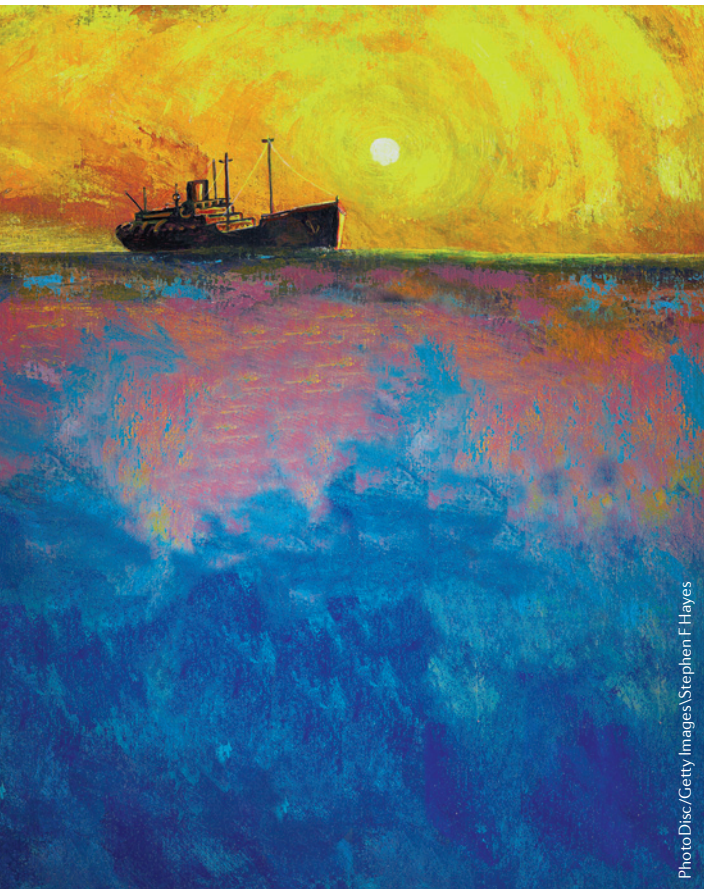
ANTIBACTERIAL DRUGS

New antibiotics on the horizon?



Staphylococcus aureus is responsible for a variety of diseases ranging from skin and soft-tissue infections to pneumonia and sepsis. The increasing prevalence of multidrug-resistant bacterial strains and the lack of new classes of antibiotics have together made the effective treatment of such infections challenging. Now, two recent papers report novel strategies for combating this prevalent bacterial pathogen.

S. aureus secretes several factors that are toxic to human immune cells, including several pore-forming leukotoxins. However, the specific range of immune cells that are targeted by such leukotoxins and the host factors responsible for their selectivity remain unclear. Torres and colleagues therefore set out to identify potential leukotoxin receptors, with the aim of identifying novel therapeutic targets.

The authors first purified recombinant leukotoxins and assessed their ability to kill a set of human cell lines. They discovered that the leukotoxin LukED only displayed cytotoxicity to human T cell lines ectopically expressing CC chemokine receptor 5 (CCR5; a co-receptor required for HIV infection). Further *in vitro* experiments showed that LukED interacted directly with CCR5 and specifically targeted human T cells, macrophages and dendritic cells.

Next, they assessed whether LukED-mediated cell killing could be prevented by blocking the CCR5–toxin interaction. They found that CCR5 antagonists, including the clinically approved HIV therapeutic maraviroc, blocked LukED-mediated pore formation and killing of $CCR5^+$ T cells. Furthermore, *S. aureus*-mediated $CCR5^+$ T cell cytotoxicity was dependent on LukED and completely blocked by maraviroc.

Finally, they examined the contribution of CCR5 to *S. aureus* pathogenesis *in vivo*. *S. aureus*-elicited lymphocytes and macrophages from wild-type mice were highly susceptible to purified LukED, whereas those from $Ccr5^{-/-}$ mice were markedly resistant. Moreover, $Ccr5^{-/-}$ mice were largely resistant to lethal *S. aureus* infections, further supporting the potential of CCR5 blockade as a novel antibacterial strategy.

Meanwhile, Oldfield and colleagues set out to inhibit the early steps of *S. aureus* cell wall peptidoglycan biosynthesis. Specifically, they targeted an enzyme in the isoprenoid biosynthesis pathway — undecaprenyl pyrophosphate synthase (UppS), which catalyses the formation of undecaprenyl pyrophosphate. UppS inhibitors are predicted to synergize with existing cell wall biosynthesis inhibitors (such as vancomycin and methicillin), which act in the later stages of peptidoglycan formation, potentially reducing toxicity or restoring drug sensitivity.

Using *in silico* high-throughput screening and hit development, the authors produced a small series of benzoic, phosphonic and diketo acids, as well as a bisamidine and a bisamine, that were active against UppS. Analysis of the X-ray crystal structures of the inhibitors bound to UppS revealed them to bind to one or more of four previously identified UppS inhibitor-binding sites, with the most potent leads binding to a site located outside the catalytic centre. The most potent inhibitor — the biphenyl bisamidine — potently synergized with methicillin to inhibit *S. aureus* growth *in vitro*. Importantly, the biphenyl bisamidine was also active *in vivo*, protecting mice from a lethal *S. aureus* strain when given post-infection.

In summary, these studies identify novel therapeutic targets and compounds that may lead to the development of new approaches for treating and preventing resistant *S. aureus* infections.

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ORIGINAL RESEARCH PAPERS Alonzo, F. *et al.* CCR5 is a receptor for *Staphylococcus aureus* leukotoxin ED. *Nature* **493**, 51–55 (2013) | Zhu, W. *et al.* Antibacterial drug leads targeting isoprenoid biosynthesis. *Proc. Natl Acad. Sci. USA* **110**, 123–128 (2013)

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