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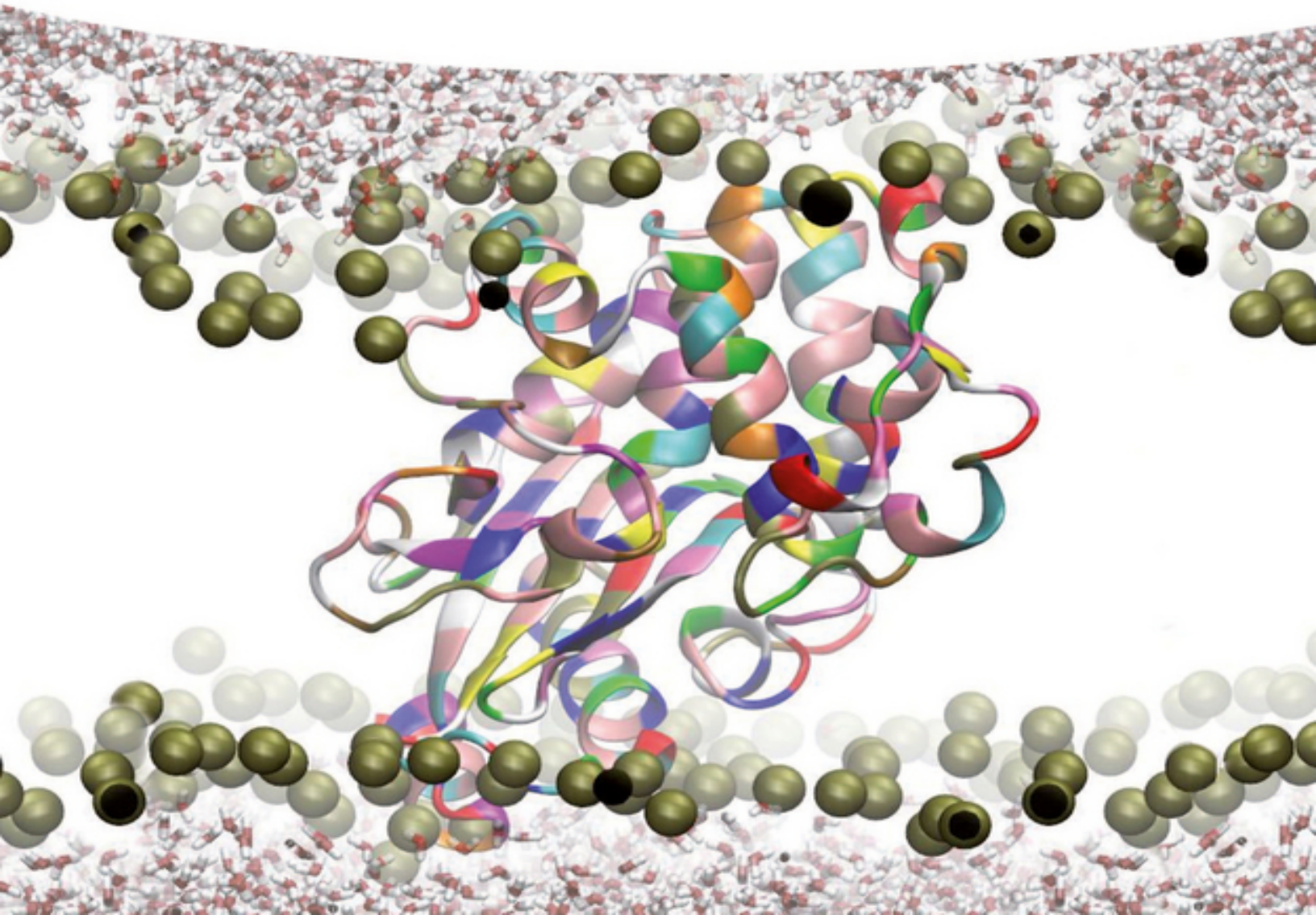
Novel Antimicrobial Agents and Strategies



