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Editorial

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Gram-Negative Resistance

Recent years have witnessed new tides of both optimism and dread in antibacterial research and development. The optimism stems from a growing collective will worldwide, in government and the private sector, to deal with the problem. The dread, however, is centered on the immense challenge presented by Gram-negative drug resistance in the clinic. Indeed, there have been no truly new Gram-negative antibiotics discovered in decades, and there are relatively few such entities currently in the development pipeline. As a result, there are drug-resistant Gram-negative infections caused by carbapenem-resistant Enterobacteriaciae and multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumanii* that are nearly untreatable. Although Gram-positive pathogens such as methicillin-resistant *Staphylococcus aureus* are also a concern, new drug discovery and development for these is largely about improving the choices of agents. With this in mind, Bob Hancock and I put together a Keystone meeting titled "Gram-negative Resistance" (http://www.keystonesymposia.org/15D1) that ran in the early spring of this year. That meeting showcased some exciting new approaches to tackle the problem, where fresh chemistry and chemical approaches are pushing the field in new directions. Indeed, that meeting catalyzed this special issue of *ACS Infectious Diseases* with several attendees, and other groups taking unconventional approaches, agreeing to contribute.

Karen Bush provides the lay of the land with a perspective piece on the state of the art with respect to new antibiotic drug discovery and development. She reviews the new regulatory backdrop as well as the intensive activity in the development of β-lactamase inhibitors in combination therapies. Some novel agents are also on the horizon; however, she indicates that most of the compounds in development are all too familiar in chemical class and mechanism.

Whereas adaptive resistance is commonly considered to be a nongenetic phenomenon, it is not trivial to tease apart the role of genetic and nongenetic elements in resistance. Anushree Chatterjee et al. contribute a creative study on adaptive resistance that investigates the hypothesis that interpopulation gene expression variability is a metric to identify key genes involved in adaptive resistance.

Systems approaches are finding increasing utility in understanding the physiological networks that underpin bacterial survival and virulence. Using clinical isolates of uropathogenic *Escherichia coli* (UPEC), Peter Mucha, Jeffery Henderson, and colleagues take a mathematical approach to identifying which virulence factor combinations predominate in patients. The work identifies resistance- and patient sex-associated virulence factors as targets for combination therapies.

Carbapenems are members of the β-lactam class of antibiotics that are particularly effective against hard-to-treat Gram-negative pathogens; however, drug resistance is eroding the usefulness of these last-resort agents. Among the most menacing resistance enzymes is the metallo-β-lactamase NDM-1, a carbapenemase that is rapidly spreading worldwide. In a structure-based approach to inhibition of this enzyme, James Spencer, Alejandro Vila, and co-workers came up with a bisthiazolidine scaffold that mimics the bicyclic nature of β-lactams while targeting the catalytic zinc of NDM-1 with chelating groups. These compounds restored the activity of imipenem against drug-resistant strains harboring NDM-1. Indeed, my own group reports in this issue on the discovery of zinc-selective spiro-indoline-thiadiazole compounds that disrupt bacterial zinc homeostasis and NDM-1 function. One such compound was shown to be an effective potentiator of meropenem in a mouse model of infection with an NDM-1-producing isolate of *Klebsiella pneumoniae*.

When absolutely nothing else works for multidrug-resistant Gram-negative bacteria, clinicians turn to the cyclic lipopeptides polymyxin and colistin. Theses agents, however, are nephrotoxic. Interestingly, commercial preparations of these medicines are complex mixtures of closely related lipopeptides obtained from fermentation. In this issue, Jian Li and co-workers characterize for the first time in vitro, in vivo, and toxicity characteristics of the major components of these preparations.

Intrinsic resistance mechanisms make Gram-negative bacteria insensitive to many antibiotics. As such, there is widespread agreement that the holy grail of antibiotic discovery for these organisms is an understanding of the permeability barriers at work in these organsims. Helen Zgurskaya and colleagues summarize the state of the art in this context with a molecular and mechanistic treatment of the role of lipopolysaccharide, outer membrane proteins, and efflux pumps.

The Gram-negative resistance problem is thus a daunting one that stands to benefit greatly from the attention of imaginative investigators such as those who have contributed herein. I am very grateful to my colleagues who have contributed their time, ideas, and research findings to this effort. It is a strong sample of creative and unconventional approaches to the Gram-negative resistance problem, and it is very rewarding to see this issue come together. Indeed, it is an exciting time to be part of this field and fitting I think that the American Chemical Society has seen fit to provide a new platform—*ACS Infectious Diseases*— to share research findings and scholarship at the interface of chemistry and infectious disease.

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Notes

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