ANTI-INFECTIVES

# New antibiotic on the horizon?

**DOI:**
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**URLs**

**Entrez Genome Project:** http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genomeprj

***Staphylococcus aureus*** http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genomeprj&cmd=Retrieve&dopt=Overview&list_uids=12304

**UniProtKB:** http://ca.expasy.org/sprot

**FabF** http://www.expasy.org/uniprot/Q5HHA1

Returning to investigating natural products as a source of antimicrobials could hold the key to tackling multi-drug resistant bacteria. Writing in *Nature*, Wang and colleagues describe the isolation and characterization of platensimycin, a small molecule that represents a new class of antibiotic and that has broad, potent activity against Gram-positive pathogens.

A pathway that has yet to be fully exploited for antibiotic drug discovery is fatty-acid biosynthesis. A key enzyme involved in this pathway is the β-ketoacyl-acyl carrier protein synthase FabF. To increase the chance of identifying a compound that selectively targets FabF, the authors engineered the Gram-positive pathogen *Staphylococcus aureus* to express antisense RNA against FabF. This renders the bacteria more sensitive to inhibitors of this enzyme, and so comparison of growth inhibition of the wild-type strain with that of the antisense strain enables the identification of genuine selective inhibitors of the FabF target present in the fermentation samples. This screen identified a potent antibiotic, platensimycin, which could otherwise have been overlooked in a conventional screening assay.

Platensimycin was found to have broad-spectrum activity against Gram-positive bacteria in *in vitro* assays and was able to eradicate systemic *S. aureus* infection in mice. Importantly, platensimycin shows no cross-resistance with other classes of antibiotics, and is active against bacterial infections that are resistant to commercially available drugs, such as meticillin-resistant *S. aureus* and vancomycin-resistant enterococci.

To verify that the mode of action of platensimycin was the selective targeting of FabF, the authors used a radioactive platensimycin derivative. Initially, the binding affinities of the derivative for FabF were much lower than anticipated, which led the authors to propose that platensimycin was targeting the transiently formed (and so difficult to detect) acyl-FabF intermediate. Indeed, preparation of a stable acyl–enzyme complex to mimic the transient form increased the binding signal and confirmed the authors' hypothesis that platensimycin only binds to the acyl intermediate.

The transient nature of acyl-FabF also made attempts to obtain a crystal structure of platensimycin bound to its target challenging. However, by substituting the cysteine residue in the active site of the enzyme with glutamine, the side chain of which is thought to mimic a bound fatty acid, the authors produced a stable FabF variant–platensimycin complex that was amenable to crystallographic analysis. From this they were able to determine that platensimycin targets the malonate-binding site of FabF, thereby blocking fatty-acid biosynthesis, and that the formation of the acyl-FabF intermediate opens up the active site of FabF, a conformational change that is essential for platensimycin binding.

In recent decades, there has been a dearth of new classes of antibiotics. Platensimycin is currently the most potent inhibitor of FabF, as well as being the only inhibitor of this enzyme that has broad-spectrum activity. Fatty-acid biosynthesis is so far an under-targeted pathway, and so it has considerable potential for drug development. On the basis of these data, and with structural information in hand, platensimycin looks to be a promising first step towards a new first-in-class antibacterial drug.

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**ORIGINAL RESEARCH PAPER** Wang, J. *et al.* Platensimycin is a selective FabF inhibitor with potent antibiotic properties. *Nature* **441**, 358–361 (2006)

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