Chemists develop a new class of antibiotics to fight resistant bacteria

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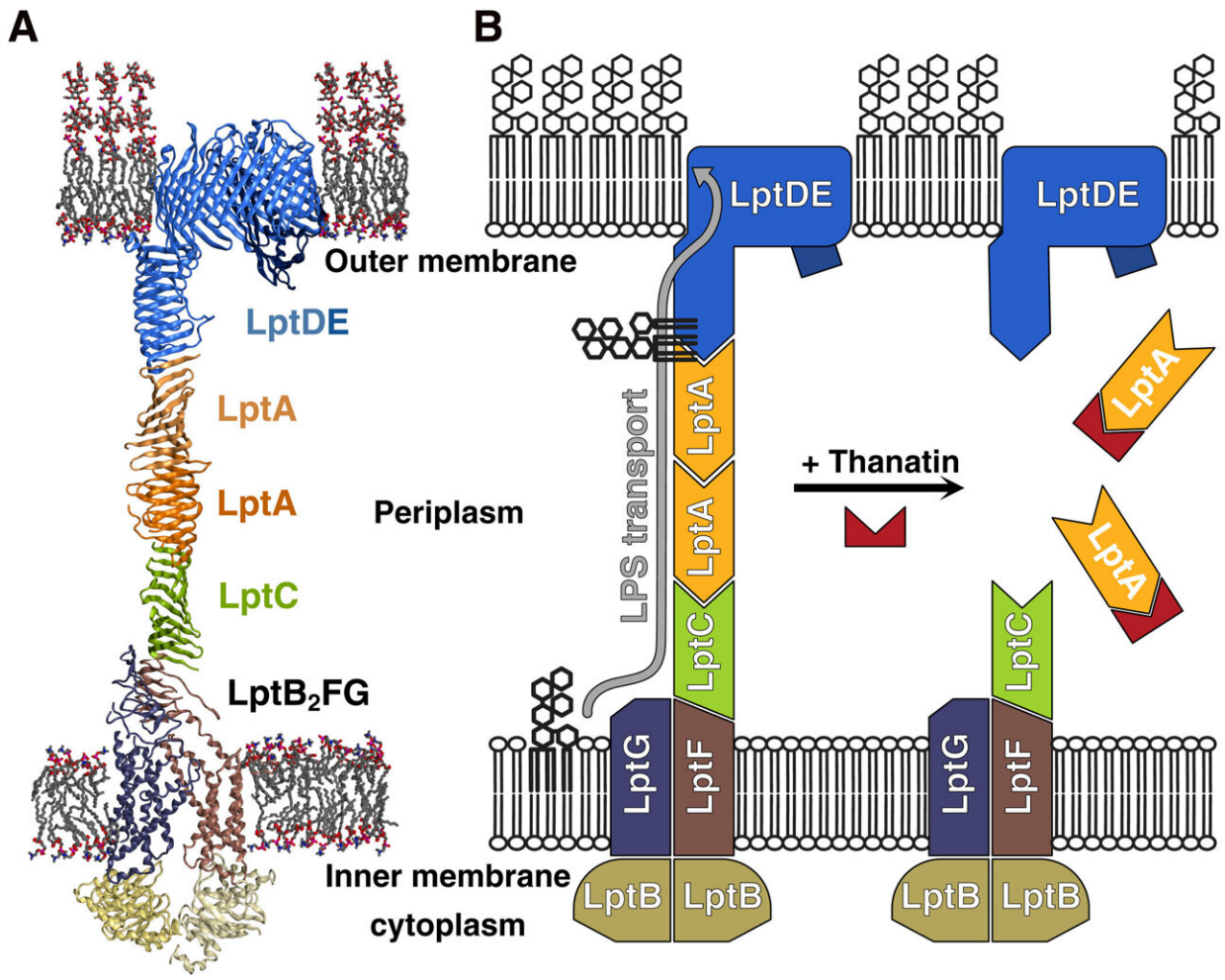

Structural model of the Lpt machinery.(**A**) Protein assembly of the Lpt in Gram-negative bacteria. (**B**) Schematic representation of the postulated mode of action based on this work: Thanatin inhibits the LptA-LptA and LptC-LptA protein-protein interactions and disassembles the Lpt periplasmic protein bridge. Note that two LptA molecules are depicted although the exact number is unknown.

Credit: *Science Advances* (2023). DOI: 10.1126/sciadv.adg3683

Health professionals are in urgent need of new antibiotics to tackle resistant bacteria. Researchers at the University of Zurich and the company Spexis have now modified the chemical structure of naturally occurring peptides to develop antimicrobial molecules that bind to novel targets in the bacteria's metabolism.

Each year, more than five million people worldwide die as a result of bacteria that are resistant to most common antibiotics. New antibiotics are urgently needed to ensure that bacterial infections in patients can still be treated successfully. "Unfortunately, the development pipeline for new antibiotics is fairly empty," says chemist Oliver Zerbe, head of the NMR facilities at the University of Zurich. "It's been more than 50 years since the last antibiotics against previously unused target molecules were approved."

In a study recently published in *Science Advances*, Zerbe now discusses the development of a highly effective class of antibiotics that fight Gram-negative bacteria in a novel way. The WHO classifies this group of bacteria as extremely dangerous. The group, whose resistance is particularly high due to their double cell membrane, includes carbapenem-resistant enterobacteria, for example. Besides the UZH team, researchers from the pharmaceutical company Spexis AG were also involved in the study.

Natural peptide chemically optimized

The starting point for the researchers' study was a naturally occurring peptide called thanatin, which insects use to fend off infections. Thanatin disrupts an important lipopolysaccharide transport bridge

between the outer and inner membrane of Gram-negative bacteria, as revealed a few years ago in a study by now retired UZH professor John Robinson.

As a result, these metabolites build up inside the cells, and the bacteria perish. However, thanatin isn't suitable for use as an antibiotic drug, among other things due to its low effectiveness and because bacteria quickly become resistant to it.

The researchers therefore modified the chemical structure of thanatin to enhance the peptide's characteristics. "To do this, structural analyses were essential," says Zerbe. His team synthetically assembled the various components of the bacterial transport bridge and then used nuclear magnetic resonance (NMR) to visualize where and how thanatin binds to and disrupts the transport bridge.

Using this information, researchers from Spexis AG planned the chemical modifications that were necessary to boost the peptide's antibacterial effects. Further mutations were made to increase the molecule's stability, among other things.

Effective, safe and immune to resistance

The synthetic peptides were then tested in mice with bacterial infections—and yielded outstanding results. "The novel antibiotics proved very effective, especially for treating lung infections," says Zerbe. "They are also highly effective against carbapenem-resistant enterobacteria, where most other antibiotics fail."

In addition, the newly developed peptides aren't toxic or harmful to the kidneys, and they also proved stable in the blood over a longer period—all of which are properties that are required for gaining approval as a drug. However, further preclinical studies are needed

before the first tests in humans can begin.

When choosing the most promising peptides for their study, the researchers made sure that they would also be effective against bacteria that have already developed resistance to thanatin. "We're confident this will significantly slow down the development of antibacterial resistance," says Zerbe. "We now have the prospect of a new class of antibiotics becoming available that is also effective against resistant bacteria."

More information: Matthias Schuster et al, Peptidomimetic antibiotics disrupt the lipopolysaccharide transport bridge of drug-resistant Enterobacteriaceae, *Science Advances* (2023). DOI: 10.1126/sciadv.adg3683

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