➡ ANTIBACTERIALS

Vive la difference!

High-throughput screens to identify novel classes of antibacterials have tended to focus on genomic targets that share little or no similarity to human proteins in order to attain bacterial selectivity. However, this approach has had limited success so far, perhaps in part because it limits the ability to apply the extensive drug discovery experience with compound classes commonly screened against major human target families, such as kinases. In a recent paper, Stover and colleagues highlight the possibilities afforded by such compound classes by identifying pyridopyrimidines that are selective for the ATP-binding site of bacterial biotin carboxylase (BC). These agents might represent a source of antibacterial leads with a previously undescribed mechanism of action.

Using a whole-cell screen of a library of 1.6 million compounds for antibacterial activity, the authors

found that a series of pyridopyrimidines — originally derived from a drug design programme targeting eukaryotic protein kinases — were also effective against a subset of gram-negative bacteria. They showed using genetic and biochemical tools that these compounds target the ATP-binding site of bacterial BC, an enzyme that catalyses the first step in fatty acid biosynthesis. Although this site is structurally similar to the ATP-binding site of eukaryotic protein kinases, crystallographic studies indicated that they are sufficiently different to allow the development of selective antibacterial agents.

In particular, two of the compounds examined displayed excellent selectivity for bacterial BC over 30 eukaryotic protein kinases. One of the compounds exhibited reasonable pharmacokinetic properties in both rats and mice, and was further tested in murine models of tissue-localized and systemic *Haemophilus influenzae* infection. In both cases, oral dosing (200 mg per kg) resulted in a significant reduction of bacterial levels and no overt toxicity.

Administering this pyridopyrimidine in combination with other antibacterial agents, including those that target gram-positive pathogens, improved its activity against *H. influenzae*, indicating that this could be a useful strategy to broaden the antibacterial spectrum of some compounds and minimize the emergence of resistance. Interestingly,

synergistic activity with triclosan, which also inhibits fatty acid biosynthesis, was observed, further validating this pathway as an antibacterial target.

Finally, the authors examined mutations in the *Escherichia coli* BC gene that decrease pyridopyrimidine binding affinity and could thus lead to resistance. The effects of one such mutation (I437T) could be overcome by a structurally related pyridopyrimidine. Similarly, structural differences between the BC active site in gram-positive and gram-negative bacteria offer the possibility of using structure-based drug design not only to overcome resistance mechanisms, but also to broaden the spectrum of this class of compounds.

In summary, this study supports the pursuit of antibacterials from leads discovered in eukaryotic drug discovery programmes. Despite sharing structurally similar binding sites, it suggests that it is possible — and potentially easier, given the more extensive drug discovery experience with common human drug-target families —to design potent inhibitors that are selective for bacterial targets.

Monica Hoyos Flight

ORIGINAL RESEARCH PAPER Millar, J. R. *et al.* A class of selective antibacterials derived from a protein kinase inhibitor pharmacophore. *Proc. Natl Acad. Sci. USA* 22 Jan 2009 (doi:10.1073/pnas.0811275106)
FURTHER READING Payne, D. J. *et al.* Drugs for bad bugs: confronting the challenges of antibacterial discovery. *Nature Rev. Drug Discov.* **6**, 29–40 (2007)