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Ectoparasites

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Ectoparasites

Drug Discovery Against Moving Targets

WILEY-VCH

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Cover
Hungry *Ixodes ricinus* females gathered on a small tree seedling questing for a host in front of a molecular cartoon of a ligand gated chloride channel (LGCC). The photo was taken by Jan Erhart in March 2012 in an oak wood in South Bohemia, Czech Rep. Courtesy of Jan Erhart and Petr Kopáček, Institute of Parasitology, BC CAS, Czech Rep. The schematic representation of the CysLGCC sectional view was taken from figure 12.4, chapter 12 by Tina Weber & Paul M. Selzer.

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>.

Print ISBN: 978-3-527-34168-9
ePDF ISBN: 978-3-527-80290-6
ePub ISBN: 978-3-527-80289-0
Mobi ISBN: 978-3-527-80291-3
oBook ISBN: 978-3-527-80288-3

Cover Design Adam Design, Weinheim, Germany
Typesetting SPi Global Private Limited, Chennai, India
Printing and Binding

Printed on acid-free paper

10 9 8 7 6 5 4 3 2 1

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Foreword

The attempts of humans to control the influence of ectoparasites on the health of themselves and their associated animals have been documented throughout recorded time. Within the past 100 years, we have witnessed major gains for ectoparasite control with the use of synthetic insecticides; but through time, we have found that these gains are episodic, primarily because of environmental issues and selection of drug resistance in arthropod populations. Therefore, the constant discovery of novel and safe drugs for ectoparasite control is a modern need. Volume 8 of the series *Drug Discovery in Infectious Diseases* provides a valuable snapshot of the timeline in the battle to control ectoparasites. The contributing authors have provided current perspectives on control of ectoparasites and transmission of agents of disease, strategies for discovery and development of drugs, and the development and potential uses of isoxazolines.

Ectoparasites have impacts on human and animal health by both direct and indirect mechanisms, and the reduction of these different impacts can be achieved by approaches that are not dependent on pesticides. The control program for the New World screwworm using the area-wide release of sterile males has been highly effective in controlling the direct impact of obligatory myiasis in North and Central America. Area-wide programs to control the indirect effects of ectoparasites, such as using vaccines for protection against agents of vector-borne diseases like yellow fever, and controlling onchocerciasis by targeting the microfilarial populations of humans also have been effective. However, the success of these programs is based on very specific parameters that lead to narrow applications, which leaves the need for broader spectrum control methods as a top priority.

The need for drug discovery for use in the control of ectoparasites of humans and animals will continue to be a major factor in the preservation of human and animal health. The One Health approach considers the facts that these entities cannot be separated and will only become more important due to global changes in the environment, as well as human population growth and movement. The majority of vector-borne human diseases have zoonotic cycles which can be affected by the effective use of ectoparasite control. Even for anthroponoses such as malaria and visceral leishmaniasis, zoonotic blood sources maintain many species of potential vectors of pathogens that are drivers of major causes of death in

humans. Ectoparasites do truly represent a moving target for control efforts relative to population density and susceptibility. The timely and rational use of extant and novel drugs against these moving targets and upon a changing global stage can provide leverage for humans in our race against ectoparasites, as long as the discovery and development of new and effective drugs can maintain the pace.

April 2018

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Preface

Infestation by ectoparasites has plagued humans, figuratively and literally, since ancient times; for example, lice are listed among the Biblical plagues visited upon Egypt (*Exodus 8:17, KJV*) and fleas transmitting bubonic plague have had devastating impacts on numerous civilizations over the centuries. Strategies for battling ectoparasites have an equally deep history, as evidenced by mummified lice found in ancient Egyptian combs and by perforated necklace beads that doubled as personal flea traps in medieval Europe. Although human ectoparasite infestations are less prevalent in modern developed countries due to dramatically improved living and hygiene conditions, infestation on domesticated animals remains a major challenge, causing nuisance in companion animals and livestock as well as lowering livestock productivity. Ectoparasites can move between animals and from animals to humans, potentially transmitting various diseases in the process. Ectoparasite control strategies must therefore contend with the ability of the target to move, often quite quickly, as anyone who has ever wanted to kill a flea can attest. This eighth volume in the Drug Discovery for Infectious Diseases series reviews strategies and models for discovery and development of ectoparasiticidal treatments for use in both human and animal health. The challenges presented by moving targets are a common theme throughout, ranging from the market requirement for a rapid speed of kill to the design of effective containment strategies in whole-organism drug screening assays.

The first section of the volume, Strategies & Resistance, presents various perspectives on what is needed to achieve effective therapeutic control of ectoparasite infestations. The section begins with a comparison by Woods *et al.* of therapeutic strategies against moving target ectoparasites with those against the less-mobile endoparasites. Weber *et al.* review strategies for preventing disease transmission by ectoparasite vectors, for which speed of kill is an important consideration. Schetters reviews promising progress toward development of vaccines against ticks. The emergence of drug resistance threatens the utility of ectoparasiticides, especially for cattle tick and human head lice. Sager *et al.* and Lovis *et al.* discuss the threat, reality, and monitoring of drug resistance in cattle tick, particularly relevant for Southern Hemisphere markets such as Brazil and Australia. Clark reviews new developments in the control of human lice.

The second section focuses on laboratory screens and *in vivo* models for discovery of new treatments against ectoparasites. Compared to human diseases,

the molecular targets of parasites, especially ectoparasites, are much less clear, and few can be utilized for screening. The chapter by Kopáček considers the challenges in identifying candidate small-molecule drug targets in ticks. Currently, discovery of new treatments against ectoparasites relies heavily on phenotypic-based screening against whole organisms such as fleas and ticks. Chapters by Clark and Pearce and by Nijhof and Tyson discuss the design and implementation of various whole-organism assays to detect different aspects of the desired treatments, for example, the flea ingestion assay to detect the ability of a compound to work through ingestion rather than through contact. Compared to drug discovery for humans, a major advantage of drug discovery for animal health is that a new investigative drug can be tested in the target host much sooner in the latter. This might seem to make testing in rodent models less critical. However, testing in rodent models remains an important step in drug discovery for animal health, because these models require much less quantity of a compound and save valuable animals of the target species, as discussed in depth by Weber *et al*. Of course, testing in the target host species is an essential aspect of late-stage development of a new drug for animal health, and in the concluding chapter of this section Clark reviews protocols for controlled laboratory testing in host species and provides numerous examples of how these testing strategies have been applied in successful ectoparasiticide development programs.

Drugs effective against ectoparasites comprise only a few chemical classes, the pyrethroids, the phenylpyrazoles, and the macrocyclic lactones being the major ones. On average a new class appears about every 20 years. The isoxazolines are the most recent addition to the roster. The last section of this volume is devoted exclusively to this fascinating new class of ectoparasiticides, which has attracted tremendous interest in the animal health and crop protection industries. Weber and Selzer first discuss the new mode of action that underlies the rapid speed of kill by the isoxazolines. Chapters by Lahm *et al*. and by Letendre *et al*. detail the complete drug discovery and development process for afoxolaner, the first commercial product launched from this class. The development of sarolaner, reviewed by Woods and McTier, gives another story from a different setting. The final chapter by Long presents a comprehensive overview of the entire isoxazoline chemical class to date.

We thank Dr. Paul M. Selzer, the series editor, and the various representatives of Wiley for the opportunity to shepherd this volume, and for their guidance and support. We also thank the authors who have generously contributed their time and expertise. The combined result of their efforts is a volume designed to be of both interest and utility to those scientists in academia and industry willing to undertake the discovery of drugs aimed at moving targets.

April 2018

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