doi:10.2533/chimia.2023.611 Chimia 77 (2023) 611–612

Anna K. H. Hirsch: Drug Design and Optimisation to Disarm Dangerous Germs

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Abstract: Anna K. H. Hirsch, Professor and Head of the Department of Drug Design and Optimisation at the Helmholtz Institute for Pharmaceutical Research in Saarbrücken (HIPS), Germany, is dedicated to fighting infectious diseases by focussing on enzymes that are central to the metabolism of parasites. Her research has led to a valuable collaboration with the Swiss Tropical and Public Health Institute (Swiss TPH).

Keywords: Antimicrobial resistance · Bacteria · Enzymes · Virulence blocking

It is the silent, yet creeping pandemic with major health and economic consequences: antimicrobial resistance. Indeed, the effect of traditional antibiotics is fading in the face of the emergence of resistance in dangerous pathogens such as *Pseudomonas aeruginosa*, a notorious and resistant hospital germ that affects people's lungs. The development of new drugs against *P. aeruginosa* and other pathogens is therefore a race against time.

Prof. Dr. Anna Hirsch. Photo credit: HIPS/Dietze.

Someone who has been sprinting for some time now is chemist ***Anna K. H. Hirsch***. The 41-year-old professor heads the Department of Drug Design and Optimisation at the renowned Helmholtz Institute for Pharmaceutical Research in Saarbrücken (HIPS), Germany. Motivated by her chemistry teacher, her fascination for chemical structures and processes dates back to her school days. Today, her interdisciplinary team at HIPS is searching for molecules with novel mechanisms of action against bacteria, parasites and viruses. The scientists use a variety of established and cutting-edge research methods. For example, Anna Hirsch and her team employ the chemical structure of the target protein as the basis for their search in classical structure-based drug design. Protein-mediated methods are a complementary and innovative approach. "We try to involve the target protein in the hit-finding process by letting it choose for itself which molecules bind best to the protein," she explains (Fig. 1).

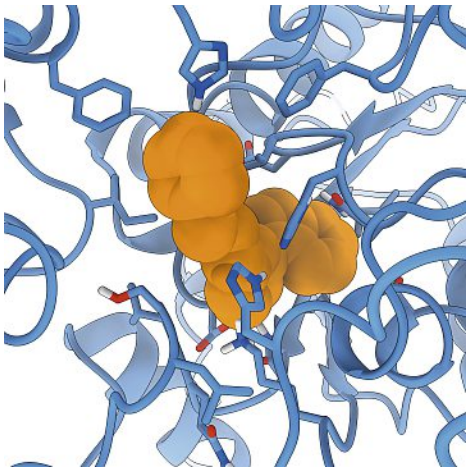

Fig. 1. Docked pose of antimalarial compound **HIPS709** docked into the predicted alpha-fold structure of PfDXPS.

Disarming Bacteria

In recent years, fighting bacterial virulence has become an attractive alternative to classical antibiotics. "We are not trying to kill the bacteria, but merely to disarm them," says Hirsch. "If we manage to do this, the immune system will be able to get rid of the harmless germs on its own in a second step." An important factor for pathogenicity (virulence) in a *P. aeruginosa* infection is the protein called elastase B (LasB). Anna Hirsch's team conducts research on a new class of molecules that showed promising activity against LasB *in vitro* and *in vivo*. "Virulence blockers have the advantage that the selection pressure on the bacteria is lower and the future development of resistance slows down," emphasises Hirsch.

New Active Agents against Infectious Diseases of Poverty

Despite the Helmholtz Institute's traditional focus on bacterial diseases, Anna Hirsch and her group are dedicated to other pathogens that are intimately related to poverty, such as malaria and, most recently, parasitic worm infections. Not surprisingly, the Swiss Tropical and Public Health Institute (Swiss TPH) in

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Allschwil has become an important research partner. Joint projects focus on enzymes that are central to the metabolism of parasites and bacteria. These enzymes might then turn out to be central 'targets' for future drug development against neglected diseases. When Prof. Pascal Mäser, Head of the Parasite Chemotherapy Unit at Swiss TPH, wants to put the collaboration with Anna Hirsch into words, Paul Ehrlich's request comes to his mind, who said: "We must learn to aim in a chemical way." Mäser further elaborates: "This is still true today, and no one aims better than Anna Hirsch! It is amazing how she combines medicinal chemistry, structural biology and evolutionary insights to first define antimicrobial targets and then hit them with high precision."

"The beauty of chemistry is that it is everywhere and you can understand a lot logically and don't have to learn much by heart," says Anna Hirsch and laughs. It is this spirit that might explain why Anna Hirsch has become such a rising star in drug discovery and development.

Received: August 22, 2023

The definitive version of this article is the electronic one that can be found at https://doi.org/10.2533/chimia.2023.611