Press Release

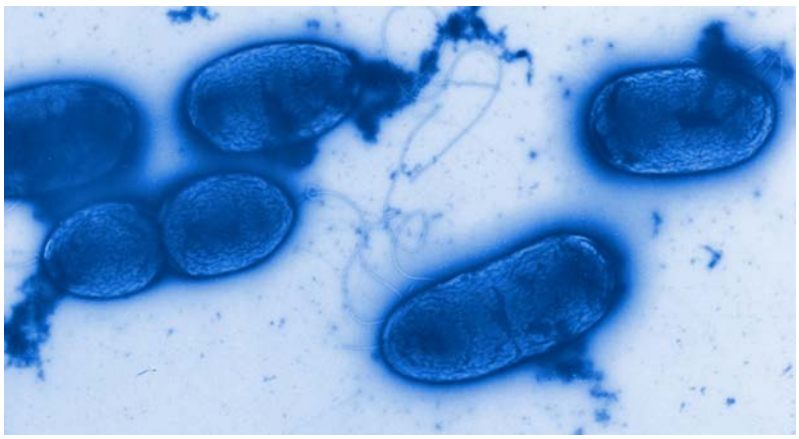
1354

11 December 2013

# COMBATING PSEUDOMONAS INFECTIONS WITHOUT THE DEVELOPMENT OF RESISTANCE

## TARGETED DRUG DESIGN HELPS RESEARCHERS ENGINEERING EFFECTIVE INHIBITORS AGAINST BACTERIA

**Resistances against antibiotics are increasing and represent a life-threatening problem, particularly when it comes to hospital-acquired infections with, for example, *Pseudomonas aeruginosa*. By using targeted drug design, scientists at the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), a branch of the Helmholtz Centre for Infection Research (HZI), have succeeded, for the first time, in developing a substance that successfully combats infections with *Pseudomonas*. It interrupts bacterial communication and prevents bacteria from producing toxins. Due to this, researchers expect that this substance reduces the risk of resistance development compared to the treatment with conventional antibiotics.**



*Pseudomonas aeruginosa* can cause hospital-acquired infections. © HZI

*Pseudomonas aeruginosa* causes hospital-acquired infections. Particularly in patients with the metabolic disorder cystic fibrosis, it can attack the lungs and generate chronic inflammation. By means of a slimy biofilm, it protects itself against the immune system and antibiotics. To this end, many bacteria cooperate with one another by jointly producing this slime. They interact using a bacterial communication system called quorum sensing. “During quorum sensing *Pseudomonas* continuously releases substances. These substances are recognized by other bacteria with the help of their receptors– however, this is only the case when the concentration is high enough,” says Cenbin Lu, scientist at the HIPS. “They then change their genetic programme together.” When the density of the bacteria population increases, the concentration of signalling substances rises as well. *Pseudomonas* also uses this form of communication to produce toxins such as pyocyanin, which damages lung cells.

Researchers at the HIPS have developed for the first time a drug that interrupts this bacterial communication process. They introduced their results in the scientific journal “Angewandte Chemie”. “A central receptor in quorum sensing is PqsR. We specifically looked for substances that block the transfer of information mediated by this protein,” says Prof Rolf Hartmann, department head at the HIPS. As a basis for their chemical syntheses, the scientists used signalling substances that typically bind to the receptor PqsR. One year ago, the researchers produced a substance that, in initial experiments, interrupted the transduction of signals at the receptor. The scientists were, however, not able to confirm this effect in *Pseudomonas aeruginosa*. “We now know that a bacterial enzyme chemically alters our substance in such a way that it activates the receptor instead of inhibiting it,” says Hartmann. A small modification at a certain position in the molecular structure was sufficient to completely reverse the effect of the substance.

By means of targeted alterations, the scientists from Saarbrücken were able to further develop the substance so that the enzyme could no longer attack at the critical location and transform the substance. The final substance showed the desired result: it prevented the receptor PqsR from being switched on. As a consequence, the bacteria produced less pyocyanin. In further tests, the substance successfully increased the survival rate of animals infected with *Pseudomonas*.

What is special about this newly-discovered substance is the unlikelihood of resistance development, in contrast to common antibiotics. “Our molecule does not interfere with any vital processes of the bacteria. Therefore, *Pseudomonas* bacteria which develop resistance in this context have no survival advantage and do not spread,” says Hartmann. “Yet, we can combat the infection since the substance interrupts the bacterial communication process.”

**Original publication**
Cenbin Lu, Christine K. Maurer, Benjamin Kirsch, Anke Steinbach und Rolf W. Hartmann
Overcoming the Unexpected Functional Inversion of a PqsR Antagonist in *Pseudomonas aeruginosa*: An vivo Potent Antivirulence Agent Targeting *pqs Quorum Sensing*
Angewandte Chemie, 2013, DOI: 10.1002/ange.201307547

The Department “**Drug Design and Optimization**” at HIPS develops substances that are meant to avoid an increase in the development of antibiotic resistance in pathogenic bacteria.

**The Helmholtz Centre for Infection Research**

At the Helmholtz Centre for Infection Research (HZI) in Braunschweig, scientists are studying microbial virulence factors, host-pathogen interactions and immunity. The goal is to develop strategies for the diagnosis, prevention and therapy of human infectious diseases. www.helmholtz-hzi.de/en

**The Helmholtz Institute for Pharmaceutical Research Saarland**

The Helmholtz Institute for Pharmaceutical Research Saarland (HIPS) is a branch of the Helmholtz Centre for Infection Research (HZI) in Braunschweig and was founded together with the Saarland University in 2009. Where do new compounds against widespread infections come from, how can they be optimised for the application to humans and how are they delivered efficiently to the target site? The scientists at HIPS are searching for answers to these questions by deploying highly modern methods of pharmaceutical sciences. www.helmholtz-hzi.de/HIPS



Centre for Infection Research
Press and Public Relations
Inhoffenstraße 7 | D-38124 Braunschweig

Phone.: 0531 6181-1401 | Fax: 0531 6181-1499
E-Mail: presse@helmholtz-hzi.de
www.helmholtz-hzi.de

Your Contact:
Dr. Birgit Manno