Uncovering the tricks of game changer antibiotic teixobactin

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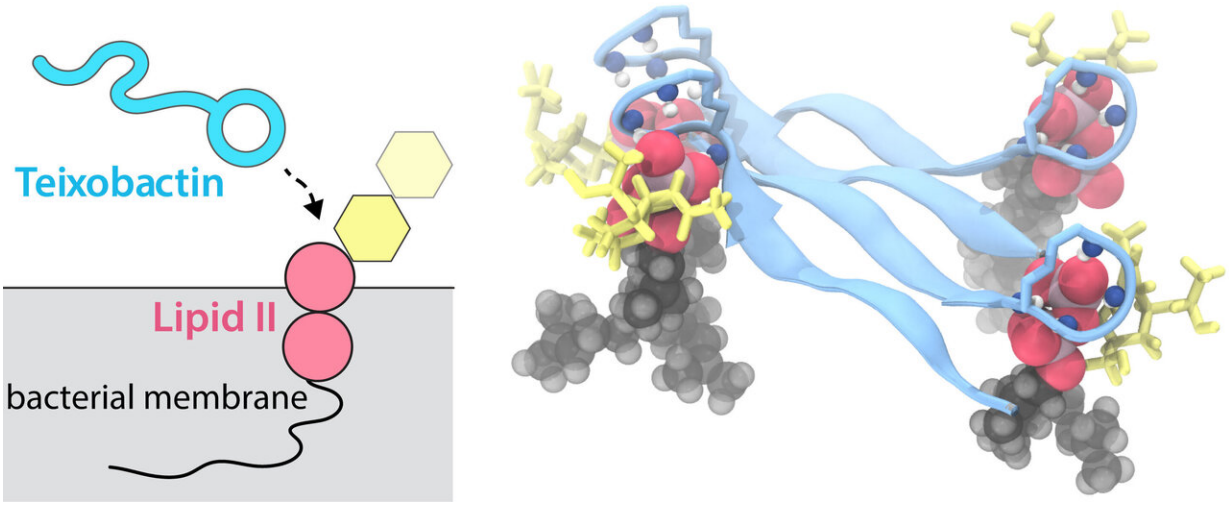


Teixobactin targets the essential cell wall-precursors Lipid II in the bacterial plasma-membrane. The high-resolution structure shows how teixobactins forms sticky fibres that effectively capture Lipid II, thereby killing the bacterium. Credit: Utrecht University

Utrecht scientists have discovered how the powerful antibiotic teixobactin kills bacteria. Heralded as a breakthrough drug, the discovery of teixobactin marked a milestone for combating drug-resistant superbugs. However, the way teixobactin binds to its target was hitherto unknown. An international group, led by Dr. Markus Weingarth of Utrecht University, presents the structure of teixobactin 5 June in *Nature*

