

The mechanism of the antibiotic Plectasin

Plectasin (*Schneider et al., Science 2010*) is a fungal peptide-antibiotic. Plectasin and its variants have excellent bactericidal activity against a variety of Gram-positive bacteria including clinically relevant strains.

Plectasin inhibits the bacterial peptidoglycan synthesis by targeting the precursor-molecule Lipid II, a special lipid that only exists in bacterial cell membranes. However, structural data on the membrane-binding mode are absent, which severely curtails the use of plectasin for drug development

We have been working on the mode of action of plectasin for several years and have discovered fascinating new insight into its mode of action (unpublished). In particular, we are striving to establish a molecular understanding why the plectasin mutant NZ2114 is highly active against the infamous hospital-superbug MRSA, while wild-type plectasin is inactive.

For these studies, we use state-of-the-art solid-state NMR supported by the strongest commercial NMR magnet available (1.2 GHz). Furthermore, we use a wide latitude of molecular biology and biophysical methods (fluorescence spectroscopy, fluorescence microscopy, isothermal calorimetry (ITC), molecular modeling). Please contact m.h.weingarth@uu.nl if you are interested in this project.

Further reading

About Plectasin:

Schneider, T.; Kruse, T.; Wimmer, R.; Wiedemann, I.; Sass, V.; Pag, U.; Jansen, A.; Nielsen, A. K.; Mygind, P. H.; Raventos, D. S.; Neve, S.; Ravn, B.; Bonvin, A. M.; De Maria, L.; Andersen, A. S.; Gammelgaard, L. K.; Sahl, H. G.; Kristensen, H. H., Plectasin, a fungal defensin, targets the bacterial cell wall precursor Lipid II. *Science* **2010**, *328* (5982), 1168-72.

Examples of our research:

Shukla, R.; Medeiros-Silva, J.; Parmar, A.; Vermeulen, B. J. A.; Das, S.; Paioni, A. L.; Jekhmene, S.; Lorent, J.; Bonvin, A. M. J. J.; Baldus, M.; Lelli, M.; Veldhuizen, E. J. A.; Breukink, E.; Singh, I.; Weingarth, M., Mode of action of teixobactins in cellular membranes. *Nature Communications* **2020**, *11* (1), 2848.

Medeiros-Silva, J.; Jekhmene, S.; Paioni, A. L.; Gawarecka, K.; Baldus, M.; Swiezewska, E.; Breukink, E.; Weingarth, M., High-resolution NMR studies of antibiotics in cellular membranes. *Nat Commun* **2018**, *9* (1), 3963.

