

New antibiotic from microbial 'dark matter' could be powerful weapon against superbugs

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The newly discovered antibiotic Clovibactin uses an unusual cage-like binding motif to tightly wrap around special lipids in bacterial cell membranes. Credit: Markus Weingarth

A new powerful antibiotic, isolated from bacteria that could not be studied before, seems capable of combating harmful bacteria and even multi-resistant "superbugs." Named Clovibactin, the antibiotic appears to kill bacteria in an unusual way, making it more difficult for bacteria to

develop any resistance against it.

Researchers from Utrecht University, Bonn University (Germany), the German Center for Infection Research (DZIF), Northeastern University of Boston (U.S.), and the company NovoBiotic Pharmaceuticals (Cambridge, U.S.) now share the discovery of Clovibactin and its killing mechanism in the scientific journal *Cell*.

Urgent need for new antibiotics

Antimicrobial resistance is a major problem for [human health](#), and researchers worldwide are looking for new solutions. "We urgently need new antibiotics to combat [bacteria](#) that become increasingly resistant to most clinically used antibiotics," says Dr. Markus Weingarth, a researcher from the Chemistry Department of Utrecht University.

However, the discovery of new antibiotics is a challenge: few [new antibiotics](#) have been introduced into the clinics over the last decades, and they often resemble older, already known antibiotics.

"Clovibactin is different," says Weingarth. "Since Clovibactin was isolated from bacteria that could not be grown before, [pathogenic bacteria](#) have not seen such an antibiotic before and had no time to develop resistance."

Antibiotic from bacterial dark matter

Clovibactin was discovered by NovoBiotic Pharmaceuticals, a small U.S.-based early-stage company, and microbiologist Prof. Kim Lewis from Northeastern University, Boston. Earlier, they had developed a device that allowed them to grow "bacterial dark matter," which are so-called unculturable bacteria.

Intriguingly, 99% of all bacteria are "unculturable" and could not be grown in laboratories previously, hence they could not be mined for novel antibiotics. Using the new device called iCHip, the U.S. researchers discovered Clovibactin in a bacterium isolated from a sandy soil from North Carolina, *E. terrae* ssp. *Carolina*.

In the joint publication in *Cell*, NovoBiotic Pharmaceuticals shows that Clovibactin successfully attacks a broad spectrum of bacterial pathogens. It was also successfully used to treated mice infected with the superbug *Staphylococcus aureus*.

A broad target spectrum

Clovibactin appears to have an unusual killing mechanism. It targets not just one, but three different precursor molecules that are all essential for the construction of the cell wall, an envelope-like structure that surrounds bacteria. This was discovered by the group of Prof. Tanja Schneider from the University of Bonn in Germany, one of the paper's co-authors.

"The multi-target attack mechanism of Clovibactin blocks bacterial cell wall synthesis simultaneously at different positions. This improves the drug's activity and substantially increases its robustness to resistance development," says Schneider.

A cage-like structure

How exactly Clovibactin blocks the synthesis of the bacterial cell wall was unraveled by the team of Dr. Weingarth from Utrecht University. They used a special technique called solid-state [nuclear magnetic resonance](#) (NMR) to study Clovibactin's mechanism under similar conditions, such as in bacteria.

"Clovibactin wraps around the pyrophosphate like a tightly sitting glove. Like a cage that encloses its target," says Weingarh. This is what gives Clovibactin its name, which is derived from Greek word "Klouvi," which means cage.

The remarkable aspect of Clovibactin's mechanism is that it only binds to the immutable pyrophosphate that is common to cell wall precursors, but it ignores that variable sugar-peptide part of the targets. "As Clovibactin only binds to the immutable, conserved part of its targets, bacteria will have a much harder time developing any resistance against it. In fact, we did not observe any resistance to Clovibactin in our studies."

Fibrils capture the targets

Clovibactin can do even more. Upon binding the target molecules, it self-assembles into large fibrils on the surface of bacterial membranes. These fibrils are stable for a long time and thereby ensure that the target molecules remain sequestered for as long as necessary to kill bacteria.

"Since these fibrils only form on bacterial membranes and not on human membranes, they are presumably also the reason why Clovibactin selectively damages bacterial cells but is not toxic to human cells," says Weingarh. "Clovibactin hence has potential for the design of improved therapeutics that kill bacterial pathogens without resistance development."

More information: Markus Weingarh, An antibiotic from an uncultured bacterium binds to an immutable target, *Cell* (2023). [DOI: 10.1016/j.cell.2023.07.038](https://doi.org/10.1016/j.cell.2023.07.038).
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