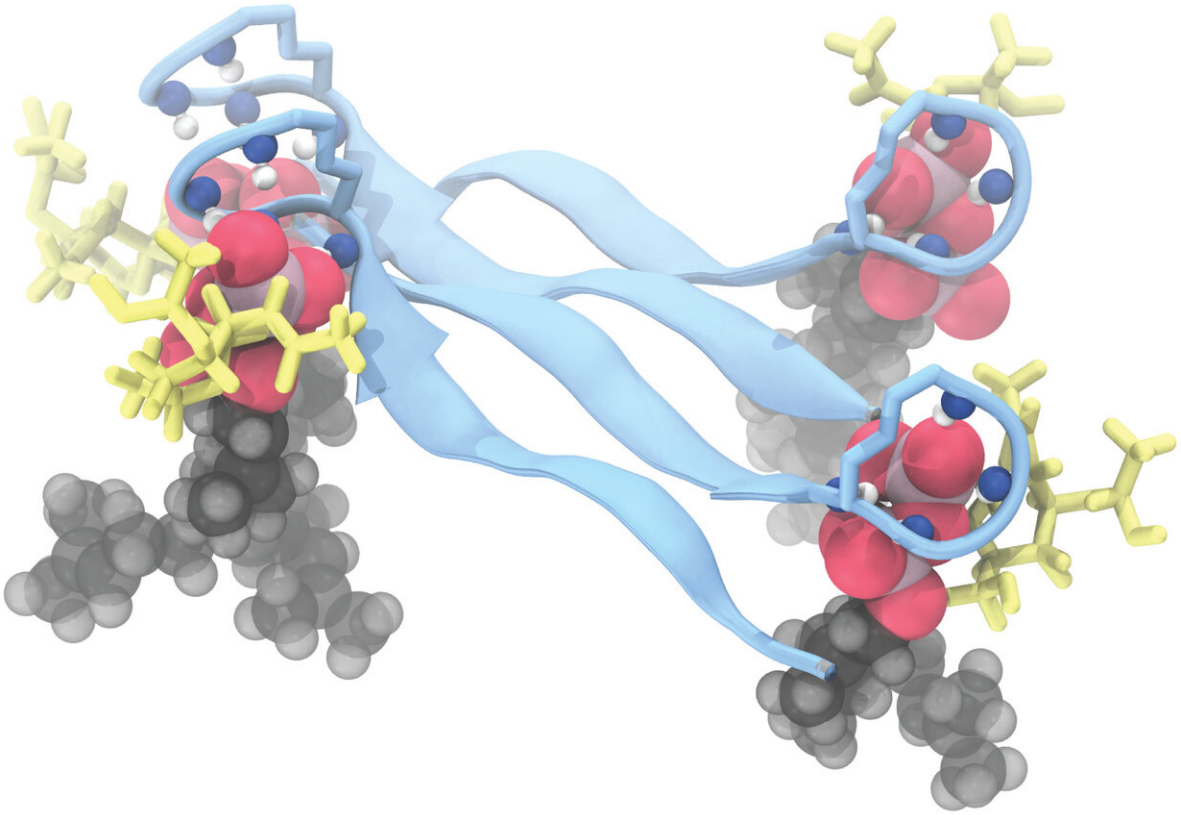
Communications.

Teixobactin is a small natural peptide produced by bacteria that live in dirt. It kills pathogenic bacteria without detectable resistance. Notwithstanding its high potential, teixobactin requires improvements due to its prohibitively high synthesis cost and unfavourable solubility. Yet, insufficient knowledge on its binding mode impedes the hunt for superior analogues.

Researchers at Utrecht University used solid-state NMR, which works like an ultra-powerful microscope, to resolve the mode of action of teixobactins directly in native bacterial cell membranes. For the first time, the researchers succeeded to solve the structure of teixobactin bound to its target Lipid II, a tiny yet essential molecule on the membrane-surface of bacteria. And they reveal how teixobactins recognize a broad spectrum of targets, which is essential to kill a broad spectrum of bacteria.

Unlock medical potential

Surprisingly, they found that teixobactin also forms large, sticky networks on the cell surface that soak up Lipid II like sponges, eventually killing the bacterium. The target molecule Lipid II, known as the Achilles' heel of bacteria, is effectively captured in the dense teixobactin meshwork. "This discovery comes as a surprise, because it was previously thought that the direct binding to Lipid II is enough to kill bacteria," says last author Markus Weingarth of Utrecht University, who specialises in understanding the mode of action of antibiotics. "Curiously, we show that the direct binding to Lipid II is relatively weak if membranes are negatively charged, which is the case for almost all bacterial cell membranes."



High-Resolution structure of the teixobactin fibre (in blue) that captures the essential Lipid II molecule on the membrane surface, thereby killing the bacterium. Credit: Utrecht University

These new findings provide critical cues to synthetically improve teixobactin, which is necessary to unlock its medical potential. "Teixobactin could be one of our sharpest weapons against pathogens such as M. tuberculosis that alone kills more than a million of people every year," explains Dr. Markus Weingarth. "Now, thanks to our study, we understand much better how teixobactin kills bacteria, and we eventually know the structure of the complex between teixobactin and its target Lipid II. We expect that this structure will enable us and researchers worldwide to design even more powerful antibiotics."

More information: Mode of action of teixobactins in cellular membranes. *Nature Communications*, 5 June 2020. DOI: 10.1038/s41467-020-16600-2

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