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Editorial

Antibiotics Special Issue: Challenges and Opportunities in Antibiotic Discovery and Development

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Antimicrobial resistance (AMR) has received increasing global attention over the past decade. The lack of antibiotics in the clinical pipeline is a direct result of the discouraging financial incentives for their commercial development. This has led to a precarious situation where the widespread emergence of highly resistant strains could threaten the viability of the worldwide health system, as seen with the current COVID-19 crisis. While a number of nonantibiotic alternative antimicrobial approaches show interesting potential, it is difficult to see how they would displace the need for new antibiotics for the foreseeable future.

This special issue on antibiotics is a combination of viewpoints, perspectives, reviews, and original research manuscripts that provides a snapshot of the current state of affairs in antibiotic discovery and development. It is anchored by a set of 10 interrelated viewpoints and two perspectives from many of the world's leading agencies and key opinion leaders with an interest in antimicrobial resistance.

The AMR division of the World Health Organization and The Pew Trust both provide overviews of the difficulties facing antibiotic development. The WHO viewpoint summarizes its recent reports on the preclinical and clinical antibacterial pipelines, with the former showing 252 antibacterial agents being developed by 145 individual institutions and the latter including 50 antibiotics and combinations. The Pew Trust shares its progress in attempting to foster the sharing of antibiotic discovery data and knowledge and discusses how to more effectively target antibiotic discovery efforts. It urges continued early stage research funding and more coordinated action and mentions efforts to support antibiotic development by The Global Antibiotic Research and Development Partnership (GARDP) and The National Institute of Allergy and Infectious Diseases (NIAID). Both of these organizations have also provided viewpoints. GARDP outlines why it was established and what it is attempting to do, while thethe NIAID delineates the free services it provides through the Division of Microbiology and Infectious Diseases. This support should be of considerable interest to antimicrobial researchers, who may not be aware of its availability. The Community for Open Antimicrobial Resistance makes the case that it is essential to provide free early stage antibiotic screening support to foster fundamental research into new antibiotics. In a similar vein, the Wellcome Trust summarizes what it is doing to encourage antibiotic development, including its coordination of investment with other AMR agencies such as GARDP and the Combating Antibacterial Resistance Bacteria Accelerator (CARB-X). CARB-X itself has written a more substantial perspective, with a detailed breakdown of the three different funding rounds to date. CARB-X has vetted over 1100 applications (over 40% from companies with ≤10 employees), funding 60 projects to date from its investment pool of US $500 million.

A joint viewpoint from authors working within the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) discusses the efforts of these agencies to reduce the barrier to antibiotic development by harmonizing regulatory requirements, while a venture capital opinion is offered by the only fund dedicated to antimicrobial resistance. Aleks Engel from The Novo REPAIR Fund explains their rationale for choosing to invest in this nonlucrative field.

These institutional viewpoints are supplemented by two submissions from David Shlaes, a key opinion leader in antibiotics. The first focuses on the economic challenges of antibiotic development and contains suggestions on how to help small antibacterial biotech companies survive. The second gives a very powerful personal view of the value of antibiotics from the front lines of patient care based on his career as an infectious diseases physician.

These overviews of the antibiotic field are followed by a collection of reviews, perspectives, and research manuscripts that nicely encapsulate the major strategies applied to antibiotic development, with contributions from both industrial and academic entities.

A number of articles focus on improving traditional antibiotic classes, which has been the most successful strategy for producing new antibiotics over the past four decades. New β-lactamase inhibitor (BLI)/β-lactam combinations form a large component of the clinical antibiotic pipeline, and this prevalence is reflected in the number of research articles. Entasis, the antibiotic-focused company formed when AstraZeneca exited antibiotic research, provides two reports on their preclinical diazabicyclooctane (DBO) class BLI. ETX1317 is being developed as an orally available prodrug (ETX0282) to be administered with a cephalosporin prodrug, cefpodoxime

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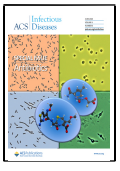

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proxetil. One article describes the *in vitro* activity of ETX1317 against a range of β-lactamase-expressing strains and 1875 *Enterobacteriales* isolates from UTI infections, with good activity against Class A, C, and D (but not B) carbapenemases. The second focuses on pharmacokinetic/pharmacodynamics, presenting both *in vitro* (hollow-fiber and chemostat) and *in vivo* (murine neutropenic thigh infection model) studies. From an academic perspective, the Schofield group at Oxford University characterize a broad spectrum BLI based on a thioether-substituted bicyclic boronate in Parkova et al. They show the potential for this class of inhibitors to provide activity against all three subclasses of metallo-β-lactamases. Tehrani et al. report that the known small molecule carboxylic acids nitrilotriacetic acid and *N*-(phosphonomethyl)iminodiacetic acid effectively inhibit the metallo-β-lactamases NDM-1 and VIM-2 by binding zinc, restoring the activity of meropenem in *in vitro* assays.

