Study sheds light on how antibiotic 'Velcro' kills bacteria

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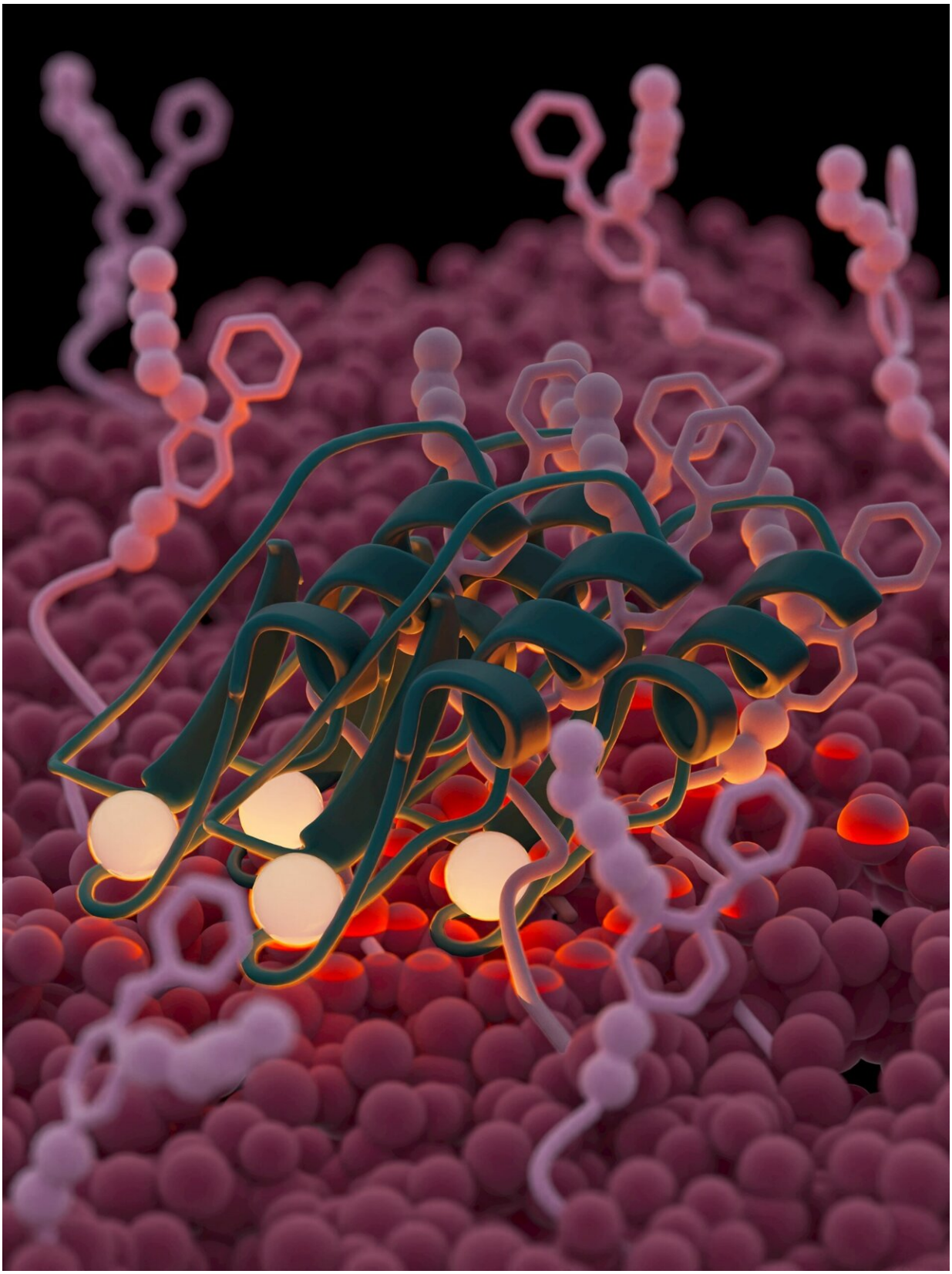


By assembling into large structures, the antibiotic plectasin latches onto its target on the bacterial cell surface. This is comparable to how both sides of Velcro form a bond. Credit: Gloria Fuentes

A small antibiotic called plectasin uses an innovative mechanism to kill bacteria. By assembling into large structures, plectasin latches onto its target on the bacterial cell surface, similar to how both sides of Velcro form a bond.

A research team, led by structural biologist Markus Weingarth and biochemist Eefjan Breukink at Utrecht University, mapped how the Velcro-structure is formed. Their discovery, published in *Nature Microbiology*, unveils a new approach that could have broad implications for the development of antibiotics to combat antimicrobial resistance.

