It is hoped that the compiled knowledge will become instrumental to shorten the time from basic discoveries to the urgently needed new drugs for the neglected diseases.

The editor’s heartfelt thanks go to the contributing authors for their excellent work, to the series editor Paul M. Selzer for his constructive advice, and to the COST Office in Brussels for financial support.

Braunschweig, Ingelheim, Potsdam, Germany
March 2013

Timo Jäger
Oliver Koch
Leopold Flohé
List of Contributors

José María Alunda*
Universidad Complutense
Department of Animal Health
Faculty of Veterinary Medicine
Avenida Puerta de Hierro s/n
28040 Madrid
Spain
jmalunda@ucm.es

María Noel Alvarez
Departamento de Bioquímica and
Center for Free Radical and Biomedical Research
Facultad de Medicina
Universidad de la República
Avenida General Flores 2125
11800 Montevideo
Uruguay

Luisana Avilán
Universidad de los Andes
Laboratorio de Fisiología
Facultad de Ciencias
La Hechicera
Av. Alberto Carnevali
Mérida 5101
Venezuela

Cyrus J. Bacchi
Pace University
The Haskins Laboratories
41 Park Row
New York, NY 10038
USA

Michael P. Barrett*
University of Glasgow
Wellcome Trust Centre for Molecular Parasitology
Institute of Infection, Immunity and Inflammation
College of Medical, Veterinary and Life Sciences
120 University Place
Glasgow G12 8TA
UK
michael.barrett@glasgow.ac.uk

Torsten Barth
Eberhard Karls Universität Tübingen
Interfakultäres Institut für Biochemie
Hoppe-Seyler-Strasse 4
72076 Tübingen
Germany
torsten.barth@uni-tuebingen.de

Mathias Beig
MSD Animal Health Innovation GmbH
Zur Propstei
55270 Schwabenheim
Germany

*Corresponding Author
Rachel Bezalel-Buch  
The Hebrew University-Hadassah Medical School  
Department of Microbiology and Molecular Genetics  
Kuvin Center for the Study of Infectious and Tropical Diseases  
Institute for Medical Research  
Israel–Canada  
PO Box 12272  
Jerusalem 91120  
Israel

Maurizio Botta*  
University of Siena  
Faculty of Pharmacy  
Via Aldo Moro 2  
53100 Siena  
Italy  
botta.maurizio@gmail.com

Barry A. Bunin  
Collaborative Drug Discovery, Inc.  
1633 Bayshore Highway Suite 342  
Burlingame, CA 94010  
USA

Ana J. Cáceres  
Universidad de los Andes  
Laboratorio de Enzimología de Parásitos  
Facultad de Ciencias  
Av. Alberto Carnevalli  
Mérida 5101  
Venezuela

Helena Castro*  
Universidade do Porto  
Instituto deBiologia Molecular e Celular  
Rua do Campo Alegre 823  
4150-180 Porto  
Portugal  
hcastro@ibmc.up.pt

Juan José Cazzulo  
Universidad Nacional General San Martín/CONICET  
Instituto de Investigaciones Biotecnológicas (IIB/INTECH)  
Campus Miguelete  
Avenida 25 de Mayo y Francia  
1650 San Martín  
Buenos Aires  
Argentina  
jcazzulo@iibintech.com.ar

Marcelo A. Comini*  
Institut Pasteur de Montevideo  
Group Redox Biology of Trypanosomes  
Mataojo 2020  
11400 Montevideo  
Uruguay  
mcomini@pasteur.edu.uy

Juan-Luis Concepción  
Universidad de los Andes  
Laboratorio de Enzimología de Parásitos  
Facultad de Ciencias  
La Hechicera  
Av. Alberto Carnevalli  
Mérida 5101  
Venezuela

Carlos Cordeiro*  
Universidade de Lisboa  
Faculdade de Ciências  
Departamento de Química e Bioquímica  
Centro de Química e Bioquímica  
Edifício C8 Campo Grande  
1749-016 Lisboa  
Portugal  
cacordeiro@fc.ul.pt
List of Contributors

María Jesús Corral-Caridad
Universidad Complutense
Department of Animal Health
Faculty of Veterinary Medicine
Avenida Puerta de Hierro s/n
28040 Madrid
Spain
mariajco@ucm.es

Maria Paola Costi
University of Modena and Reggio Emilia
Department of Life Science
Via Campi 183
41125 Modena
Italy
mariapaola.costi@unimore.it

Darren J. Creek
University of Glasgow
Wellcome Trust Centre for Molecular Parasitology
Institute of Infection, Immunity and Inflammation
College of Medical, Veterinary and Life Sciences
120 University Place
Glasgow G12 8TA
UK

