Preface

Antibiotic resistance is a global issue that has become a critical concern of many health organizations, infectious disease specialists, and basic scientists in laboratories. Antibiotics have provided an accepted and inexpensive way for humans to counteract infections that previously would have killed them. However, with the increased use of antibiotics comes increased resistance, not only in numbers of resistant bacterial strains, but also as a result of increased varieties of resistance mechanisms. As we have seen multiple times since the introduction of antibiotics, the emergence of a new resistance mechanism in a relatively isolated geographical area is rapidly followed by identification of that resistance in a distant region due to rapid and unrestrained global travel. The Centers for Disease Control (CDC) has coined the phrase "Resistance anywhere is resistance everywhere" to describe this phenomenon. This proliferation of resistance mechanisms active against our mainstay antibiotics, and, as with the finding of transmissible colistin resistance, against antibiotics of last resort, has occasioned the publication of this volume.

Here we have assembled contributions from some of the foremost experts in antibiotic resistance to describe some of the basic, as well as the newest, resistance mechanisms for well-known and well-used antibiotics. In the first two contributions, Strachan and Davies and Perry et al. remind us that natural products from the ancient environment provided us with both the first antibiotics and the first antibiotic-resistance mechanisms. Judicious use of these agents will be critical for them to retain their utility in the future. Silver follows with comments on the nature of appropriate targets for antibacterial drugs, based on existing drug classes and on lessons learned from the (generally poor) results of the search for new antibiotics.

Useful antibiotics have been grouped into sections according to their targets associated with inhibition of bacterial growth. Among those agents that interfere with cell wall synthesis are the β-lactams, the most widely used class of antibiotics. The most important of these drugs are described historically by Bush and Bradford, as is the expansion of their therapeutic utility by the addition of β-lactamase inhibitors to overcome hydrolysis by β-lactamases, the major β-lactam-resistance mechanism in Gram-negative bacteria. Fisher and Mobashery follow with a discussion of β-lactam resistance in the Gram-positive bacteria and *Mycobacterium tuberculosis*, with special emphasis on interference with peptidoglycan synthesis on a molecular level. Bonomo then examines the most critical β-lactamases in Gram-negative pathogenic bacteria. Glycopeptides are presented by Zeng et al., who describe their mechanism of action and the emergence of resistance over several decades as a result of both chromosomal and plasmid-encoded mechanisms. Silver discusses fosfomycin, an antibiotic inhibiting cell wall synthesis at its first committed step, which has been long in use for treatment of urinary tract infections with relatively low incidence of resistance. The recent promotion of much broader use of fosfomycin against MDR pathogens raises the possibility of acceleration of the spread of fosfomycin resistance.

Drugs that act by interfering with membrane synthesis or membrane integrity include daptomycin and the polymyxins. The lipopeptide daptomycin is frequently used for the treatment of infections caused by multidrug-resistant staphylococci and enterococci. Miller et al. discuss its novel mechanism of action and the molecular basis for daptomycin resistance in these organisms. The cyclic cationic polypeptides polymyxin B and colistin have become essential components of many antibacterial regimens for treatment of multidrug-resistant Gram-negative bacterial infections. Trimble et al. provide new insight into the mechanism of action of these agents based, in part, on recently described resistance mechanisms, including horizontal transfer of the *mcr-1* gene among

species of Enterobacteriaceae in both food animals and humans. Two chapters involve investigational single-target inhibitors of enzymes in the lipopolysaccharide biosynthetic pathway. Investigational inhibitors of the enoyl-acyl carrier protein reductase (FabI) are described by Yao and Rock, who note the ability to utilize structure-guided design to obtain pathogen-specific inhibitors, but also note the negative impact of a single-base-pair mutation on the eventual clinical utility of single-target inhibitors. Erwin presents information concerning inhibitors of LpxC, the second enzyme in the Lipid A biosynthetic pathway, and its low selection of resistance in vitro. Although various groups have attempted to identify clinically useful candidates that inhibit LpxC, only one agent has advanced into a therapeutic clinical trial.

