ACS Infectious Diseases

Editorial

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Antibiotic Discovery for Mycobacteria

The World Health Organization (WHO) recently announced that tuberculosis (TB) has overtaken HIV as the leading cause of infectious disease mortality (http://www.who.int/mediacentre/news/releases/2015/tuberculosis-mortality/en/). Infections caused by *Mycobacterium tuberculosis* (*Mtb*) and the lesser studied, but clinically significant, nontuberculous mycobacteria (NTM) are incredibly difficult to treat compared to infections caused by other microorganisms. This is due to the unique physiology of mycobacteria, which allows them to adapt to different environmental conditions, and to the resulting host pathology, which presents as a heterogeneous mix of lesions containing different microenvironments. Mycobacteria are also intrinsically resistant to many antibiotics owing to their thick waxy cell walls that can hinder antibiotic penetration and to the presence of efflux pumps, whose contributions to resistance are only beginning to be appreciated. Additionally, mycobacteria are able to subvert the host immune system by hiding out within host macrophages and other phagocytic cells. Although tremendous gains have been made during the past century to combat these insidious pathogens, the dissemination of drug-resistant mycobacterial strains threatens this progress, and a sustained effort in antibiotic discovery is imperative. To further these efforts, we have assembled this special issue of *ACS Infectious Diseases*, which highlights some of the exciting and diverse strategies being used at the interface of chemistry and infectious disease research to directly address these formidable challenges in antibiotic discovery for mycobacteria.

Clifton Barry III cogently describes the difficulties of TB drug discovery and offers guidance with his Viewpoint "The Death of the Three Ms" (DOI: 10.1021/acsinfecdis.5b00124). His thesis is that the current paradigm of antibacterial drug discovery, which involves empiric whole cell screening of compounds to determine their minimum inhibitory concentration (MIC), evaluation in a mouse model, and subsequent testing in man, fails to take advantage of the explosion of biological data and our enhanced understanding of mycobacterial physiology.

The power of target-based approaches in cancer and virology is undisputed. However, this strategy has been notably unsuccessful in antibacterial discovery. One of the most frequently mentioned reasons for this failure is the inability to translate biochemical activity into whole-cell activity. This is attributed to our incomplete understanding of the chemical properties and molecular features of antibiotics that facilitate their cellular accumulation. As a result of these aforementioned difficulties, the TB community has embraced classical target-agnostic whole-cell phenotypic screening. Over the past decade, we have learned that medicinal chemistry optimization based solely on frank growth inhibition of bacteria is also challenging due to a number of factors including potential involvement of multiple low-affinity targets and differential cellular accumulation across a compound series that can confound interpretation of structure−activity relationships (SAR). Empiric whole-cell screening has thus not been the expected panacea. Target-based whole-cell screening (TBWCS) has been developed as a hybrid method, which merges the strengths of target-based approaches with the practical advantages of whole-cell screening. In this issue, Argyrou, Besra, Ballell, and colleagues (DOI: 10.1021/acsinfecdis.5b00065) use a variation of TBWCS employing target overexpression to identify inhibitors of decaprenylphosphoryl-β-D-ribose oxidase (DprE1) by screening against a publicly available GlaxoSmithKline (GSK) antimycobacterial compound set (TB-Box). This approach allowed the authors to link the previously observed whole-cell activity of GSK710, a compound in the TB-Box, to inhibition of a target DprE1. Their work provides a foundation for future structure-based drug design efforts against this essential and highly vulnerable target.

The article by Sherman, Guardia, and co-workers (DOI: 10.1021/acsinfecdis.5b00063) describes a target repurposing strategy for antibacterial development by focusing on the essential and well-established target dihydrofolate reductase (DHFR). DHFR is a clinically validated cancer and antimicrobial target, but the approved DHFR inhibitors are either poorly active against the mycobacterial DHFR or lack whole-cell antimycobacterial activity. The investigators compiled a 2500-member antifolate library from historical folate programs in other therapeutic areas and used in silico screening of the entire 2 million compound GSK screening collection to identify close analogues. Compounds were initially screened for growth inhibition of *Mtb*, and the reconfirmed hits were then counter-screened against an *Mtb* strain overexpressing DHFR to discern potential on-target activity by a diagnostic shift in MIC value. Further biochemical evaluation against recombinant human and *Mtb* DHFR was used to confirm target engagement. Five compounds with different chemotypes were identified that possessed potent whole cell activity through inhibition of DHFR. These results emphasize the potential of DHFR as a viable antimycobacterial target and more generally indicate the utility of repurposing classes of proven targets in other therapeutic areas.

The ability of mycobacteria to enter a nonreplicating state is thought to contribute to the lengthy treatment regimen required for TB and nontuberculous mycobacteria. The paper by Nathan, Mendoza-Losana, and co-workers (DOI: 10.1021/acsinfecdis.5b00025) in this issue describes a whole-cell screen run under conditions that are meant to mimic an environment in which the bacteria are nonreplicating due to pressure by different effectors of the immune system. Intriguingly, very few compounds identified as active under nonreplicating conditions would have been discovered by a standard replicating assay, emphasizing how strongly these different physiological states impinge on inherent drug susceptibility.

Historically, drug efflux has not been considered a major source of intrinsic antibiotic resistance in mycobacteria. A

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growing number of papers have challenged this dogma, and it is increasingly recognized that drug efflux can play a significant role, especially for experimental therapeutic agents. Modification of the parent scaffold to evade efflux-mediated resistance represents one strategy. Another approach, as described in this issue by Sabatini, Viveiros, and colleagues (DOI: 10.1021/acsinfecdis.5b00052), uses efflux pump inhibitors to restore susceptibility to the parent drug. The authors show that efflux pump inhibitors initially designed for *Staphylococcus aureus* are also effective against several for nontuberculous mycobacteria (NTM) and confer hypersensitivity to the macrolide class of antibiotics, which are the drugs of choice for NTMs. This paper highlights the growing awareness of the importance of efflux in mycobacterial diseases.

Mycobacteria are located both extracellularly and intracellularly in host phagocytic cells in vivo. Many TB drugs are substantially more effective against extracellular bacilli. The intracellular reservoirs of mycobacteria could potentially contribute to the long treatment duration and relapses after antibiotic therapy. In this issue, Kelley and co-workers (DOI: 10.1021/acsinfecdis.5b00099) engineered a peptide−prodrug conjugate that targets intracellular mycobacteria using a peptide sequence to deliver the prodrug to the macrophage phagolysosome. Subsequent cleavage by a mycobacterial specific enzyme was shown to release the active drug. A complementary approach has just been described by Lehar and co-workers (*Nature* (2015), DOI: 10.1038/nature16057) for *S. aureus*, but using an antibody−prodrug conjugate that releases the antibiotic in the proteolytic environment of the phagolysosome. The small-molecule peptide−prodrug conjugate described by Kelley represents an elegant and substantially simpler solution to intracellular delivery for mycobacteria.

We hope this special issue of *ACS Infectious Diseases* captures some of the excitement in the TB field as well as the diversity of approaches to tackle the extraordinarily challenging problem of drug resistance. This issue coincidentally contains several papers resulting from successful industrial−academic partnerships that combine the knowledge of an academic laboratory for a given molecular or phenotypic target (DprE1, DHFR, nonreplicating *Mtb*) with the considerable drug discovery expertise and resources of a major pharmaceutical company. In closing, I would like to express my gratitude to the authors and reviewers for their contributions to this special issue.

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AUTHOR INFORMATION

Notes

Views expressed in this editorial are those of the author and not necessarily the view of the ACS.

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