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The Editors

Prof. David A. Phoenix

London South Bank University

Borough Road 103

London

SE1 0AA

United Kingdom

Dr. Frederick Harris

University of Central Lancashire

Forensic & Investigative Science

Preston, Lancashire

PR1 2HE

United Kingdom

Dr. Sarah R. Dennison

University of Central Lancashire

Pharmacy and Biomedical Science

Preston, Lancashire

PR1 2HE

United Kingdom

Cover design

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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List of Contributors

Waqar Ahmed

University of Central Lancashire

Institute of Nanotechnology and Bioengineering

School of Medicine and Dentistry

Corporation street

Preston

PR1 2HE

UK

Hiroki Ando

Department of Electrical Engineering and Computer Science and Department of Biological Engineering

Massachusetts Institute of Technology

Massachusetts Avenue

Cambridge, MA 02139

USA

and

Massachusetts Institute of Technology

MIT Synthetic Biology Center

Technology Square

Cambridge, MA 02139

USA

Glenda M. Beaman

University of Central Lancashire
School of Forensic and Investigative Sciences
Corporation Street
Preston
PR1 2HE
UK

Jianfeng Cai
University of South Florida
Department of Chemistry
E. Fowler Avenue
Tampa, FL 33620
USA

Clemente Capasso
Istituto di Biochimica delle Proteine-CNR
via Pietro Castellino
- 80131 Napoli
Italy

and

Istituto di Bioscienze e Biorisorse-CNR
via Pietro Castellino
- 80131 Napoli
Italy

Nicola Cioffi
Università degli Studi di Bari Aldo Moro

Dipartimento di Chimica

via Orabona 4

Bari

Italy

Robert Citorik

Department of Electrical Engineering and Computer Science and Department of Biological Engineering

Massachusetts Institute of Technology

Massachusetts Avenue

Cambridge, MA 02139

USA

and

Massachusetts Institute of Technology

MIT Synthetic Biology Center

Technology Square

Cambridge, MA 02139

USA

and

Massachusetts Institute of Technology

MIT Microbiology Program

Massachusetts Avenue

Cambridge, MA 02139

USA

Sara Cleto

Department of Electrical Engineering and Computer Science and Department of Biological Engineering

Massachusetts Institute of Technology

Massachusetts Avenue

Cambridge, MA 02139

USA

and

Massachusetts Institute of Technology

MIT Synthetic Biology Center

Technology Square

Cambridge, MA 02139

USA

Anthony Coates

St George's University of London

Medical Microbiology

Institute of Infection and Immunity

Cranmer Terrace

London

SW17 0RE

UK

Sarah R. Dennison

University of Central Lancashire

Institute of Nanotechnology and Bioengineering

School of Pharmacy and Biomedical Sciences

Corporation Street
Preston
PR1 2HE
UK

Dzung B. Diep
Norwegian University of Life Sciences
Laboratory of Microbial Gene Technology
Department of Chemistry
Biotechnology and Food Science
P.O Box 5003
Å s
Norway

Abdelbary M.A. Elhissi
University of Central Lancashire
Institute of Nanotechnology and Bioengineering
School of Pharmacy and Biomedical Sciences
Corporation street
Preston
PR1 2HE
UK

Frederick Harris
University of Central Lancashire
School of Forensic and Investigative Science
Corporation street

Preston
PR1 2HE
UK

Maryam Hassan
Zanjan University of Medical Sciences
Pharmaceutical Biotechnology Research Center
Zanjan
Iran

David Hill
University of Wolverhampton
School of Biology, Chemistry, and Forensic Science
Faculty of Science and Engineering
Wulfruna Street
Wolverhampton
WV1 1LY
UK

Yanmin Hu
St George's University of London
Medical Microbiology
Institute of Infection and Immunity
Cranmer Terrace
London
SW17 0RE
UK