Elisabeth Davioud-Charvet
UMR CNRS 7509
European School of Chemistry, Polymers and Materials (ECPM)
Bioorganic and Medicinal Chemistry
25 rue Becquerel
67087 Strasbourg Cedex 2
France
elisabeth.davioud@unistra.fr

Harry P. de Koning
University of Glasgow
Institute of Infection
Immunity and Inflammation
College of Medical
Veterinary and Life Sciences
120 University Place
Glasgow G12 8TA
UK
Harry.de-Koning@glasgow.ac.uk

Vincent Delespaux
Institute of Tropical Medicine
Antwerpen
Department of Biomedical Sciences
Nationalestraat 155
2000 Antwerp
Belgium

Patricia S. Doyle
University of California
San Francisco
Department of Pathology and Sandler Center for Drug Discovery
1700 4th Street 508
San Francisco, CA 94158-2330
USA
patricia.doyle.engel@gmail.com

and

University of Melbourne
Department of Biochemistry and Molecular Biology
Bio21 Molecular Science and Biotechnology Institute
Flemington Road
Parkville
Victoria 3010
Australia
List of Contributors

Michael Duszenko
Eberhard Karls Universität Tübingen
Interfakultäres Institut für Biochemie
Hoppe-Seyler-Strasse 4
72076 Tübingen
Germany
michael.duszenko@uni-tuebingen.de

Sean Ekins
Collaborative Drug Discovery, Inc.
1633 Bayshore Highway Suite 342
Burlingame, CA 94010
USA
sekins@collaborativedrug.com

and

Collaborations in Chemistry
5616 Hilltop Needmore Road
Fuquay Varina, NC 27526
USA

and

University of Maryland
Department of Pharmaceutical Sciences
20 North Pine Street
Baltimore, MD 21201
USA

and

University of Medicine & Dentistry of New Jersey (UMDNJ)
Robert Wood Johnson Medical School
Department of Pharmacology
675 Hoes lane
Piscataway, NJ 08854
USA

Juan C. Engel
University of California
San Francisco
Department of Pathology and Sandler Center for Drug Discovery
1700 4th Street 508
San Francisco, CA 94158-2330
USA
juan.engel@ucsd.edu

Alan Fairlamb
Division of Biological Chemistry & Drug Discovery
College of Life Sciences
University of Dundee
Dundee DD1 5EH
UK
a.h.fairlamb@dundee.ac.uk

Stefania Ferrari
University of Modena and Reggio Emilia
Department of Life Science
Via Campi 183
41125 Modena
Italy

António E.N. Ferreira
Universidade de Lisboa
Faculdade de Ciências
Departamento de Química e Bioquímica
Centro de Química e Bioquímica
Edifício C8 Campo Grande
1749-016 Lisboa
Portugal

Leopold Flohé
Otto-von-Guericke-Universität Magdeburg
Chemisches Institut
Universitätsplatz 2
39106 Magdeburg
Germany
List of Contributors

Thibault Gendron
UMR CNRS 7509
European School of Chemistry, Polymers and Materials (ECPM)
Bioorganic and Medicinal Chemistry
25 rue Becquerel
67087 Strasbourg Cedex 2
France

Vadim N. Gladyshev
Harvard Medical School
Division of Genetics
Department of Medicine
Brigham and Women’s Hospital
75 Francis Street
Boston, MA 02115
USA
vgladyshev@rics.bwh.harvard.edu

Ricardo Gomes
Universidade de Lisboa
Faculdade de Ciências
Departamento de Química e Bioquímica
Centro de Química e Bioquímica
Edifício C8 Campo Grande
1749-016 Lisboa
Portugal

Melisa Gualdrón-López
Université catholique de Louvain
Research Unit for Tropical Diseases
de Duve Institute
Avenue Hippocrate 74
La Héchicera
Av. Alberto Carnevalli
1200 Brussels
Belgium

Martín Hugo
Departamento de Bioquímica and Center for Free Radical and Biomedical Research
Facultad de Medicina
Universidad de la República
Avenida General Flores 2125
11800 Montevideo
Uruguay

Robert T. Jacobs
Scynexis, Inc.
PO Box 12878
Research Triangle Park
NC 27709-2878
USA

Timo Jäger
German Centre for Infection Research (DZIF)
Inhoffenstraße 7
38124 Braunschweig
Germany
timo.jaeger@dzif.de

Oliver Koch
Junior Research Group Leader
“Medicinal Chemistry”
Chemical Biology – Faculty of Chemistry
Technische Universität Dortmund
Otto-Hahn-Straße 6
44227 Dortmund
Oliver.Koch@tu-dortmund.de

