The impact of peptide drugs on antibacterial research – it is time to resist!

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There is a strong demand for new antibacterial drugs to encounter the threat of human health by multi-resistant bacteria. In the past years, research efforts in the discovery and further profiling of antibacterials have shifted to smaller biotech companies and academic institutions. Nevertheless, there are still big pharma companies being involved in antibacterial research. The lecture gives an overview over established and more recent antibacterial drug targets, e.g. membrane proteins and membrane biosynthesis, as well as on the performance of selected compounds.[1] A particular emphasis is laid on antibacterials, which showed proof-of-concept in animal infection models. Particularly for Gram-negative bacteria, the addressed drug targets have shifted from cytoplasmic components to the bacterial membrane and membrane-related pathways. Remarkably, as the presentation will show, peptides and peptide-derived compounds could perform very well as antibacterials.

One particular example will be the non-ribosomally synthesized peptide antibiotic albicidin from the plant pathogenic bacterium *Xanthomonas albilineans*.[2] Albicidin inhibits gyrase, an established and highly effective antibacterial target. Albicidin is highly potent against Gram-positive and Gram-negative bacteria and has a bactericidal action. Contributions from our group over the past years deal with chemical synthesis, structure-activity-relations (SAR),[3,4] the mode-of-action (MOA)[5] as well as the investigation of mechanisms of resistance.[6,7] Proof of concept was achieved by a thigh mouse infection model.[6,7] The results could qualify albicidin as a future antibacterial for application in human.

[1] R.D. Süssmuth, S. Kosol, P. Gao, M. Kulike, **2024**, *submitted*.
[2] S. Cociancich, A. Pesic, …, M. Royer, R.D. Süssmuth, *Nat. Chem. Biol.* **2015**, *11*, 195-197
[3] J. Kretz, D. Kerwat, …, M. Royer, R.D. Süssmuth, *Angew. Chem. Int. Ed.* **2015**, *54*, 1969-1973
[4] L. Zborovsky[#], L. Kleebauer[#], …, J. Weston, R.D. Süssmuth, *Chem. Sci.* **2021**, *12*, 14606-14617
[5] E. Michalczyk. K. Hommernick, …., A. Mainz, R.D. Süssmuth, D. Ghilarov, *Nat. Catal.* **2023**, *6*, 52–67
[6] M. Saathoff, S. Kosol, ….., R.D. Süssmuth, M. Fulde, *PLOS Biology* **2023**, *21*, e3002186
[7] S. Kosol, L. Rostock, ….., A. Mainz, R.D. Süssmuth, *Chem. Sci.* **2023**, *14*, 5069-5078