Morten Kjos

Norwegian University of Life Sciences

Laboratory of Microbial Gene Technology

Department of Chemistry

Biotechnology and Food Science

P.O Box 5003

Å s

Norway

and

University of Groningen

Molecular Genetics Group

Groningen Biomolecular Sciences and Biotechnology Institute

Centre for Synthetic Biology

Nijenborgh 7

AG Groningen

The Netherlands

Sebastien Lemire

Department of Electrical Engineering and Computer Science and Department of Biological Engineering

Massachusetts Institute of Technology

Massachusetts Avenue

Cambridge, MA 02139

USA

and

Massachusetts Institute of Technology

MIT Synthetic Biology Center

Technology Square

Cambridge, MA 02139

USA

Farzaneh Lotfipour

Tabriz University of Medical Sciences

Hematology & Oncology Research Center and Faculty of Pharmacy

Tabriz

51664

Iran

Timothy Lu

Department of Electrical Engineering and Computer Science and Department of Biological Engineering

Massachusetts Institute of Technology

Massachusetts Avenue

Cambridge, MA 02139

USA

and

Massachusetts Institute of Technology

MIT Synthetic Biology Center

Technology Square

Cambridge, MA 02139

USA

and

Massachusetts Institute of Technology

MIT Microbiology Program

Massachusetts Avenue

Cambridge, MA 02139

USA

Claire Martin

University of Wolverhampton

School of Pharmacy

Faculty of Science and Engineering

Wulfruna Street

Wolverhampton

WV1 1LY

UK

Mark Mimee

Department of Electrical Engineering and Computer Science and Department of Biological Engineering

Massachusetts Institute of Technology

Massachusetts Avenue

Cambridge, MA 02139

USA

and

Massachusetts Institute of Technology

MIT Synthetic Biology Center 500 Technology Square

Cambridge, MA 02139
USA

and

Massachusetts Institute of Technology
MIT Microbiology Program
Massachusetts Avenue
Cambridge, MA 02139
USA

Ingolf F. Nes
Norwegian University of Life Sciences
Laboratory of Microbial Gene Technology
Department of Chemistry
Biotechnology and Food Science
P.O Box 5003
Å s
Norway

David A. Phoenix
London South Bank University
Office of the Vice Chancellor
Borough Road
London
SE1 0AA
UK

Rosaria Anna Picca

Università degli Studi di Bari Aldo Moro
Dipartimento di Chimica
via Orabona 4
Bari
Italy

Iza Radecka
University of Wolverhampton
School of Biology
Chemistry and Forensic Science
Faculty of Science and Engineering
Wulfruna Street
Wolverhampton
WV1 1LY
UK

Muhammad Saleem
The Islamia University of Bahawalpur
Department of Chemistry
Baghdad-ul-Jadeed Campus
Bahawalpur, 63100
Pakistan

Maria Chiara Sportelli
Università degli Studi di Bari Aldo Moro
Dipartimento di Chimica
via Orabona 4

Bari

Italy

Claudiu T. Supuran

Università degli Studi di Firenze

Dipartimento di Scienze Farmaceutiche

Via della Lastruccia

3, Polo Scientifico

Sesto Fiorentino (Florence)

Italy

and

Sezione di Scienze Farmaceutiche e Nutraceutiche, Neurofarba Department

Università degli Studi di Firenze

Via Ugo Schiff 6

Sesto Fiorentino (Florence)

Italy

Kevin M.G. Taylor

University College London

Department of Pharmaceutics School of Pharmacy

29-39 Brunswick Square

London

WC1N 1AX

UK

and

Department of Pharmaceutics
UCL School of Pharmacy
29-39 Brunswick Square
London
WC1N 1AX
UK

Peng Teng
University of South Florida
Department of Chemistry
E. Fowler Avenue
Tampa, FL 33620
USA

Haifan Wu
University of South Florida
Department of Chemistry
E. Fowler Avenue
Tampa, FL 33620
USA

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 identity 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,