R. Luise Krauth-Siegel
Heidelberg University
Biochemistry Center
Im Neuenheimer Feld 328
69120 Heidelberg
Germany
Bruno K. Kubata
Research for Health Africa & Pharma Innovation
AU/NEPAD Agency Regional Office in Nairobi
C/o the AU/Inter African Bureau for Animal Resources
P.O. BOX 13601-00800
Kenya
brunokubata@yahoo.com

Don Antoine Lanfranchi
UMR CNRS 7509
European School of Chemistry, Polymers and Materials (ECPM)
Bioorganic and Medicinal Chemistry
25 rue Becquerel
67087 Strasbourg Cedex 2
France

Alexei V. Lobanov
Harvard Medical School
Division of Genetics
Department of Medicine
Brigham and Women’s Hospital
75 Francis Street
Boston, MA 02115
USA

Philippe M. Loiseau
Université Paris-Sud 11
Faculté de Pharmacie
UMR 8076 CNRS
Chimiothérapie Antiparasitaire
5 rue Jean-Baptiste Clément
92290 Châtenay-Malabry
France

Valeria Losasso
University of Modena and Reggio Emilia
Department of Life Science
Via Campi 183
41125 Modena
Italy

and

Scientific Computing Department,
Science and Technology Facilities Council
Daresbury Laboratory
Keckwick Lane
Warrington WA4 4AD
UK

Anita Masic
University of Würzburg
Institute for Molecular Infection Biology
Josef-Schneider-Strasse 2/D15
97080 Würzburg
Germany

Paul A.M. Michels
Université catholique de Louvain
Research Unit for Tropical Diseases de Duve Institute
Avenue Hippocrate 74
1200 Brussels
Belgium
paul.michels@uclouvain.be

Stefan Mogk
Eberhard Karls Universität Tübingen
Interfakultäres Institut für Biochemie
Hoppe-Seyler-Strasse 4
72076 Tübingen
Germany
labor@virtualmogk.de

Heidrun Moll
University of Würzburg
Institute for Molecular Infection Biology
Josef-Schneider-Strasse 2/D15
97080 Würzburg
Germany
heidrun.moll@uni-wuerzburg.de
Mattia Mori
University of Siena
Faculty of Pharmacy
Via Aldo Moro 2
53100 Siena
Italy

Frank Oellien
MSD Animal Health Innovation GmbH
Zur Propstei
55270 Schwabenheim
Germany

Cecilia Ortiz
Institut Pasteur de Montevideo
Group Redox Biology of Trypanosomes
Mataojo 2020
11400 Montevideo
Uruguay
cortiz@pasteur.edu.uy

Gonzalo Peluffo
Departamento de Bioquímica and Center for Free Radical and Biomedical Research
Facultad de Medicina
Universidad de la República
Avenida General Flores 2125
11800 Montevideo
Uruguay

Lucía Piacenza
Departamento de Bioquímica and Center for Free Radical and Biomedical Research
Facultad de Medicina
Universidad de la República
Avenida General Flores 2125
11800 Montevideo
Uruguay

Sébastien Pomel*
Université Paris-Sud 11
Faculté de Pharmacie
UMR 8076 CNRS
Chimiothérapie Antiparasitaire
5 rue Jean-Baptiste Clément
92290 Châtenay-Malabry
France
sebastien.pomel@u-psud.fr

Ana Ponces Freire
Universidade de Lisboa
Faculdade de Ciências
Departamento de Química e Bioquímica
Centro de Química e Bioquímica
Edificio C8 Campo Grande
1749-016 Lisboa
Portugal

Wilfredo Quinones
Universidad de los Andes
Laboratorio de Enzimología de Parásitos
Facultad de Ciencias
La Hechicera
Av. Alberto Carnevalli
Mérida 5101
Venezuela

Rafael Radi*
Departamento de Bioquímica and Center for Free Radical and Biomedical Research
Facultad de Medicina
Universidad de la República
Avenida General Flores 2125
11800 Montevideo
Uruguay
rradi@fmed.edu.uy
Boris Rodenko
University of Glasgow
Institute of Infection, Immunity and Inflammation
College of Medical, Veterinary and Life Sciences
120 University Place
Glasgow G12 8TA
boris.rodenko@glasgow.ac.uk

and

The Netherlands Cancer Institute
Department of Chemical Biology
Division of Cell Biology
Plesmanlaan 121
1066 CX Amsterdam
The Netherlands

Poonam Salotra
National Institute of Pathology (ICMR)
Safdarjung Hospital Campus
Post Box 4909
New Delhi 110029
India