Acting similarly to BLIs are other combination therapies that use a potentiator to restore the activity of an existing antibiotic against resistant bacteria. Researchers from McMaster University have worked with Spero Therapeutics to characterize the mechanism of action of their clinical potentiator SPR741, a polymyxin analog that potentiates several classes of antibiotics against resistant Gram-negative pathogens by disrupting the bacterial outer membrane. Ramirez et al. show that a bis(3-aminopropyl)glycine scaffold with three Arg residues capped with lipophilic tails could potentiate rifampicin and novobiocin to a similar extent as polymyxin B nonapeptide, at least *in vitro*. Ongwae et al. used polymyin B as a membrane-targeting scaffold to deliver a quaternary ammonium "warhead" onto the surface of bacterial pathogens, replacing the normal fatty acid tail with a lipophilic quaternary ammonium group: the adducts tended to be less potent than polymyxin B but retained the ability to potentiate rifamycin. In Hussein at al., Polymyxin B itself was found to work synergistically with sertraline, a selective serotonin reuptake inhibitor, against both polymyxin-susceptible and polymyxin-resistant isolates.In contrast, Dai et al. explore how nerve growth factor can work in combination with polymyxin to reduce its peripheral neurotoxicity.

The use of potentiators is included in a review by Gray and Wenzel on multitarget approaches to treating resistant infections. The article has a broader scope than just potentiators and includes antibiotics that act on multiple targets, hybrid molecules designed to act on two targets, and antibiotic combination therapies. Rineh et al. provide an example of a conjugate that adds additional functionality to an existing traditional antibiotic. They modify a cephalosporin antibiotic scaffold with a prodrug moiety that releases nitric oxide as a biofilm dispersant. The best hybrid showed superior biofilm reduction compared to ceftazidime in *in vitro* testing and similar efficacy in an acute *Pseudomonas aeruginosa* murine lung infection model.

The antibiotic discovery strategy of developing novel chemical scaffolds against a known target is exemplified in a review from Entasis that describes the development of Zoliflodacin, currently in Phase 3 clinical trials in partnership with GARD for drug resistant infections caused by *Neisseria gonorrheae*. Zoliflodacin is a new spiropyrimidinetrione scaffold that targets the bacterial type II topoisomerases but with a unique binding site (the GyrB subunit of DNA gyrase) and distinct mechanism of action compared to fluoroquinolones such as ciprofloxacin. In a similar vein, Spero Therapeutics offers a perspective on the development of GyrB inhibitors to treat infections caused by *Mycobacterium tuberculosis* and nontuberculous mycobacteria. Their examples start with the prototype aminocoumarin natural product inhibitor novobiocin and end with Spero's benzimidazole urea clinical candidate SPR720, a prodrug originally developed by Vertex Pharmaceuticals.

New chemical scaffolds acting on new bacterial targets are the "holy grail" of antibiotic discovery programs. Ma et al. from the Novartis Institutes for BioMedical Research present a structural analysis of their small molecule inhibitors of *E. coli* LpxD, an enzyme involved in lipid A biosynthesis in Gram-negative bacteria. This story highlights some of the pitfalls of drug discovery, as the actual inhibitors were found to be generated by *in situ* aromatization of the tested hexahydropyrazolo-quinolinone compounds. Post et al. describe their development of analogs of promalysin, a small-molecule natural product first isolated in 2011 that specifically inhibits *P. aeruginosa*. On the basis of its putative target of succinate dehydrogenase, they use computational modeling to identify a new binding cleft. Another potential new class of antibiotics is represented by pyrimidine analogs derived from 5-fluorouracil, described by Oe et al. These Gram-positive compounds target the same pathway as trimethoprim-sulfamethoxazole but probably act via inhibition of thymidylate synthetase. Notably, this paper employs RPMI medium with 10% fetal calf serum for the bacterial assays, rather than the standard Mueller Hinton (MH) broth. The RPMI mixture includes thymidine and serum proteins, which more closely approximates the environment where bacterial infections occur. This highlights a key question: should our quest for new antibiotics use screening conditions that are more reflective of the environs of infections?

The search for inhibitors of new targets requires the development of target-specific assays, and Mitachi et al. contribute to this field with a fluorescence-based assay for the bacterial glycosyltransferase MurG, an enzyme involved in the conversion of lipid I to lipid II during peptidoglycan biosynthesis.

Finally, an alternative strategy to treat resistant bacteria is taken by Vinagreiro et al., who describe the use of porphyrin photosensitizers to effectively kill multidrug-resistant clinical isolates and inactivate bacteria in biofilms. This antibacterial photodynamic inactivation approach obviously has practical limitations but could be useful for surface wound (skin, eye) or cavity (mouth, ear) infections.

In closing, I would like to express my appreciation to all the authors and reviewers who have taken time from their busy schedules to contribute to this special issue. The articles in this *ACS Infectious Diseases* joint special issue are supplemented by additional articles in *ACS Pharmacology & Translational Science*. Hopefully, the collection will inspire new ideas and new researchers to contribute to the fight against antimicrobial resistance.

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Notes

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

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