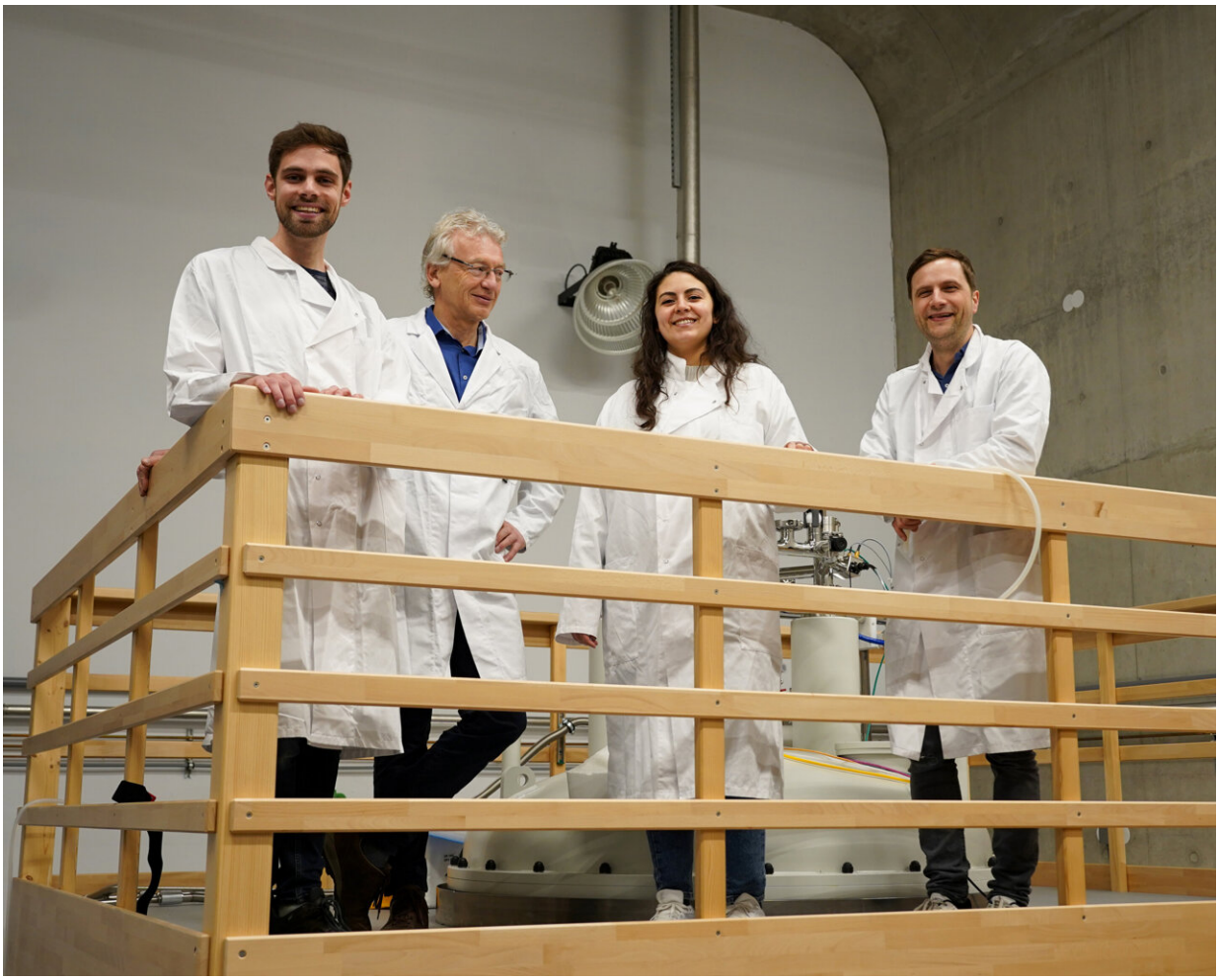
The research team investigated the workings of plectasin, an antibiotic derived from the fungus Pseudoplectania nigrella. The team employed advanced biophysical techniques, including solid-state NMR, and in collaboration with Wouter Roos from Groningen, atomic force microscopy.

Traditionally, antibiotics function by targeting specific molecules within bacterial cells. However, the mechanism behind plectasin's action was not fully understood until now. Previous studies suggested a conventional model where plectasin binds to a molecule called Lipid II, crucial for bacterial cell wall synthesis, akin to a key fitting into a lock.

The new study reveals a more intricate process. Plectasin doesn't just act like a key in a lock; instead, it forms dense structures on bacterial membranes containing Lipid II. These supramolecular complexes trap their target Lipid II, preventing it from escaping. Even if one Lipid II

breaks free from plectasin, it remains contained within the Velcro-structure, unable to escape.

Weingarth compares this structure to Velcro, where plectasin forms the microscopic hooks that attach to bacterial "loops." In normal Velcro, if one of the loops breaks free from its hook, it is still trapped by the entire structure. The same goes for bacteria trapped in the plectasin superstructure: They can break free from the plectasin's binding, but stay trapped in the superstructure. This prevents the bacteria from escaping and causing further infections.



Maik Derks, Eefjan Breukink, Shehrazade Miranda Jekhmane, and Markus Weingarth (from left to right). Credit: Utrecht University

Moreover, the researchers found that the presence of calcium ions further enhances plectasin's antibacterial activity. These ions coordinate with specific regions of plectasin, causing structural changes that significantly improve the antibacterial effectiveness. That ions play a critical part in the action of plectasin was discovered by Ph.D. students Shehrazade Miranda Jekhmane and Maik Derks, co-first authors of the study. They realized that plectasin samples had a peculiar color, which hinted at the presence of ions.

Markus Weingarth, the lead author of the study, expects that this finding could open new avenues for developing superior antibiotics.

"Plectasin is presumably not the ideal antibiotic candidate due to safety concerns. However, in our study, we show that the 'Velcro-mechanism' appears widely used among antibiotics, which was thus far ignored. Future drug design efforts hence not only need to focus on how to bind targets, but also how drugs can self-assemble efficiently. Thereby, our study closes a major knowledge gap which could have broad implications for the design of better drugs to combat the growing threat of antimicrobial resistance," he says.

More information: Host defense peptide plectasin targets bacterial cell wall precursor Lipid II by a calcium-sensitive supramolecular mechanism, *Nature Microbiology* (2024). DOI: 10.1038/s41564-024-01696-9

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