

Edited by David A. Phoenix,
Frederick Harris, and Sarah R. Dennison

Novel Antimicrobial Agents and Strategies

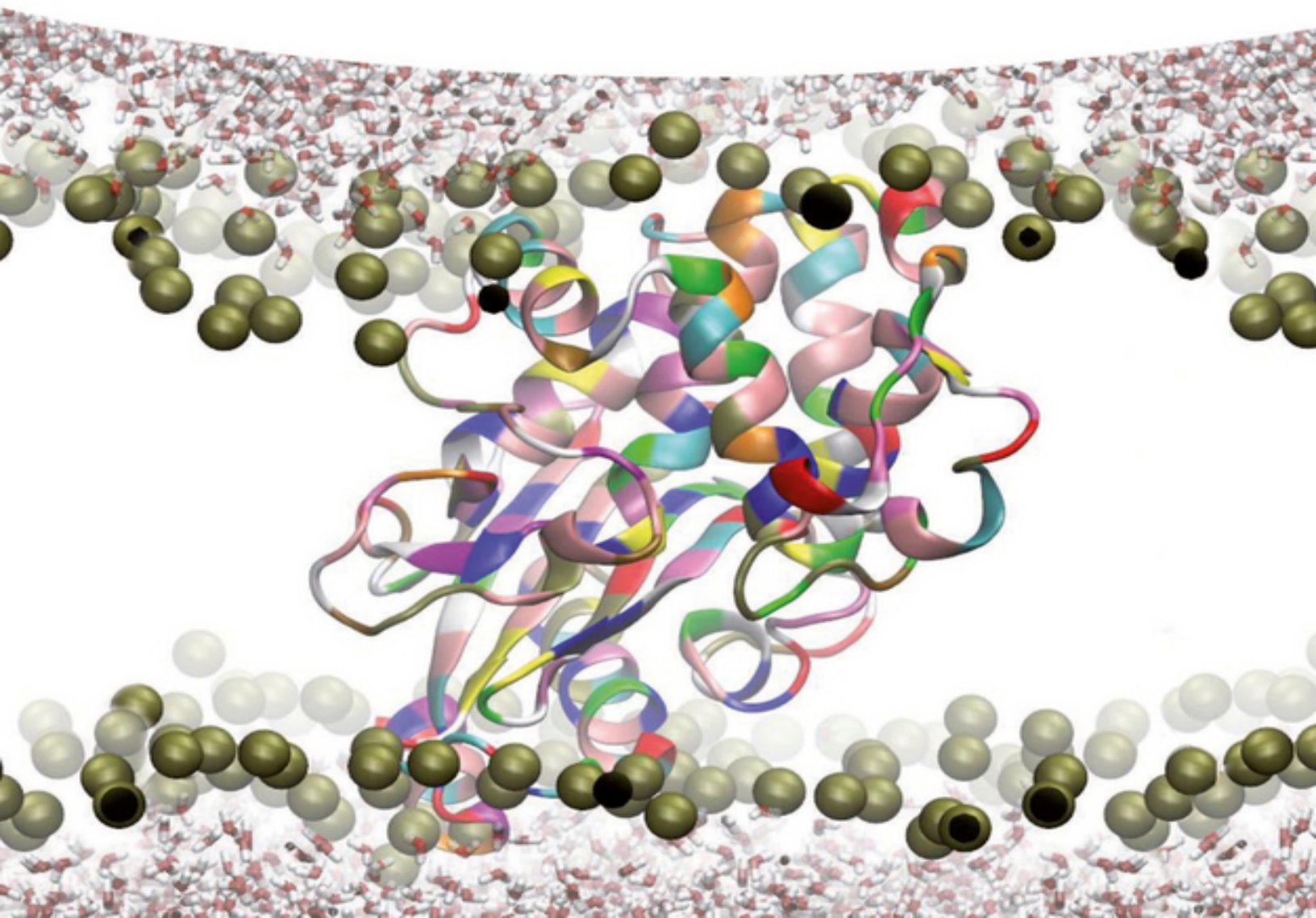


Table of Contents

[Cover](#)

[Related Titles](#)

[Title Page](#)

[Copyright](#)

[List of Contributors](#)

[Preface](#)

[Reference](#)

[Chapter 1: The Problem of Microbial Drug Resistance](#)

[1.1 Introduction](#)

[1.2 History of the Origins, Development, and Use of Conventional Antibiotics](#)

[1.3 Problems of Antibiotic Resistance](#)

[1.4 Multiple Drug-Resistant \(MDR\), Extensively Drug-Resistant \(XDR\), and Pan-Drug-Resistant \(PDR\) Organisms](#)

[1.5 MDR Mechanisms of Major Pathogens](#)

[1.6 Antimicrobial Stewardship Programs](#)

[1.7 Discussion](#)

[Acknowledgment](#)

[References](#)

[Chapter 2: Conventional Antibiotics - Revitalized by New Agents](#)

[2.1 Introduction](#)

[2.2 Conventional Antibiotics](#)

[2.3 The Principles of Combination Antibiotic Therapy](#)

[2.4 Antibiotic Resistance Breakers: Revitalize Conventional Antibiotics](#)

