An ‘invincible’ antibiotic that is bound to be defeated

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The following paper was published as recently as yesterday, but already caused a bit of a stir on social media. Let's see why.

A new antibiotic kills pathogens without detectable resistance

Losee L. Ling et al. http://dx.doi.org/10.1038/nature14098 Nature

The isolation and characterisation of the gram-positive antibiotic teixobactin performed by the authors has been conducted with the highest standards, and uses complementary methods to provide strong evidence for their claims. Personally, I've found the combination of next generation sequencing and metabolic complementation analysis particularly enjoyable and a good reminder that more than 'new' vs 'old' techniques, it's only a matter of which are the most relevant ones for any given biological question.

The reported potency and MIC values for the antibiotic suggest teixobactin could play an important role in fighting bacterial virulence, e.g. for MRSA. Bacterial growth is inhibited (by inducing cell lysis) both in pure suspensions and in animal models, significantly increasing survival rates. The proposed mechanism of action indicates peptidoglycan biosynthesis is the target, and that teixobactin most likely acts by masking/mimicking lipid substrates, not by inhibiting any biosynthetic enzyme. This mechanism explains the broad spectrum of teixobactin and its efficiency.

The generality of its action mechanism made the authors argue that teixobactin is very unlikely to generate resistance: no one enzyme can be mutated (as teixobactin does not act on one), its target is an essential component in gram-positive bacteria (and major biosynthetic changes would be required to replace it), not even the host as a defence mechanisms (besides passively inhibiting diffusion inside the cell, being a gram-negative). And this is where the controversy lies. Even though the authors carefully mention ‘no detectable resistance’ in the title, and mention the potential of gene transfer in the discussion, assuming that nature (and bacteria in particular) will not find a way around a new antibiotic goes against everything we know. The 'long evolution' experiment the authors perform on S. aureus (27 days) is dwarfed by the tens-of-thousands the likes of Richard Lenski, David Liu and others got us used to. In these reports, it is shown that even core metabolic processes (as growth on citrate) can be brought about if enough time to cope with a new selective pressure is given to a large enough population.

Although the efficacy and elegance of teixobactin is out of question, and this paper is a beautiful example of how top class research is performed, part of it read as if there could be an 'ultimate compound' in biology that evolution cannot deal with. However, it is not difficult to imagine scenarios in which internalisation could be inhibited (by permeability changes or efflux pumps), binding to its target prevented (e.g. by the action of a trimming enzyme so common in NRPS pathways) or teixobactin sequestered entirely (by a protein/metabolite with higher affinity that its target), to mention a few.

In conclusion, I believe the 'ultimate weapon' is not the most relevant point this paper makes, but is the
one that will be criticised the most.

ABOUT @P.GL

My interests range from the understanding of natural processes at molecular level to the use of biochemical approaches for applications in Biotech and Synthetic Biology. Besides research, I developed a strong interest in scientific publishing and am a strong supporter of open access models and new publication formats.