

The development of novel peptide antibiotics based on the Thanatin scaffold to help
overcoming antimicrobial resistance
Oliver Zerbe, Dep. of Chemistry, University of Zurich

Resistance to antibiotics represent an enormous thread to mankind and the death toll due to antimicrobial resistances was recently estimated as 4.7 millions (1). Recently, novel cyclic peptide antibiotics were developed based on the protegrin scaffold (2) that target the lipopolysaccharide (LPS) transport pathway (3,4,5). They represent the first new class of antibiotics developed in the last 50 years.

We recently discovered that the naturally occurring peptide thanatin binds to LptA, that is part of the LPS transport bridge across the periplasm (5). Based on the thanatin scaffold, we developed in collaboration with Spexis a series of compound that bind to components of the periplasmic protein bridge (6). Peptide-protein complexes are determined by solution NMR techniques. We could demonstrate that the protein bridge is completely disassembled upon addition of the peptides *in vitro*.

We are now developing peptides that are adopted to LPS transport proteins from other pathogens. Moreover, I will present a very efficient design pipeline for a soluble mimic of LptD, a β -barrel membrane protein, using computational protein design and heteronuclear NMR, that is suitable for screening and binds to the cognate ligands LptA and Thanatin. NMR techniques are critical to identify suitable candidates from the designed candidates. Examples are shown for LptD mimics from all Gram-negative pathogens of the ESKAPE list.

References:

1. Antimicrobial Resistance Collaborators. Lancet. 2022, [https://doi.org/10.1016/S0140-6736\(21\)02724-0](https://doi.org/10.1016/S0140-6736(21)02724-0)
2. D. J. Sherman, R. Xie, R. J. Taylor, A. H. George, S. Okuda, P. J. Foster, D. J. Needleman, D. Kahne, Science 359, 798–801 (2018).
3. N. Srinivas, P. Jetter, ..., L. Eberl, K. Riedel, S. J. DeMarco, J. A. Robinson, Science 327, 1010–1013 (2010).
4. i) Karanbir, S.P.,...Kahne,D., Nature 625 (2024), pages 572–577, ii) Zampaloni, C...Bradley, K.A., Nature, 625(2024), pages 566–571.
5. S. U.Vetterli, K. Zerbe, M. Müller, M. Urfer, M. Mondal, S.-Y. Wang, K. Moehle, O. Zerbe, A. Vitale, G. Pessi, L. Eberl, B. Wollscheid and J. A. Robinson, Science Advances, 4 (2018), eaau2634.
6. M. Schuster, E. Brabet, K. Oi...O. Zerbe, Science Advances, 9 (2023), eadg368.