[2.5 Discussion](#)

[Acknowledgments](#)

[References](#)

[Chapter 3: Developing Novel Bacterial Targets: Carbonic Anhydrases as Antibacterial Drug Targets](#)

[3.1 Introduction](#)

[3.2 Carbonic Anhydrases](#)

[3.3 CA Inhibitors](#)

[3.4 Classes of CAs Present in Bacteria](#)

[3.5 Pathogenic Bacterial CAs](#)

[3.6 \$\alpha\$ -CAs in Pathogenic Bacteria](#)

[3.7 \$\beta\$ -CAs in Pathogenic Bacteria](#)

[3.8 \$\gamma\$ -CAs from Pathogenic Bacteria](#)

[3.9 Conclusions](#)

[References](#)

[Chapter 4: Magainins – A Model for Development of Eukaryotic Antimicrobial Peptides \(AMPs\)](#)

[4.1 Introduction](#)

[4.2 Magainins and Their Antimicrobial Action](#)

[4.3 Magainins as Antibiotics](#)

[4.4 Other Antimicrobial Uses of Magainins](#)

[4.5 Future Prospects for Magainins](#)

[References](#)

[Chapter 5: Antimicrobial Peptides from Prokaryotes](#)

[5.1 Introduction](#)

[5.2 Bacteriocins](#)

[5.3 Applications of Prokaryotic AMPs](#)

5.4 Development and Discovery of Novel AMP

References

Chapter 6: Peptidomimetics as Antimicrobial Agents

6.1 Introduction

6.2 Antimicrobial Peptidomimetics

6.3 Discussion

Acknowledgments

References

Chapter 7: Synthetic Biology and Therapies for Infectious Diseases

7.1 Current Challenges in the Treatment of Infectious Diseases

7.2 Introduction to Synthetic Biology

7.3 Vaccinology

7.4 Bacteriophages: A Re-emerging Solution?

7.5 Isolated Phage Parts as Antimicrobials

7.6 Predatory Bacteria and Probiotic Bacterial Therapy

7.7 Natural Products Discovery and Engineering

7.8 Summary

Acknowledgments

References

Chapter 8: Nano-Antimicrobials Based on Metals

8.1 Introduction

8.2 Silver Nano-antimicrobials

8.3 Copper Nano-antimicrobials

8.4 Zinc Oxide Nano-antimicrobials

8.5 Conclusions

References

Chapter 9: Natural Products as Antimicrobial Agents - an Update

9.1 Introduction

9.2 Antimicrobial Natural Products from Plants

9.3 Antimicrobial Natural Products Bearing an Acetylene Function

9.4 Antimicrobial Carbohydrates

9.5 Antimicrobial Natural Chromenes

9.6 Antimicrobial Natural Coumarins

9.7 Antimicrobial Flavonoids

9.8 Antimicrobial Iridoids

9.9 Antimicrobial Lignans

9.10 Antimicrobial Phenolics Other Than Flavonoids and Lignans

9.11 Antimicrobial Polypeptides

9.12 Antimicrobial Polyketides

9.13 Antimicrobial Steroids

9.14 Antimicrobial Terpenoids

9.15 Miscellaneous Antimicrobial Compounds

9.16 Platensimycin Family as Antibacterial Natural Products

References

Chapter 10: Photodynamic Antimicrobial Chemotherapy.

10.1 Introduction

10.2 The Administration and Photoactivation of PS

10.3 Applications of PACT Based on MB

10.4 The Applications of PACT Based on ALA

10.5 Future Prospects

References

Chapter 11: The Antimicrobial Effects of Ultrasound

11.1 Introduction

11.2 The Antimicrobial Activity of Ultrasound Alone

11.3 The Antimicrobial Activity of Assisted Ultrasound

11.4 Future Prospects

References

Chapter 12: Antimicrobial Therapy Based on Antisense Agents

12.1 Introduction

12.2 Antisense Oligonucleotides

12.3 First-Generation ASOs

12.4 Second-Generation ASOs

12.5 Third-Generation ASOs

12.6 Antisense Antibacterials

12.7 Broad-Spectrum Antisense Antibacterials

12.8 Methicillin-Resistant *Staphylococcus aureus* (MRSA)

12.9 RNA Interference (RNAi)

12.10 Progress Using siRNA

12.11 Discussion

References

Chapter 13: New Delivery Systems - Liposomes for Pulmonary Delivery of Antibacterial Drugs

13.1 Introduction

13.2 Pulmonary Drug Delivery

13.3 Liposomes as Drug Carriers in Pulmonary Delivery

13.4 Present and Future Trends of Liposome Research in Pulmonary Drug Delivery

[13.5 Conclusions](#)

[References](#)

[Index](#)

[End User License Agreement](#)

List of Illustrations

[Figure 3.1](#)

[Figure 4.1](#)

[Figure 5.1](#)

[Figure 5.2](#)

[Figure 6.1](#)

[Figure 6.2](#)

[Figure 6.3](#)

[Figure 6.4](#)

[Figure 6.5](#)

[Figure 6.6](#)

[Figure 6.7](#)

