How to make an old antibiotic 100 times more potent

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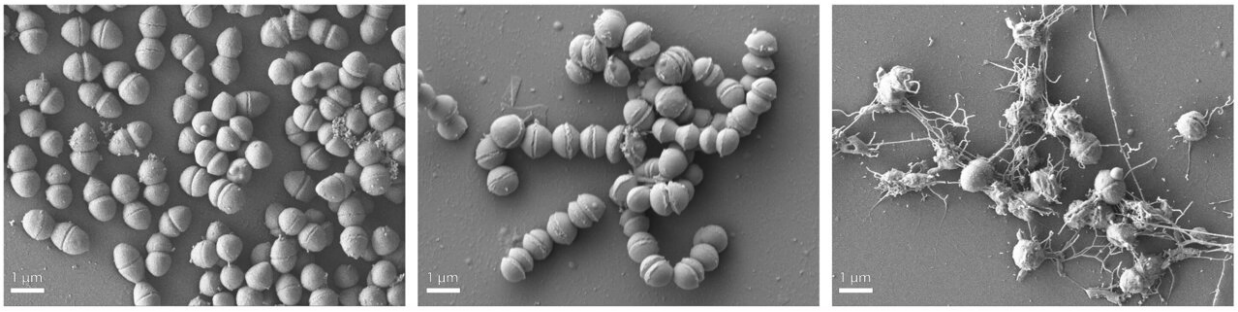

Scanning electron micrographs at 10,000× magnification of vancomycin resistant E. faecium E155 cells. Left: untreated cells, middle: cells treated with bacitracin, and right: cells treated with next-generation bacitracin. Credit: *Proceedings of the National Academy of Sciences* (2024). DOI: 10.1073/pnas.2315310121

Nathaniel Martin, Professor of biological chemistry, wondered what would happen if you took an antibiotic that has been known for 70 years and tried to improve it with the latest tools of modern chemistry. Turns out it can become up to a hundred times more potent and prevent the growth of some drug-resistant bacteria. His team's research is published in *PNAS*.

The name bacitracin might not sound familiar to everyone, but it's one of the most widely used antibiotics in the world. While not commonly used in the Netherlands, most households in North America have some form

of bacitracin in their medicine cabinet. It's usually applied topically. Think of cream for a skinned knee that might get infected.

Martin always had a specific interest in bacitracin because it 'attacks' bacteria in a unique way compared to other types of antibiotics. It attaches itself to a specific part of the membranes of bacteria, on the outer layer of the cell. By doing so, bacitracin prevents bacteria from building their cell wall and thereby inhibits their growth.

Something no one up until then had really understood

A few years ago, Martin read a paper that showed in detail how bacitracin binds to its bacterial target, and it caught his attention.

"I realized there was something really interesting about how bacitracin kills bacteria, something that no one up until then had really understood," he says. The clue was in the so-called crystal structure, which shows the precise arrangement of atoms of the antibiotic.

Put simply, the paper revealed that a bacitracin molecule has five points that make contact with the bacterial cell membrane. You could compare them to arms, reaching out and grabbing hold of the bacteria.

"It made me wonder as a chemist: what would happen if we could make these arms longer and more sticky? Would they be able to bind better with the cell and make the antibiotic more effective?"

Building an 'improved' version of bacitracin

Martin and his group of researchers at the Institute of Biology Leiden (IBL) went to work, using chemical synthesis to build an 'improved' version of bacitracin.

Keep in mind that antibiotics are typically produced by soil-dwelling microorganisms. That means they are not necessarily optimized for use as medicines in the human body. Some classes of antibiotics, such as the penicillins, have been synthetically improved by medicinal chemists over the years. But bacitracin is still used in its natural, unchanged form. That means its full potential might not yet have been unlocked.

That's precisely what Martin wanted to address with this study. And it turns out he was right. Synthetically enhancing bacitracin can improve it by a huge margin. "In many cases, we saw that our new version of bacitracin was ten to a hundred times more potent compared to the natural form," Martin says.

Preventing the growth of drug-resistant bacteria

The researchers made a second discovery while testing the drug on lab-grown bacteria. The enhanced bacitracin was also much more effective in preventing the growth of certain drug-resistant bacteria. Bacterial resistance is a growing problem that worries infectious disease doctors around the globe. The World Health Organization even calls it a 'top global public health threat.'

Martin's research was not done with the intention of creating a commercially viable product at this point.

"First, we needed to show it can be done." But now that step has been taken, he is already considering a follow-up study to find out how the enhanced bacitracin could be used to treat serious, drug-resistant infections.

More information: Ned P. Buijs et al, A classic antibiotic reimagined: Rationally designed bacitracin variants exhibit potent activity against vancomycin-resistant pathogens, *Proceedings of the National Academy of*

Sciences (2024). DOI: 10.1073/pnas.2315310121

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