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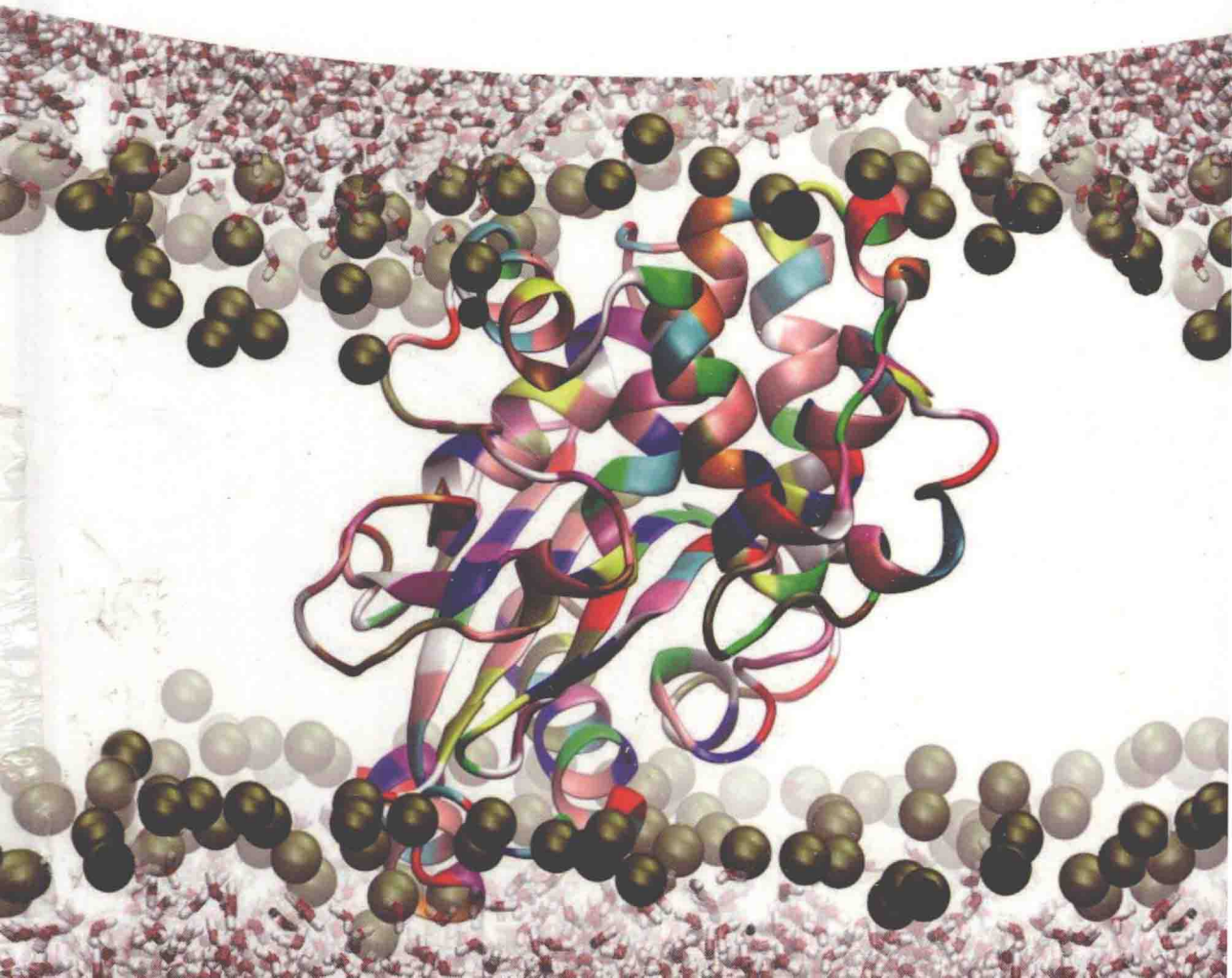
Novel Antimicrobial Agents and Strategies



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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 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 3, 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, which are assembled by large multifunctional enzyme complexes. Gene-encoded AMPs from prokaryotes include microcins from Gram-negative bacteria, lantibiotics, and nonmodified bacteriocins from Gram-positive bacteria. The potential uses of these molecules are reviewed for their potential in food biopreservation and healthcare. However, both eukaryotic and prokaryotic AMPs have a range of challenges to overcome, such as the cost of production and design complexity of these molecules. For this reason, work has been under way to design mimics and peptidomimetics of these peptides, which is reviewed in Chapter 6 by Cai and coworkers. Major examples of these molecules include : peptoids [16], β-peptides [17], arylamide oligomers [18], AApeptides [19, 20], and other compounds [21–25], which may be considered second-generation AMPs. These molecules are designed to possess properties conducive to therapeutic application and retain key structural characteristics of naturally occurring AMPs, such as positive charge, hydrophobicity, and amphiphilicity, which facilitate their membranolytic and antimicrobial activity. Tuning these properties has led to superior levels of microbial selectivity and antimicrobial activity as compared to both natural AMPs and conventional antibiotics. This Chapter considers the recent development of these synthetic mimics of AMPs based on a variety of peptide backbones other than canonical peptides, including β-peptides, peptoids, and AApeptides.

It is interesting to note that, in addition to direct action, AMPs are part of more complex innate immune systems and a further approach to developing treatments for the future has involved review of how aspects of such immune systems could be adapted to support treatment of infections. Prior to the discovery and widespread use of antibiotics, it was believed that bacterial infections could be treated by the administration of bacteriophages, which are viruses that infect and kill bacteria via lytic mechanisms but have no effect on humans. With the advent of penicillins and other antibiotics, clinical studies with bacteriophages were not vigorously pursued in the United States and Western Europe, but phage therapy was extensively used in Eastern European countries mainly in the former Soviet Union and Georgia.

