ACS Infectious Diseases

In This Issue

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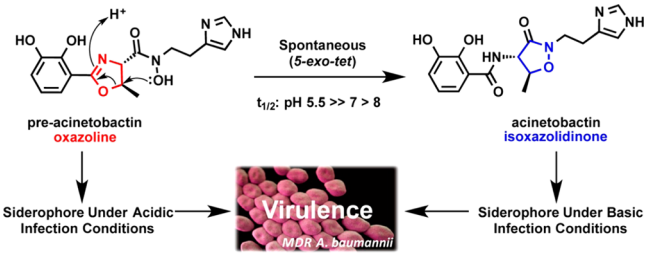
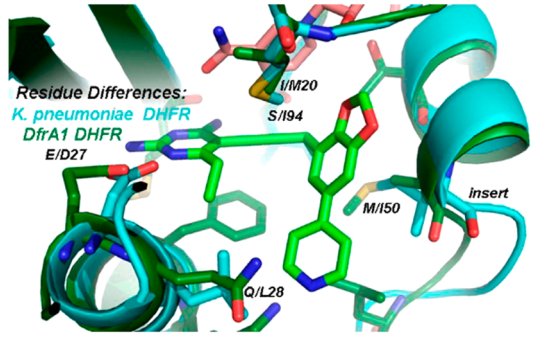
## FORAGING IRON




*Acinetobacter baumanii* has emerged as an important nosocomial pathogen capable of causing a multitude of infections including urinary tract infections, bacteremia, pneumonia, meningitis, and wound infections. Its versatility as a pathogen can be attributed to its array of virulence factors, which include its siderophores that act to scavenge iron from the host.

In the article featured on this month's cover Shapiro and Wencewicz (DOI: 10.1021/acsinfecdis.5b00145) define a biological advantage for the pH-dependent isomerization of *A. baumanii* siderphores. The authors demonstrate that through an energy-efficient siderophore-swapping mechanism, *A. baumannii* is able to expand the pH range for effective iron acquisition during infection. This pH-dependent siderophore swapping may facilitate transmission of infection from a site of infection with low pH to another site with a higher pH.

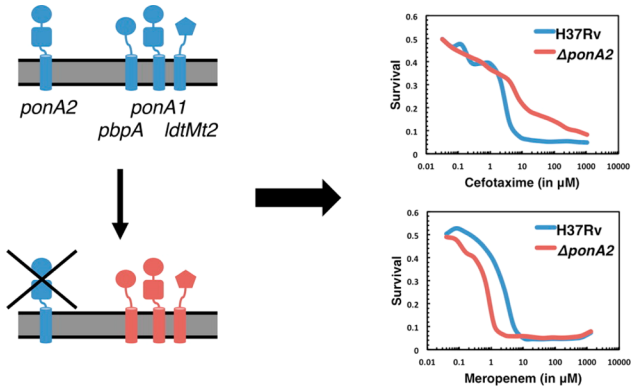
## TRIMETHOPRIM RESISTANCE BECOMES CRYSTAL CLEAR




The antifolate antibiotics trimethoprim and sulfamethoxazole have been used successfully to treat infections caused by *Klebsiella pneumoniae* and *Escherichia coli*; however, clinical resistance to these agents has been increasing. This resistance is often mediated by transposon-encoded enzymes that confer resistance not only to trimethoprim but also to other classes of antibiotics. In particular, DfrA1 is the most prevalent of these enzymes to confer trimethoprim resistance.

Here, Lombardo et al. (DOI: 10.1021/acsinfecdis.5b00129) demonstrate that propargyl-linked antifolates are effective inhibitors of the transposon-encoded DfrA1 dihydrofolate reductase (DHFR) in addition to the wild-type DHFR in *K. pneumoniae* and *E. coli*. Additionally, the authors report two high-resolution crystal structures of DfrA1 DHFR bound to two of these propargyl-linked antifolates. The findings presented here serve as a critical starting point for tackling the problem of anti-folate design for both wild-type and trimethoprim-resistant strains.

## OLD DRUGS, DIFFERENT BUGS




*Mycobacterium tuberculosis* poses an enormous burden to public health. An estimated one-third of the world's population harbors latent *M. tuberculosis* with 95% of cases occurring in the developing world. Despite these devastating numbers, infections caused by *M. tuberculosis* are curable with proper antibiotic treatment. Unfortunately, treatment regimens are complicated, requiring administration of multiple antibiotics over a long period of time, and multidrug resistance has become an increasing problem. Recently, the use of $\beta$-lactam antibiotics, which have not previously been used for *M. tuberculosis* infections, has been investigated. Despite the success of $\beta$-lactams for other bacterial infections, little is known about the molecular mechanism leading to cell death in *M. tuberculosis*.

In this issue Wivagg et al. (DOI: 10.1021/acsinfecdis.5b00119) present work that extends our understanding of the molecular mechanism of action of $\beta$-lactams in *M. tuberculosis*. The authors identify a novel mechanism of $\beta$-lactam resistance in *M. tuberculosis* and a loss of function mutations in ponA2 and demonstrate that ponA2 mutants resistant to the cephalosporin subclass of $\beta$-lactams show different responses to the carbapenem subclass. As new drugs can take decades to develop, this work addresses the need to better understand the molecular mechanisms of currently available drugs.

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