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Expert Opinion

# Antibiotics versus resistant bacteria: a continual challenge

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At times it seems that almost every publication concerning antimicrobial agents begins with a comment about the emergence and spread of resistance in microbes to such agents. These continual statements of concern represent the recognition of critical problems potentially facing the future for control and treatment of infectious diseases. These future resistance problems first became widely recognized in the late 1980s and early 1990s prompted by the unexpected appearance of resistance to vancomycin. At that time, research on infectious diseases was often perceived as a lower priority within many pharmaceutical companies and other organizations.

Since then, approximately 20 years of calls for action have slowly been heeded. Of particular note, many smaller pharmaceutical and biotechnology companies, start-up ventures and academic institutions have moved into the void that was created by the exit or downsizing of infectious disease research at many larger pharmaceutical companies. Research personnel in many different settings have been designing, screening, preparing and evaluating new antibiotics to meet the medical challenges for new agents that show superior pharmacotherapeutic properties, including activity against strains resistant to existing agents. From these rejuvenated efforts, a few new agents have been approved for treating Gram-positive bacteria, including certain resistant strains, while some other compounds are moving through the development and registration processes. In addition, more attention is being devoted toward finding new agents to treat previously overlooked resistant Gram-negative bacteria.

Patents are an important early report for the creation of new compounds. They may often be the initial indicator of research strategies, directions and results for an organization. Knowledge of the patent literature in a research area is as important as familiarity with current journal publications and conference presentations. This issue of *Expert Opinion on Therapeutic Patents* reviews some of the results from recent research devoted to finding new antibacterial agents that will improve treatment of infectious diseases, including those caused by strains resistant to current antibiotics.

The first review in this issue provides an overview of problems caused by antimicrobial resistance in many bacteria, which is the principal driving force for continuing to conduct antibacterial research. If bacteria did not continuously evolve to become resistant to current antibiotics, there would be much less motivation for continuing to search for new antibiotics.

A traditional time-tested strategy in medicinal chemistry is to expand an established class of compounds by further exploring structure-activity relationships and preparing and evaluating new analogs. This approach is often favored as less risky because the early successful compounds have established proof-of-concept in treating diseases. The challenge is to significantly improve on those initial successes with new compounds having improved properties, an endeavor in which researchers are well-experienced. This strategy continues to be explored within many established antibiotic families and has successfully developed analogs having activity against strains resistant to older members of those classes. Reviews of four important classes examine this particular approach and describe newer developments with beta-lactam, fluoroquinolone, aminoglycoside and macrolide antibiotics.

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New antibiotic substances are also being sought that are unlimited by previously known structures and, thus, may provide breakthrough discoveries such as novel mechanisms of action against resistant bacteria. Fermentation of microorganisms is a well-honored tradition for the discovery of such novel and unanticipated materials. The sixth review surveys antibiotics that have recently been discovered by new approaches to this older technology so that it is still successfully uncovering unknown structures. These compounds are also potential candidates for structure-activity studies that may sufficiently improve their properties and provide semi-synthetic clinical candidates.

In addition to organizing reviews using a compound-oriented system, a therapy-oriented organization can also be used. The next two reviews survey the treatment of certain medical conditions caused either by bacterial biofilms or by gastrointestinal diseases, which occur in specialized body environments having unique features. Although some overlap exists with the major antibiotic classes, other diverse antimicrobial agents are also being investigated, particularly ones having selective activity against specific pathogens rather than broad-spectrum activity. The lack of activity against non-pathogenic bacteria should also provide an advantage that limits resistance in such microbes.

A long-considered alternative to the traditional paradigm of killing unwanted bacteria has been to diminish the virulence and pathogenicity of these organisms. This strategy may also limit the development of resistance in these bacteria by removing the antibiotic pressure that selects for resistance and thus allows their survival. The final review describes current research efforts to develop such agents that will potentially complement the antibiotic arsenal.

Finally, since this issue cannot cover all strategies and all antibiotics, other relevant recent reviews of antimicrobial research from the Expert Opinion journals are listed for reference.

In summary, the competition between evolution of resistance to antimicrobial agents and the development of new agents to overcome such resistance will most likely continue. This dynamic has existed since the discovery of antibiotics and no change is foreseen soon. The reviews in this issue reflect the current state of this competition by describing a variety of recent research efforts that have led to new antibacterial agents that are now proceeding through development and regulatory pathways. Overcoming resistance to antibiotics in bacteria is a principal feature of many of these new agents. Although not every avenue of research will ultimately be successful, the future seems promising that enough new ideas will eventually succeed and the results will increase the number and quality of new antimicrobial agents to combat resistant bacteria. However, as we witnessed with the earlier appearance of resistance to vancomycin, microbes are not going to cease their evolution of resistance. Thus, it is imperative that the pharmaceutical industry does not cease its efforts to overcome that resistance. Hopefully, we will not repeat the mistake of underestimating microbial evolutionary capabilities and assume we have conquered infectious diseases.

## Declaration of interest

H Kirst is the Guest Editor of this issue and is a consultant for Cempra Pharmaceuticals and is a former employee of Eli Lilly and Company. He declares no other conflicts of interest with any of the papers in this issue.

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