However, with the current rise of antibiotic-resistant bacteria, there has been a revitalization of interest in phage therapy in Western countries. In Chapter 7, Lu and coworkers discuss the use of synthetic biology and whether bacteriophages are a re-emerging solution to the current problem of pathogenic microbes. Bacteriophage therapy has a number of potential advantages over the use of conventional antibiotics, such as high bacterial specificity and efficacy against bacteria with MDR, although there are concerns over its use, such as the possibility of inducing immunological responses. Nonetheless, phage therapy is generally regarded as one of the most promising strategies to provide antimicrobial alternatives for fighting antibiotic-resistant bacteria and could lead to the development of new and improved therapies and diagnostics to combat infectious threats of the present and the future.

In addition to the above approaches, there is a wide range of additional natural compounds that have the potential in the treatment of infection. The antimicrobial properties of metals such as copper and silver have been known for centuries especially in use for the treatment of burns and chronic wounds [26]. Recently, the confluence of nanotechnology and the search for new agents in the fight against microbes with MDR has brought metals in the form of nanoparticles to the fore as potential antimicrobial agents. In Chapter 8, Sportelli and coworkers present several examples of nanomaterials based on three of the main inorganic materials with known antimicrobial action (i.e., silver, copper, and zinc oxide) along with the mechanisms underlying their antimicrobial action. The potential applications of these nanoparticles as antimicrobials in areas such as prophylaxis and therapeutics, medical devices, the food industry, and textile fabrics are discussed in more detail. In addition, there are numerous examples of naturally produced organic compounds with antibacterial properties. In the period 2000–2008, over 300 natural metabolites with antimicrobial activity were reported, and in Chapter 9, Saleem reviews these compounds and describes candidates with potentially useful antimicrobial activity with reference to a variety of molecules, including : alkaloids, acetylenes, coumarins, iridoids, terpenoids, and xanthones.

A range of organic compounds with the potential to serve as anti-infectives are those that are known to sequester within bacterial cells and can be light-activated to induce antimicrobial activity. For example, phenothiazinium-based molecules [27, 28], whose antimicrobial properties were first noted in dyes that were used for the histological staining of cellular components, have been shown to be more efficacious than conventional antibiotics [28, 29]. These dyes photoinactivate bacteria, viruses, yeasts, fungi, and protozoa via the production of reactive oxygen species (ROS) such as such as hydroxyl radicals and hydrogen peroxide. Over the last few decades, photosensitizers (PS) have attracted increasing attention as antimicrobial agents with therapeutic potential, and, when applied in this context, the use of PS is known as *photodynamic antimicrobial chemotherapy* (PACT). Phoenix co-workers provide an overview of the photophysics and photochemistry involved in PACT, and illustrate the therapeutic uses of this action with reference to a variety of PACT agents such as methylene blue and 5-aminolevulinic acid. Whilst this area has clear potential, there are also challenges that need to

be overcome if the use of such compounds is to become more widespread. One such limitation is the challenge of ensuring effective light penetration of tissue and in this respect, it has been suggested that ultrasound could be used as part of a new antimicrobial strategy that addresses this limitation based on its superior capacity for tissue penetration. Ultrasound has been shown to have an antibacterial effect comparable to some conventional antibiotics as recently reported in the case of rhinosinusitis. It has also been shown that the application of ultrasound in conjunction with conventional antibiotics such as gentamycin is able to synergize the effects of these drugs when applied to both planktonic and sessile bacteria. More recently, it has been shown that irradiation with ultrasound can activate some PS, which are generally termed *sonosensitizers* (*SS*) in this capacity, and based on these observations it was hypothesized that ultrasound and SS may be exploited for the treatment of infectious diseases. This system has been designated sonodynamic antimicrobial chemotherapy (SACT) and most recently has been shown to be able to eradicate both Gram-positive and Gram-negative bacteria. In Chapter 11, Harris coworkers provides an overview of the impact of SACT.

In considering approaches to combat growing drug resistance and to identify new means of treatment, the potential of oligonucleotides as antibacterial agents has been investigated. Such molecules are able to act as antisense agents to prevent translation, or, alternatively, can be designed to bind DNA to prevent gene transcription: these approaches are reviewed in Chapter 12 by Beaman coworkers. In this area, a range of new and exciting approaches are being developed. For example, it may be that such agents can inhibit microbial resistance mechanisms by interrupting the expression of resistance genes and hence restore susceptibility to key antibiotics, which would be co-administered with the antisense compound. Such an approach will clearly have significant applications.

Finally, it is worth considering whether antibiotic efficacy can be increased by enhancing the targeting of such molecules to their site of action. In the final chapter, Ehlissi coworkers review an example of such an approach by looking at targeting via the development of antimicrobial agent carrier systems such as the use of nanoparticle constructs. Here, the authors discuss the development of nanostructures for the entrapment and delivery of antimicrobials as an alternative to the direct application of these substances. Specific reference is made to structures formed from liposomes and the effects of the carrier on the activity of the compound are discussed.

In conclusion, it is clear that new approaches are needed if we are to maintain our ability to deal with infection. These approaches have to be holistic and integrated and must involve consideration of stewardship programs as well as the development of new antibiotics and novel approaches to enhancing activity through improved targeting or combination therapies. The need for the development of new antibiotics and antibacterial design strategies has never been greater.

March 2014 *David A. Phoenix, Frederick Harris, and Sarah R. Dennison*

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