

# Antimicrobials

## Antimicrobials in the 21<sup>st</sup> century

### Editorial overview

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The antibiotic discovery process, which is barely over a half-century old, has focused on two primary issues: spectrum of activity, limited initially by intrinsic microbial resistance mechanisms, and acquired resistance. Indeed the first wave of antibiotic discovery was driven by intrinsic resistance, whereby screening for novel natural product antibiotics that broadened the activity of antibacterials was gradually succeeded by classical chemical modifications of existing antibiotics to overcome known resistance mechanisms. In addition to the use of medicinal chemistry approaches to improve potency, spectrum of activity, pharmacokinetics and the resistance profiles of existing classes of compounds (e.g.  $\beta$ -lactams, macrolides and quinolones) antibiotic discovery programs have been searching for novel structures and mechanisms of action. The recent successful development and introduction of the new antibacterial, Linezolid® (Pharmacia Corporation, New Jersey, USA), and the new antifungal, Cancidas® (Merck, New Jersey, USA), mark the first new structural classes to be registered in many years. Despite these efforts, the increase in antibiotic resistance is gradually creating a critical situation that promises to reverse the enormous medical gains experienced as a result of effective antibiotics.

The series of reviews presented here touch on these issues. The first three describe the evolution in our understanding of resistance. For decades now, antibiotics have been intensively used in agriculture as growth promoters, prophylactic agents and therapeutics. There has been a strong sense of denial in the food industry that this is a concern. The review by Teuber (pp 493–499) describes instances in which human antibiotic resistance has clearly arisen from veterinary usage and provides a clear rationale for reconsidering our strategies in this arena.

Resistance can be caused by a broad number of mechanisms, involving decreased antibiotic accumulation, physical modification or destruction of the antibiotics, and alteration of the enzyme target of antibiotic action. In recent years, a mechanism of resistance involving the active efflux of antibiotics by pumps has been elucidated. Interest in this

mechanism is driven by the observations that: first, the intrinsic resistance of Gram-negative bacteria is largely due to a collaboration between low outer-membrane permeability and intrinsic active efflux systems; and second, efflux-mediated resistance can result in the inactivation of multiple structural classes of antibiotics simultaneously. Reviews by Poole (pp 500–508) on Gram-negative bacteria and Markham and Neyfakh (pp 509–514) on Gram-positive bacteria discuss these issues and their implications in terms of potential future drug design.

New challenges require novel solutions. Antibiotic discovery has dramatically altered from the 1970s and 1980s when a combination of screening of natural samples and classical chemical modifications met with some limited success. One new concept is based on the observation that not all potential antibiotic targets will be expressed in a test tube, as microbes alter their metabolism substantially to permit *in vivo* growth and infection. Lehoux, Sanschagrin and Levesque (pp 515–519) describe strategies for discovering genes that are essential to the growth of bacteria during infections.

Once appropriate targets for antibiotic intervention have been discovered, lead molecules can be obtained through screening, but the final compound for clinical use must be optimized chemically to improve safety and efficacy. This was traditionally done through the gradual methodologies employed by organic chemists. However, Trias (pp 520–525) describes an improved approach involving combinatorial chemistry (combiChem) that permits rapid sampling of chemical modifications of a scaffold compound. A separate approach involves the use of the microorganism as a test tube to modulate the structure of known antimicrobials, a process termed combinatorial biosynthesis. This method, described by Rodriguez and McDaniel (pp 526–534), involves the genetic rearrangement of cellular biochemistries to permit the production of novel compounds.

The final two reviews discuss the evolution of antivirals (reviewed by Miller and Hazuda pp 535–539) and antifungals (reviewed by Tkacz and DiDomenico pp 540–545). Like the antibiotic discovery area, problems with resistance and toxicity of existing agents are the driving forces behind the discovery of novel drugs in these areas. However, the fact that fungi are eukaryotes and thus share metabolic pathways with humans (whereas viruses actually exploit human metabolism) makes the issue of toxicity (the ability to do harm to a patient) and therapeutic index (the ratio between the harmful [toxic] concentration and the useful [therapeutic] concentration) an especially critical one.

We are entering an era of great promise for antimicrobial drug discovery. Improved understanding of resistance, combined with novel avenues and approaches for drug discovery, has an enormous potential to yield new efficacious antibiotics. Nevertheless, considering the enormous effort that has gone into the discovery and development of existing antibiotics, one may contend that a shift in paradigms may also be required to succeed in the face of increasing microbial resistance. Most traditional antibacterials in use today have been developed and are used as monotherapeutics. The notable exceptions to this paradigm include: Augmentin® (GlaxoSmithKline, Uxbridge, UK), which has both the  $\beta$ -lactam antibiotic oxacillin and the  $\beta$ -lactamase inhibitor clavulanic acid; Primaxin® (Merck, New Jersey, USA), which contains the carbapenem, imipenem, and the dehydropeptidase inhibitor, cilastatin (to improve its pharmacokinetics); and Synercid® (Aventis, New Jersey, USA), which contains the streptogramins, quinupristin and dalfopristin, each of which is static when used alone but, when used in combination, are cidal for many organisms. Combination therapy using multiple

compounds, however, is used widely today in cancer chemotherapy and in therapy for AIDS (e.g. the HAART therapy regimen). As pointed out by Markham and Neyfakh and Poole in their reviews, with the increased knowledge of resistance mechanisms found in both Gram-positive and Gram-negative bacteria, it may be reasonable to develop new antibacterial therapeutics to be used in combination therapy with existing drugs. The proposed use of cationic peptides as antimicrobial facilitators also fits into this overall strategic approach. The greatest impediment in the development of combination antibiotic therapeutics has been the difficulty and cost in simultaneously discovering and developing multiple safe, potent, and efficacious products that lack significant drug–drug interactions. Nevertheless, this inertia has been overcome for therapeutic treatment of cancer and AIDS, in which it has been required; bacteria resistance may indeed be the next hurdle requiring a more significant use of this approach. Indeed, if we play our cards right, history may record this as the second golden era of antimicrobial discovery.