Puneet Saxena
University of Modena and Reggio Emilia
Department of Life Science
Via Campi 183
41125 Modena
Italy

Caroline Schönfeld
Eberhard Karls Universität Tübingen
Interfakultäres Institut für Biochemie
Hoppe-Seyler-Strasse 4
72076 Tübingen
Germany
caroline.schoenfeld@uni-tuebingen.de

Uta Schurigt
University of Würzburg
Institute for Molecular Infection Biology
Josef-Schneider-Strasse 2/D15
97080 Würzburg
Germany

Karin Seifert
London School of Hygiene & Tropical Medicine
Faculty of Infectious and Tropical Diseases
Keppel Street
London WC1E 7HT
UK
karin.seifert@lshtm.ac.uk

Paul M. Selzer
MSD Animal Health Innovation GmbH
Zur Propstei
55270 Schwabenheim
Germany
paul.selzer@msd.de

and

University of Tübingen
Interfaculty Institute of Biochemistry
Hoppe-Seyler-Strasse 4
72076 Tübingen
Germany

and

University of Glasgow
Institute of Infection, Immunity and Inflammation
120 University Place
Glasgow G12 8TA
UK
List of Contributors

Joseph Shlomai*
The Hebrew University-Hadassah
Medical School
Department of Microbiology and
Molecular Genetics
Kuvin Center for the Study of
Infectious and Tropical Diseases
Institute for Medical Research
Israel–Canada
PO Box 12272
Jerusalem 91120
Israel
josephs@ekdm.huji.ac.il

Ruchi Singh
National Institute of Pathology
(ICMR)
Safdarjung Hospital Campus
Post Box 4909
New Delhi 110029
India

Marta Sousa Silva
Universidade de Lisboa
Faculdade de Ciências
Departamento de Química e
Bioquímica
Centro de Química e Bioquímica
Edifício C8 Campo Grande
1749-016 Lisboa
Portugal

Jasmin Stein
Eberhard Karls Universität Tübingen
Interfakultäres Institut für
Biochemie
Hoppe-Seyler-Strasse 4
72076 Tübingen
Germany
Jasmin_Stein@gmx.de

Dietmar Steverding*
University of East Anglia
BioMedical Research Centre
Norwich Medical School
Norwich Research Park
Norwich NR4 7TJ
UK
dsteverding@hotmail.com

Ana M. Tomás
Universidade do Porto
Instituto de Biologia Molecular e
Celular
Rua do Campo Alegre 823
4150-180 Porto
Portugal

and

Universidade do Porto
Instituto de Ciências Biomédicas
Abel Salazar
Rua de Jorge Viterbo Ferreira 228
4050-313 Porto
Portugal

and

Faculdade de Ciências
Departamento de Química e
Bioquímica
Centro de Química e Bioquímica
Edifício C8 Campo Grande
1749-016 Lisboa
Portugal

Madia Trujillo
Departamento de Bioquímica and
Center for Free Radical and
Biomedical Research
Facultad de Medicina
Universidad de la República
Avenida General Flores 2125
11800 Montevideo
Uruguay
Julio A. Urbina*  
Instituto Venezolano de Investigaciones Científicas  
Centro de Biofísica y Bioquímica  
Apartado 21827  
Caracas 1020A  
Venezuela

and

200 Lakeside Drive No. 503  
Oakland, CA 94612-3503  
United States  
jurbina@mac.com

Isabel M. Vincent  
University of Glasgow  
Wellcome Trust Centre for Molecular Parasitology  
Institute of Infection, Immunity and Inflammation  
College of Medical, Veterinary and Life Sciences  
120 University Place  
Glasgow G12 8TA  
UK

and

Université Laval  
Centre de Recherche en Infectiologie du CHUL  
2705 Boulevard Laurier  
Québec G1V 4G2  
Canada

Roderick A.M. Williams*  
University of Strathclyde  
Strathclyde Institute for Pharmacy and Biological Sciences  
161 Cathedral Street  
Glasgow G4 0RE  
UK  
roderick.williams@strath.ac.uk

and

University of the West of Scotland  
School of Science  
High Street  
Paisley PA1 2BE  
UK  
roderick.williams@uws.ac.uk

Nurit Yaffe  
The Hebrew University-Hadassah Medical School  
Department of Microbiology and Molecular Genetics  
Kuvin Center for the Study of Infectious and Tropical Diseases  
Institute for Medical Research  
Israel–Canada  
PO Box 12272  
Jerusalem 91120  
Israel

Nigel Yarlett*  
Pace University  
The Haskins Laboratories and Chemistry and Physical Sciences  
41 Park Row  
New York, NY 10038  
USA  
nyarlett@pace.edu