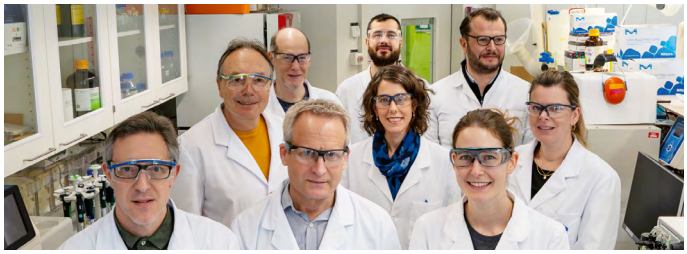
Targeting multidrug-resistant Gram-negative bacteria

Section for Organic and Medicinal Chemistry



Team at Competence Center Drug Discovery
Front, from left: David Frasson, Tobias Wermelinger, Alexandra Brandenberger; Centre, from left: Martin Sievers, Steffi Lehmann, Ina Albert; Rear, from left: Rainer Riedl, Aureliano Zana, Patrick Hauswirth

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Research Project
Targeting multidrug-resistant Gram-negative bacteria

Project leader:
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Timeline:
October 2023 to April 2025

Partner / Funding:
Innosuisse

Antibiotic resistance is one of the biggest threats to global health today. This can affect anyone of any age and in any country. This problem is particularly pronounced in Gram-negative bacteria. We are therefore working on new types of antibiotics that are effective against multidrug-resistant Gram-negative bacteria.

The problem!

Since the pioneering work of Alexander Fleming, Paul Ehrlich and others on antibiotics about 100 years ago, these "miracle drugs" have been taken for granted in the treatment of infectious diseases. Unfortunately, the effectiveness of the antibiotics administered has deteriorated dramatically in recent years: more and more bacteria are developing resistance to antibiotics. As the pharmaceutical industry has not developed a significant number of new antibiotic chemotherapies in recent decades, we are running out of treatment options for infectious diseases. In other words, the post-antibiotic age is just around the corner.

According to the World Health Organization (WHO), antimicrobial resistance currently causes over 1 million deaths every year and contributes to 5 million deaths. By 2050, it could cause up to 10 million deaths per year if no action is taken. For this reason, the WHO has classified the development of new antibiotics as critical for three pathogens and high for six others. Gram-negative bacteria such as carbapenem-resistant Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacteriaceae are of critical priority. These also belong to the ESKAPE acronym, i. e. they are pathogens that have developed resistance mechanisms to many of the existing antibiotics and pose a major threat to humans. Antibiotics with new target structures or mechanisms of action that prevent the development of resistance are therefore urgently needed.

A solution?

Starting from the natural product pseudouridimycin (PUM, Fig. 1), the first selective bacterial RNA polymerase (RNAP) inhibitor with a novel binding mode, we were able to develop a series of small molecule antibiotics with a novel chemical scaffold through ligand-based drug design and organic synthesis. The unique binding mode of PUM makes it much harder for the bacteria to develop resistance. Our currently most potent compounds are effective against the Gram-negative multidrug-resistant pathogens Acinetobacter baumannii and Pseudomonas aeruginosa, both of which are classified as critical by the WHO.

Thanks to a research grant from Innosuisse, we will explore the therapeutic potential of this class of compounds by synthesizing rationally designed derivatives in combination with susceptibility testing in vitro against multidrug-resistant bacterial strains (Fig. 2), followed by toxicological evaluation in vitro with mammalian cells and efficacy studies in vivo in zebrafish. Our overall goal is to develop this class of compounds into clinical drug candidates for the treatment of infections caused by multidrug-resistant Gram-negative bacteria.

Competence Center
Drug Discovery

This project is being carried out entirely at the Competence Center for Drug Discovery: The novel small molecule antibiotics were discovered in the Medicinal Chemistry Group and are now being further developed synthetically there, their antibacterial efficacy in vitro is being tested on multidrug-resistant bacteria in the Micro- and Molecular Biology Group, and finally the efficacy in vivo is being investigated in infection models in the Pharmacology and Pharmaceutical Technology Group. We hope that, through this work, we can make a small but significant contribution to the future availability of antibiotics. ■

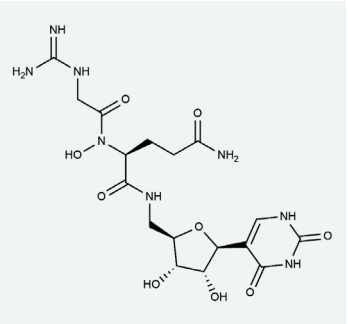

Fig. 1: Structure of pseudouridimycin, PUM.

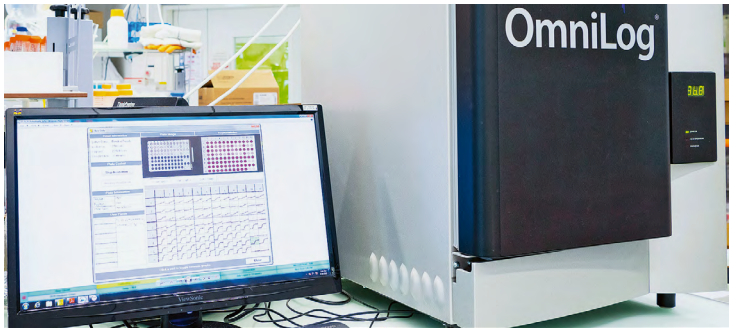

Fig. 2: Antibacterial efficacy testing. Photo: Frank Brüderli