ANTIMICROBIALS

New drugs for the antibacterial pipeline?

> these studies highlight the importance of investing in discovery platforms

Over the past 50 years, the rate of antibiotic discovery has plummeted while the incidence of resistance has soared. The decreasing effectiveness of antibiotics is one of the greatest health threats of our time and in response, the WHO has published a list of bacteria for which new antibiotics are urgently needed. Now, two recent studies report new compounds that could be useful in combatting antibiotic resistance.

Imai, Meyer et al. discovered a new antibiotic that selectively kills Gram-negative pathogens. In their search, the authors reasoned that useful compounds might be found in symbionts that have a need to produce antibiotics (for example, to fend off invasive species) that are non-toxic to their host. The authors focused on symbionts of entomopathogenic nematodes and screened a library of *Photorhabdus* and *Xenorhabdus* strains for the ability to inhibit *Escherichia coli* growth in vitro. A concentrated extract of *Photorhabdus khanii* produced a zone of inhibition, and using high performance liquid chromatography, the active fraction of the extract was identified. Subsequent mass spectrometric fragmentation and NMR elucidated the structure of the active compound, named darobactin.

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Next, the authors sequenced the *P. khanii* genome and found that darobactin production is encoded by a silent biosynthetic gene cluster (*dar* operon) and is ribosomally synthesized.

Darobactin was found to have activity against a range of Gram-negative pathogens (for example, *E. coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*), including polymyxin-resistant, extended spectrum β-lactamase-producing or carbapenem-resistant clinical isolates, in vitro and in a mouse model. By contrast, low activity was detected against Gram-positive bacteria.

To identify the target of darobactin, the authors performed evolution experiments with *E. coli*, which led to the isolation of darobactin-resistant mutants. All mutations mapped to BamA, an essential chaperone of the β-barrel assembly machinery (BAM) complex, which catalyses the folding and insertion of β-barrel outer membrane proteins. Darobactin was found to interact directly with BamA and inhibit BAM activity, and NMR studies suggest that darobactin stabilizes the BAM complex in a gate-closed conformation, preventing the assembly of a functional outer membrane.

In a different study, El-Halfawy et al. discovered an antivirulence compound that reverses β-lactam resistance in methicillin-resistant *Staphylococcus aureus* (MRSA). Antivirulence compounds are a promising alternative or adjuvant to antibiotics as they do not impose strong selective pressures that lead to the evolution of resistance. The authors performed a high-throughput cell-based screen of ~45,000 compounds in *S. aureus*, with the aim of identifying molecules that both attenuate virulence and reverse antibiotic resistance; the screen was designed to identify compounds that target cell envelope virulence factors and synergize with the β-lactam cefuroxime. The authors identified a potent compound (MAC-545496) that reversed resistance to various β-lactam antibiotics (that is, decreased the minimum inhibitory concentration), including penicillins, cephalosporins and the carbapenem imipenem. MAC-545496 was found to target GraR, a regulator of the cell envelope stress response and an important virulence factor and determinant of antibiotic resistance. MAC-545496 could inhibit virulence alone in *Galleria mellonella* larvae infected with *S. aureus* and was found to inhibit biofilm formation and reduce survival of *S. aureus* within macrophages, suggesting that it could be useful in treating MRSA infections.

Together, these studies highlight the importance of investing in discovery platforms, as they can uncover new sources of urgently needed antibacterial drugs.

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ORIGINAL ARTICLES Imai, Y., Meyer, K. J. et al. A new antibiotic selectively kills Gram-negative pathogens. *Nature* https://doi.org/10.1038/s41586-019-1791-1 (2019) | El-Halfawy, O. M. et al. Discovery of an antivirulence compound that reverses β-lactam resistance in MRSA. *Nat. Chem. Biol.* https://doi.org/10.1038/s41589-019-0401-8 (2019)

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