[Figure 6.8](#)

[Figure 6.9](#)

[Figure 7.1](#)

[Figure 7.2](#)

[Figure 7.3](#)

[Figure 7.4](#)

[Figure 7.5](#)

[Figure 7.6](#)

[Figure 7.7](#)

[Figure 7.8](#)

[Figure 7.9](#)

[Figure 7.10](#)

[Figure 7.11](#)

[Figure 7.12](#)

[Figure 7.13](#)

[Figure 8.1](#)

[Figure 8.2](#)

[Figure 8.3](#)

[Figure 8.4](#)

[Figure 8.5](#)

[Figure 8.6](#)

[Figure 8.7](#)

[Figure 10.1](#)

[Figure 10.2](#)

[Figure 10.3](#)

[Figure 11.1](#)

[Figure 11.2](#)

[Figure 12.1](#)

[Figure 12.2](#)

[Figure 12.3](#)

[Figure 12.4](#)

[Figure 13.1](#)

[Figure 13.2](#)

[Figure 13.3](#)

[Figure 13.4](#)

[Figure 13.5](#)

[Figure 13.6](#)

[Figure 13.7](#)

[Figure 13.8](#)

[Figure 13.9](#)

[Figure 13.10](#)

List of Tables

[Table 1.1](#)

[Table 1.2](#)

[Table 1.3](#)

[Table 2.1](#)

[Table 3.1](#)

[Table 4.1](#)

[Table 4.2](#)

[Table 4.3](#)

[Table 4.4](#)

[Table 5.1](#)

[Table 8.1](#)

[Table 10.1](#)

[Table 10.2](#)

[Table 10.3](#)

[Table 10.4](#)

[Table 10.5](#)

[Table 11.1](#)

[Table 12.1](#)

[Table 12.2](#)

[Table 12.3](#)

[Table 12.4](#)

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The cover shows beta-lactamase, an enzyme produced by some bacteria, which provide bacterial resistance to beta-lactam antibiotics in the presence of a lipid bilayer. The image was created by Dr. Manuela Mura, University of Central Lancashire, UK.

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Preface

The “Golden age of antibiotics” was between 1929 and the 1970s when over 20 antibiotic classes were marketed [1, 2]. Since the 1960s, the rise in the emergence of microbial pathogens with multiple drug resistance (MDR) has led to the realization that the “Golden age” had ended. The pharmaceutical industry has been constantly battling with MDR because of the overprescription and misuse of antibiotics [3–5]. In Chapter 1, Radecka and coworkers give an insight into bacterial resistance being a major threat to public health. They also discuss the implications arising from the threat posed by MDR pathogens in relation to factors such as medical practice and economics, along with an overview of recent practices and measures proposed to contain this threat, such as the introduction of stewardship programs. Concern regarding our future ability to combat infection has been further intensified by the decreasing supply of new agents [3, 6–8], and in the remainder of the book we review approaches being taken to identify and develop the antimicrobials of the future.

In response to the challenges outlined, in this book there has been increasing research into maximizing opportunities to develop and revitalize established classes of antibiotics. Coates and Hu consider this area in Chapter 2 where they look at opportunities to extend the life of old antibiotics such as β -lactams by the addition of agents that can overcome drug resistance factors, such as β -lactamase inhibitors. Identification of new, effective derivatives remains a challenge, and another approach in the search for new antibiotics has been to seek out new targets that would enable new classes of antibacterials to be developed. In Chapter 4, Capasso and Supuran review the cloning and

characterization of carbonic anhydrases (CAs). In this chapter, they make reference to the impact of inhibitors that target the α -, β -, and γ -CAs from many pathogenic bacteria and suggest that this provides evidence that these proteins could provide novel antibacterial targets for the development of new antimicrobial compounds.

There remain concerns, though, that only a small number of drugs are currently under research and development as antibacterial agents [9]. It has been suggested that a further approach could be to revisit naturally occurring compounds with antibacterial potential. Due to the arrival of antibiotics, there has been a rapid loss of interest in the therapeutic potential of natural host antibiotics such as lysozyme [3, 4]. However, more recently, there has been an awakened interest in host defense molecules, such as antimicrobial peptides (AMPs) [10, 11]. Since the early 1990s, the potential of AMPs has been investigated using, for example, magainins isolated from the African clawed frog *Xenopus laevis*, to investigate the effect of the structural and physiochemical properties of these peptides on their antimicrobial action. These AMPs have the potency to target and kill a wide range of Gram-negative and Gram-positive bacteria, fungi, viruses, and some tumor cells [12]. Based on this ability, AMPs are attractive propositions for development as therapeutically useful antimicrobial and anticancer agents [13]. The first clinical trials of these AMPs as potential novel antibiotics have been for topical treatments [14], and Dennison *et al.* review this area in Chapter 4. AMPs are not only produced by eukaryotes but are also generated by prokaryotes, and Lotfipour and coworkers review this class of peptides, generally known as bacteriocins, in Chapter 5. These prokaryotic peptides are produced by gene-encoded or ribosome-independent pathways [15]. Non-ribosomal prokaryotic AMPs generally include examples such as vancomycin and daptomycin,