DNA or RNA replication has been a major target for some of the most frequently prescribed antibiotics in both the hospital and community setting. Hooper and Jacoby describe the mechanism of action of the fluoroquinolones that specifically target bacterial topoisomerases, enzymes involved directly in DNA synthesis. Because of their widespread use, resistance to fluoroquinolones has arisen in a variety of ways, including both chromosomally mediated and plasmid-encoded mechanisms, thus limiting their therapeutic utility, especially against Gram-negative pathogens. In contrast, the rifamycins target RNA polymerase and are used primarily for treatment of Gram-positive and mycobacterial infections. As described by Rothstein, rifamycin clinical utility has been compromised by resistance issues, primarily involving mutations in the bacterial RNA polymerase.

Bacterial protein synthesis provides an attractive target for antibacterial drug discovery, especially now that structure-based design is able to be guided by the recent availability of x-ray crystallographic data for the bacterial ribosome. Arenz and Wilson describe how advances in structural and biochemical analyses of the ribosome can lead to major advances in the development of new protein synthesis inhibitors. Among the antibacterial agents that target the 30S ribosome are the aminoglycosides and the tetracyclines, two of the oldest and most widely used antibiotic classes. Krause et al. provide an overview of the history of the aminoglycosides and the emergence of both enzymatic and nonenzymatic resistance mechanisms. They then describe the development of new aminoglycosides that are microbiologically active against multidrug-resistant Gram-negative bacteria, with potentially safer dosing regimens compared to the older agents. Grossman describes the tetracyclines, agents with broad-spectrum activity and utility as both oral and systemic antibiotics. Although the older tetracyclines are subject to both intrinsic and acquired resistance mechanisms, newer analogs have been developed to circumvent many of these mechanisms. The 50S ribosome is the target of another set of agents, with macrolides representing the largest class of antibiotics in this set. Fyfe et al. focus on the various resistance mechanisms known for the class, with molecular and structural interpretations provided for phenotypic observations of resistance. The mechanism of action and mechanisms of resistance for the lincosamides, streptogramins, phenicols, and pleuromutilins are described by Schwarz et al. Because these four diverse classes of 50S ribosomal inhibitors are used in both human and veterinary medicine, the opportunity is increased for multiple resistance mechanisms that can be transferred horizontally. However, Paukner and Riedl present information about a novel pleuromutilin with low rates for selection of resistance in vitro that is in late-stage clinical development.

Other antibacterial agents described in this volume include the steroidal antibiotic fusidic acid, an inhibitor of elongation factor G that has been used extensively throughout much of the world as an oral agent to treat infections caused by methicillin-resistant *Staphylococcus aureus*. Fernandes describes its unique mechanism of action and the multiple resistance mechanisms that have arisen during its use for over 50 years. The next set of agents includes the antifolates, agents that inhibit bacterial folic acid synthesis. Among these are the sulfa drugs that were used therapeutically as early as World War II and the dihydrofolate reductase inhibitor trimethoprim. Estrada et al. provide descriptions of the mechanisms of action and resistance that accompany these drugs, and introduce preclinical and investigational agents that were selected in an attempt to overcome common resistance mechanisms. In the final chapter, Leeds tackles the challenge of developing agents that display

activity against a single organism (e.g., *Clostridium difficile*). Mechanisms of action are discussed for the recently approved *C. difficile*–specific RNA polymerase inhibitor fidaxomicin and the exploratory EF-Tu inhibitor LFF571, together with associated resistance mechanisms for each agent.

Antibiotic resistance is a fact of life, and presents a challenge for any antibacterial agent that is used to inhibit the growth of bacteria. In this volume, the major classes of antibiotics, together with their modes of action and common mechanisms of resistance, are described. Old drugs, as well as investigational agents, have all selected for resistant bacteria in natural environments. Resistance may occur either as a result of a single nucleotide substitution in a chromosomal gene, or as the result of the transfer of mobile resistance determinants across species. Common resistance mechanisms such as efflux pumps or decreases in drug uptake due to altered outer membrane proteins result in cross-class resistance, whereas resistance mechanisms involving target alteration or drug inactivation may be drug-specific. In the contributions outlined above, resistance can be described for every molecule that has the capability of preventing bacterial growth. As a result, new antibacterial agents will continue to be needed. Antibiotic discovery and development efforts must proceed without interruption. Resistance will not be overcome long term, but efforts must be made to try to contain the resistant bacteria that already exist through good stewardship of existing drugs, appropriate dosing, and continued basic research into the discovery of new molecules. And, finally, we hope that this volume will provide insight into antibiotic-resistance mechanisms in order to aid ongoing discovery efforts—since these must take into account the propensity for and rapidity with which resistance to new agents can arise.

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