

Press Release

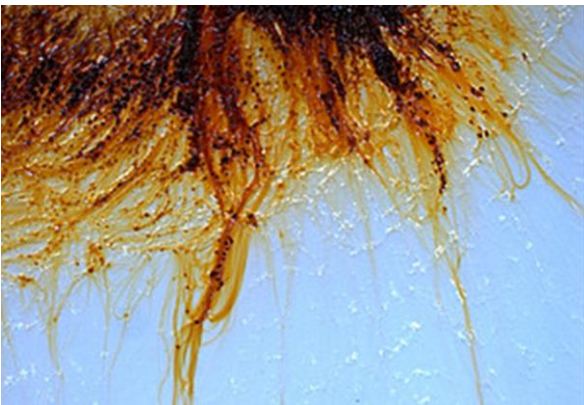
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RESEARCHERS DISCOVER BACTERIA-KILLER FROM NATURAL SOURCE

RESEARCHERS OF THE HIPS AND THE HZI DISCOVER NEW ANTIBIOTIC WITH AN EFFECT AGAINST GRAM-NEGATIVE BACTERIA

Pathogens of infectious diseases like *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, share two major features: They are gram-negative bacteria and they are feared very much in hospital settings. Scientists from the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS) and the Helmholtz Centre for Infection Research (HZI) in Braunschweig, Germany, just discovered a potential new antibiotic that shows an effect against these bacteria, which are difficult to control. They published their results in the renowned professional journal, *Angewandte Chemie International Edition*.



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Ever more pathogens develop resistance to antibiotics which means that the "silver bullets" of the past are losing their magic. Specifically in hospitals, the rising number of resistant pathogens is a major challenge to be faced by the staff. "The group of gram-negative bacteria is the most difficult to control. These bacteria possess two cell membranes. Potentially active substances need to cross both these membranes to have an effect," say Prof Rolf Müller, Managing Director of the HIPS. As a result, the requirements for potential agents are much more complex than with gram-positive bacteria, which have just one cell membrane.

Despite the complex requirements, Müller and his co-workers from the "Microbial Natural Products" group of the HIPS and the "Microbial Agents" group of the HZI successfully isolated a substance with an activity against gram-negative bacteria from the myxobacterium, *Cystobacter* sp. "We discovered a novel chemical class of substances, which we named cystobactamides," says Müller. "We showed in our experiments that these substances possess an effect against gram-negative bacteria such as *Escherichia coli* and *Acinetobacter baumannii*." This means that these agents successfully penetrate through the two cell membranes and then control the bacteria.

The scientists already demonstrated the mechanism underlying the effect of these substances. "We were able to show that cystobactamides act as gyrase inhibitors. They prevent the DNA of the bacteria from being compacted in a space-saving manner much like a twisted garden hose," says Müller. Interfering with this process causes the DNA to no longer be read correctly and the metabolism is impaired significantly.

Gyrase inhibitors are not really new though. Quite the contrary, many of the previous most active antibiotics are based on this principle. "But we were the first to successfully isolate an agent with this mechanism of action from natural products," says Müller. The potential of the known gyrase inhibitors produced by chemical synthesis is basically exhausted, as there is little room for further improvement after decades of use. In contrast, the new substance class of cystobactamides still offers much in the way of optimisation opportunities.

"We are hopeful that chemical modifications will enhance and broaden the effect against gram-negative bacteria," says Müller. "If this works out, then cystobactamides are a true beacon of hope in the fight against hospital pathogens and other gram-negative bacteria."

Original Publication:

Baumann, S., Herrmann, J., Raju, R., Steinmetz, H., Mohr, K. I., Hüttel, S., Harmrolfs, K., Stadler, M. and Müller, R. (2014), Cystobactamide: Topoisomerase-Inhibitoren aus Myxobakterien mit hoher antibakterieller Aktivität. *Angew. Chem.*, DOI: 10.1002/ange.201409964.

The **Helmholtz Centre for Infection Research (HZI)** contributes to the achievement of the goals of the Helmholtz Association of German Research Centres and to the successful implementation of the research strategy of the German Federal Government. The goal is to meet the challenges in infection research and make a contribution to public health with new strategies for the prevention and therapy of infectious diseases. www.helmholtz-hzi.de