The challenge of resistance in antimicrobial drug development

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Man has long battled the infectious diseases caused by pathogenic bacteria, fungi, protozoa and viruses. Since the late 1930s, the discovery and development of chemotherapeutic agents has been the central effort toward combating infectious disease. Although many of the major causes of historical pandemics no longer present the threat they once did and we have experienced a multidecade era in which safe and effective antibiotics were plentiful, we are now witnessing the emergence of organisms resistant to the most efficacious agents. The adaptive nature of the pathogens necessitates the discovery of new effective compounds or the re-engineering of existing molecules to combat the resistant organisms. This iterative cycle of discovery and development is a unique hallmark of drug discovery targeting proliferating cells.

All major classes of agents with antibacterial, antifungal, antiprotozoal and antiviral activity are subject to lost efficacy owing to resistance through a multitude of pathways. Common mechanisms of resistance and examples of affected classes include point mutations in the target (HIV reverse transcriptase inhibitors), upregulation of efflux pumps (fluoroquinolones), gene amplification or development of bypass pathways (fluconazole) and drug alteration (β -lactamase activity targeting cephalosporins). As each of these mechanisms is unique to the particular drug:organism system, carefully tailored solutions are necessary to overcome the resistance. Modern medicinal chemistry has confronted numerous resistant organisms with a variety of approaches including the discovery of novel agents without cross-resistance, use of combination therapy, or most frequently, alteration of the chemical structure to circumvent the resistance mechanism. For example, the discovery and development of daptomycin to treat methicillin-resistant *Staphylococcus aureus* relied on a natural product with a novel mechanism of action. The development of highly active antiretroviral therapy (HAART), a combination of multiple antiviral agents, revolutionized the treatment of HIV. Finally, no class better exemplifies the value of refinement through medicinal chemistry than the β -lactam antibiotics; many successive generations in this class have overcome β -lactamase activity while increasing the spectrum of coverage.

In this issue, notable advances in understanding and overcoming resistance in a variety of disease states are presented, including a modern overview of natural product sources for discovery [1], application of combination therapy to prevent resistance [2] and a description of a structure-based approach to antibiotic redesign to evade resistant drug targets [3]. This is followed by more specific approaches to antibiotic resistance in tuberculosis [4], as well as discussion of the critical issue of

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bacterial biofilms [5]. Treatment of infectious disease caused by viral pathogens is frequently complicated by resistance owing to the error-prone replication of viral genomes that often produce mutations in the target. Thus, there is comment on the difficult nature of combating resistance in small-molecule antiviral agents [6,7,8]. Finally, there is discussion about the complicated issues of drug resistance in the treatment of parasitic infections [9].

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