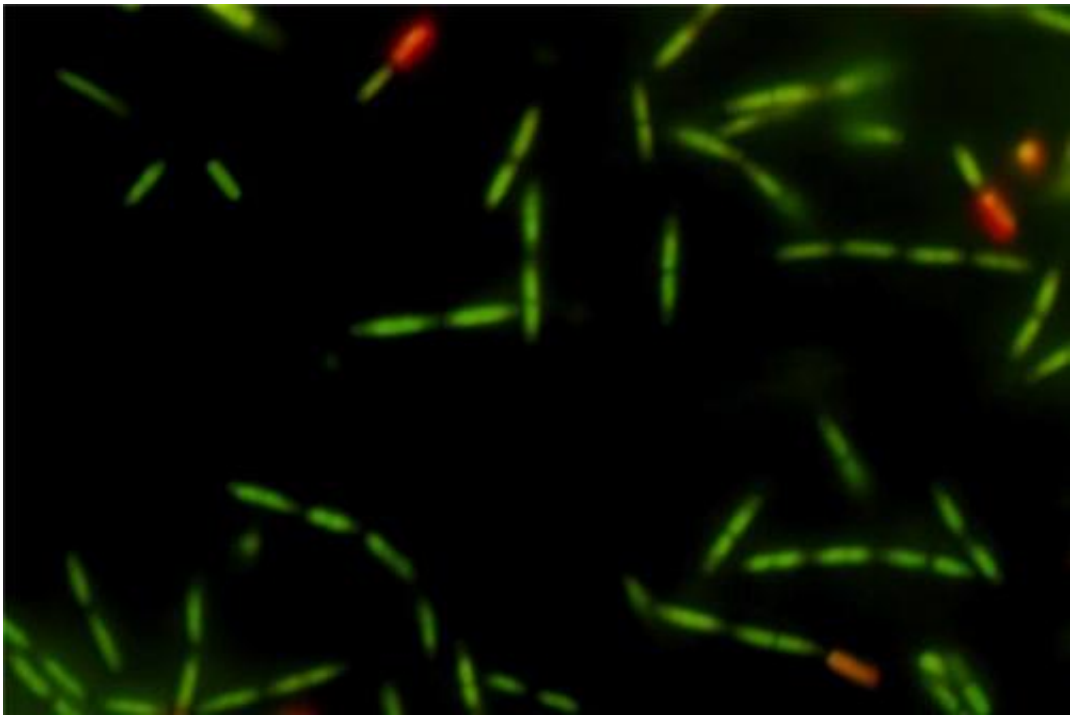
# Small peptides as potential antibiotics

March 25 2014



Bacillus subtilis. Credit: RUB/Michaela Wenzel

Small peptides attack bacteria in many different ways and may well become a new generation of antibiotics. Biologists at the Ruhr-Universität Bochum (RUB) have been researching how such peptides kill bacterial cells. "It is quite possible that, in ten years time, all of the currently marketed antibiotics will lose their power, because bacteria will have become resistant against all active agents," says Junior Professor Dr Julia Bandow. Consequently, it is high time to develop new antibacterial drugs.

Together with colleagues from Germany, Austria, and Canada, she reports on the peptide's mode of action in the journal *Proceedings of the National Academy of Sciences* (*PNAS*).

## Drug approval requires a deep understanding of the mechanism of action

The team of Julia Bandow, who heads the RUB's Junior Research Group Microbial Antibiotic Research, has been studying the MP196 peptide as a representative of a group of very small positively charged peptides that consist of some four to ten amino acids. Earlier studies had shown that MP196 is efficient against various bacteria, including particularly problematic multi-resistant pathogens that frequently cause sepsis. How MP196 kills bacteria remained unclear. However, in order for a new substance to be approved as a drug, its mechanism of action has to be fully understood.

## Peptide disrupts cell wall biosynthesis and cell respiration

The biologists have closed this gap. They showed that the MP196 peptide integrates into the bacterial cell membrane. In doing so, it delocalises proteins localised at the bacterial cell membrane that participate in vital processes. Two processes in particular are severely affected: MP196 disrupts the biosynthesis of the cell wall, i.e. of the outer envelope that encloses the cell membrane and provides physical stability. It also inhibits cell respiration and, consequently, the production of the energy-storing molecule ATP. This results in cellular energy deficiency, thus preventing the synthesis of macromolecules vital for bacterial growth.

## Developing resistances against MP196 may be

## particularly difficult

"By delocalising crucial membrane proteins, MP196 disrupts a number of cellular processes that take place at the membrane," says Julia Bandow. "As a result, the development of resistance against the peptide seems particularly difficult." The researchers are confident that MP196 can serve as a scaffold to develop drugs that attack certain classes of bacteria without damaging human cells. The interaction of MP196 with the cell membrane was dependent on the fatty acids present in the membrane. The membrane composition varies not only between human and bacterial cells, but also between different classes of bacteria.

## The project "Innovative Antibiotics from NRW"

This study was part of the project "Innovative Antibiotics from NRW" (InA) that was co-financed by the State of North Rhine-Westphalia and the European Union's European Regional Development Fund "Investing in your Future" within the framework of the "BIO.NRW.red" cluster. Together with partners from academia and industry, the RUB microbiologists and chemists also study the antibiotic potential of organometallic compounds (rubin.rub.de/en/international- … /bacteria-under-fire).

**More information:** Michaela Wenzel, Alina Iulia Chiriac, Andreas Otto, Dagmar Zweytick, Caroline May, Catherine Schumacher, Ronald Gust, H. Bauke Albada, Maya Penkova, Ute Krämer, Ralf Erdmann, Nils Metzler-Nolte, Suzana K. Straus, Erhard Bremer, Dörte Becher, Heike Brötz-Oesterhelt, Hans-Georg Sahl, and Julia Elisabeth Bandow. "*Small* cationic antimicrobial peptides delocalize peripheral membrane proteins." *PNAS* 2014 ; published ahead of print March 24, 2014, DOI: 10.1073/pnas.1319900111

Provided by Ruhr-Universitaet-Bochum