ANTIMICROBIALS

Z-ring Achilles' heel for MRSA

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Antibiotic-resistant bacteria are an increasing threat to public health because the rise of resistance has resulted in a dwindling pool of effective antibiotics. New drugs are urgently needed to fight meticillin resistant *Staphylococcus aureus* (MRSA) and other resistant bacterial pathogens. Publishing in *Science*, Haydon and colleagues describe a new compound that kills MRSA and other bacteria by targeting the essential cell division protein FtsZ.

By screening more than 500 derivatives of 3-methoxybenzamide, a known inhibitor of FtsZ, Haydon *et al.* identified PC190723, which kills MRSA, together with many species of *Staphylococcus* and *Bacillus subtilis*. *Streptococcus* species, Gram-negative bacteria and eukaryotic cells were unaffected by PC190723. Sequence analyses indicated that bacteria that are not killed by PC190723 have replaced valine 307 in FtsZ with a bulky histidine or arginine residue. This probably prevents the drug from accessing its putative binding site.

Importantly, mice that had been given a lethal intraperitoneal dose of *S. aureus* were protected by a single injection of PC190723 to the same level as a standard vancomycin treatment. The authors used an *in vitro* assay to show that PC190723 inhibits the GTPase activity of purified FtsZ. In *B. subtilis* cells, treatment with PC190723 caused FtsZ, which usually polymerizes to form a ring that encircles the mid-point of the cell, to aggregate into amorphous clumps that were dispersed throughout the cell. Treated *B. subtilis* failed to divide but continued to grow into long tubules instead of individual rod-shaped cells. PC190723 also inhibited cell division in *S. aureus*, resulting in the formation of enlarged cells, and ultimately killed the cells. Spontaneous PC190723-resistant *S. aureus* mutants arose at a rate of 2×10^{-8}; these carried mutations in the *ftsZ* gene, providing further proof that this drug targets FtsZ.

Despite the potential for resistance to evolve, PC190723 is a promising starting point for the future development of anti-staphylococcal drugs, and the authors propose that it could be useful as part of a combination drug regime.

Christiaan van Ooij

ORIGINAL RESEARCH PAPER Haydon, D. J. *et al.* An inhibitor of FtsZ with potent and selective anti-staphylococcal activity. *Science* **321**, 1673–1675 (2008)