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Editorial Overview: Recent Advances in Antimicrobial Drug Discovery and Resistance

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The discovery, development, and use of antimicrobials represent one of humankind's most significant scientific achievements. For nearly a century, civilization has enjoyed significantly lower morbidity and mortality rates from infectious diseases than at any other time in human history. However, given the tremendous evolutionary capacity of microbes, overuse of antibiotics, and the declining rate of discovery and development of new anti-infective agents, we find ourselves entering the post-antibiotic era as resistance to our anti-infective armamentarium increasingly impacts clinical care.[1] The need for discovering and developing new antimicrobials has never been more critical.[2,3] Moreover, to preserve and sometimes reclaim the use of anti-infectives, we must advance our understanding of the molecular and genetic mechanisms underpinning anti-infective resistance and drug tolerance and learn to use these agents more judiciously and effectively. For this edition on Antimicrobials, we have assembled opinion pieces from some of the foremost scientists and thought leaders reviewing individual areas of antibacterial and antifungal drug discovery and resistance.

In this issue, the challenge of targeting and developing drugs to treat bacterial infections is explored in an opinion piece examining the physiological role of Resistance–Nodulation–Division (RND) superfamily drug efflux pumps that are critical to Gram-Negative drug resistance to many antibiotic classes.[4] In the review, Zgurskaya et al. explore the native function of these efflux pumps. The RND pumps are classified into three categories: constitutively expressed, regulated, and silent. Their differential expression is critical for small-molecule accumulation within cells. However, the specific physiological substrates transported by RND pumps are still largely unclear. Making sense of RND drug-efflux transporters and how they function naturally will provide actionable information for Gram-Negative drug discovery.[5]

Lui and Stokes provide a brief guide to machine learning, an important emerging computational technique for antibiotic discovery.[6] Combining wet lab data with machine-learning and deep-learning methods is a powerful approach to drug discovery providing the input data is rigorous. The authors urge community members to share their data sets to train antibiotic prediction models. These models can then be used to discover new antibiotics taking advantage of the huge untapped areas of chemistry space available and the ability to rapidly screen *in silico* without the need to synthesize or isolate the probe molecules.

The potential for drugging the human microbiome with a focus on manipulating small molecules that play an important role in this ecosystem is explored in an opinion piece by Aldrich et al.. The human microbiome is an extensive collection of mucosal microbes that provides an essential role in regulating mammalian immune system homeostasis, nutrient capture, and drug metabolism. In the piece, the authors explore key microbiome-related metabolic processes and products and how they can be manipulated by modern medicinal chemistry approaches to generate microbiome-directed therapeutics.

The potential for selective targeting of one pathogen associated with the human microbiome, *Helicobacter pylori,* is examined in a review by Vita et al.[7] Chronic *H. pylori* infection is a leading cause of gastric cancers, and *H. pylori* isolates are becoming increasingly resistant to standard-of-care antibiotic therapies. The review focuses on opportunities to develop novel, non-broad spectrum therapies for *H. pylori*. The authors propose taking advantage of recent advances in understanding the disease biology of this unique pathogen that resides within the gastric glands of the stomach, pairing the knowledge with advanced methods in antibacterial drug discovery including high throughput and virtual screening.

Another important obligate human pathogen is *Mycobacterium tuberculosis*. Craggs et al. examine the “bottlenecks and opportunities in antibiotic discovery against *Mycobacterium tuberculosis*” in an excellent summary of the tuberculosis drug discovery field. The authors highlight the need to embrace new technologies and chemotypes to maintain a strong pipeline to overcome the threat of the spread of multi-drug resistant tuberculosis.[8] Opportunities highlighted include using advances in genomics, metabolomics, and *M. tuberculosis* physiology to identify and prioritize the most vulnerable targets with the highest likelihood of producing efficacious drugs that partner well with other tuberculosis agents. The application of repurposing and chemically refining antibiotics specific for tuberculosis originally developed and derisked with associated use to treat other bacterial infections is examined. Hijacking nutrient limitation pathways and understanding permeation rules for mycobacterial drug uptake are discussed as areas of future drug discovery promise.

For all antimicrobials to be successful, their pharmacokinetic and pharmacodynamic (PK/PD) responses must be carefully examined and optimized to ensure that the best clinical response is obtained. Luterbach and Rao examine the PK/PD dose optimization of the recently introduced novel aminoglycoside, plazomicin.[9] The importance of understanding drug tissue distribution variability, especially in the lung for the treatment of pneumonia is highlighted. The studies demonstrate that accurate computational models can be developed *in vitro* and *in vivo* infection models, and be applied to develop a “learn and confirm” approach to ensure that the drug dosing is best optimized for personalized medicine to

tackle highly drug-resistant organisms such as Carbapenem-resistant Enterobacterales. Dose optimization can also be used to improve patient safety such as for those with renal impairment to minimize nephrotoxicity.

There is also a tremendous need for novel antifungals and an understanding of how resistance emerges to the currently available agents. Only three classes of antifungals are available to treat invasive fungal infections, and all have limitations. New classes of antifungals are therefore needed. In the opinion piece by Robbins and Cowen,[10] the current state of the art in approaches to antifungal discovery is examined, with specific examples of some of the most promising new agents in the antifungal pipeline highlighted. Moreover, an in-depth discussion of some of the most intriguing new antifungal targets is discussed, including lipid homeostasis, glycosylphosphatidylinositol-anchor biosynthesis, calcineurin, Hsp90, kinases, and vesicle trafficking.

One of the most significant threats to existing antifungal therapy is the emergence of resistance. Of particular concern is *Candida auris* which represents a major public health threat owing largely to the frequency with which it exhibits resistance to multiple antifungal agents, its rapid global emergence, its proclivity for transfer within healthcare settings, and. In the review by Rybak et al. our current understanding of the molecular and genetic basis of antifungal drug resistance in this important emerging fungal pathogen is examined.[11] Resistance to the triazole antifungals is due in part to mutations in the gene encoding the target enzyme sterol demethylase, as well as in genes encoding transcription factors that regulate the expression of drug efflux pumps. Echinocandin resistance has been shown to be primarily due to mutations in the gene encoding the target enzyme of this class, glucan synthase. Resistance to the polyene amphotericin B is poorly understood in *C. auris*, but in some clinical isolates has been shown to be due to loss of function mutations in the gene encoding sterolmethyltransferase leading to altered sterol composition.

We are excited by the diverse and representative scope of opinion pieces found in this special issue that each in its own way highlights the challenges of discovering and developing new antimicrobial agents at a time of high pre-existing resistance to current therapies.

Biographies

P. David Rogers, Pharm.D., Ph.D., FCCP is currently Member and Chair of the Department of Pharmacy and Pharmaceutical Sciences at St. Jude Children’s Research Hospital and holds the St. Jude Endowed Chair in Pharmaceutical Sciences. His research is focused on improving antifungal pharmacotherapy through the study of how pathogenic fungi develop resistance to antifungal agents.

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