DISCOVERY OF THE FIRST ANTIBACTERIAL AGENT INHIBITING THE ENERGY-COUPLING FACTOR (ECF) TRANSPORTERS BY STRUCTURE-BASED VIRTUAL SCREENING

Anna K. H. Hirsch

Helmholtz Institute for Pharmaceutical Research (HIPS) − Helmholtz Centre for Infection Research (HZI), Department for Drug Design and Optimization and Department of Pharmacy, Saarland University, Campus Building E 8.1, D-66123, Saarbrücken, Germany

The emergence of drug resistance against important pathogens poses an ever-growing health threat. The pipeline of novel drug candidates should be filled with molecules featuring an unprecedented mode of action and a novel chemical structure. We tackle both challenges by adopting several established and unprecedented hit-identification strategies such as structure-based design, virtual screening and dynamic combinatorial chemistry[1] on an unexplored anti-infective target. [2] ECF transporters are a class of ATP-binding cassette (ABC) transporters that mediate the uptake of vitamins in prokaryotes. They consist of an energizing module and a substrate-binding protein (S-component). Different S-components can interact with the same energizing module.[3]

We embarked on a structure based drug design (SBDD) of thiamine analogue as binders of the integral membrane protein ThiT, the S-component for thiamine. We designed and synthesized thiamine analogues in order to elucidate the mechanism of substrate binding and transport. The new compounds bind with high affinity to ThiT (K_d = 4–660 nM) and the predicted binding mode was confirmed by co-crystallization studies .[4,5]

A structure-based virtual screening campaign afforded the first allosteric inhibitors of the transporter for folate.[6] We synthesized a series of derivatives that display good *in vitro* activity, excellent ADMET properties and antibacterial activity (MIC = 4 μM) against a range of pathogenic Gram positive bacteria (*Staphylococcus aureus*, *Enterococcus faecium* and *Streptococcus pneumoniae*).[7] A pharmacokinetic study showed them to be present in plasma at high concentration. Thus, the inhibitors constitute an excellent starting point for the development of novel antibiotics and are currently being investigated in an *in vivo* infection model.[7]

———

[1] M. Mondal, A. K. H. Hirsch, Chem. Soc. Rev. 2015, 44, 2455–2488.

[2] S. Bousis, I. Setyawati, E. Diamanti, D. J. Slotboom, A. K. H. Hirsch, Adv. Ther. 2018, accepted.

[3] D.J. Slotboom. Nature Rev. Microbiol. 2014, 12, 79-87.

[4] L. Monjas, L.J.Y.M. Swier, A. Guskov, A.R. de Voogd, G.B. Erkens, D.J. Slotboom, A.K.H. Hirsch. ChemBioChem 2015, 16, 819–826.

[5] L. Monjas, L.J.Y.M. Swier, A.R. de Voogd, R. C. Oudshoorn, A.K.H. Hirsch, D.J. Slotboom. MedChemComm 2016, 7, 966–971.

[6] L. J. Y. M. Swier, A. Guskov, D. J. Slotboom, Nat. Commun. 2016, 7, 11072.

[7] E. Diamanti, L. Monjas, L. J. Y. M. Swier, I. Setyawati, S. Bousis, D. J. Slotboom, A. K. H. Hirsch, under review.