Project Nils Metzler-Nolte

**Site-specific conversion of bacterial fatty acid substrates by membrane-anchored organometallic catalysts**

**Background and preliminary work:** In many applications outside biology, organometallic complexes perform catalytic reactions with excellent efficiency and high selectivity. In contrast, only a few organometallic catalysts have been used to perform catalytic transformations in living cells, most of which were mammalian. This project aims to investigate organometallic catalysts with the aim to perform selective, site-specific catalytic transformations in bacterial membranes. Devising a strategy for modifications of unsaturated fatty acids by chemical reactions could not only be a valuable tool for fundamental studies in membrane biology but has the potential to become an antibiotic strategy. We have recently demonstrated how displacement of vital enzymes like MurG from the bacterial membrane is a potent antibacterial strategy.[1] Moreover, the Metzler-Nolte group has a long- standing experience with peptide conjugates.[2] In this project, we will capitalize on these experiences and design catalytically competent metal-peptide conjugates that will perform their catalytic function in and nearby the bacterial membrane.

**Work planned:** This project aims to develop transition metal complexes that are capable of catalytically transforming double bonds in bacterial membrane lipids. The goal is to explore such permanent and irreversible transformations of natural membrane components by catalytic metallodrugs, with the prospect to develop such reactions as a novel antibiotic strategy. Transition metal complexes will be covalently linked to known bacterially specific membrane-anchoring peptides. The complexes will be chosen from catalytically competent metals such as Rh and Ir.

A proof-of-concept study will be performed *in vitro* on model bacterial membranes and liposomes (in collaboration with Narberhaus).[3] Membrane fluidity changes as a consequence of chemical modification will be detected by quartz crystal microbalance, and mass spectrometry will be used to detect and quantify saturated and unsaturated lipids in the model membrane (in collaboration with Schulz). The best catalysts will be identified, and the insight gained from model studies will be transferred to bacteria. In conclusion, a bacterially specific activity is achieved by targeting compounds that are exclusively found in the bacterial membrane, and localizing the metallodrug at the membrane.

**Selected references:**


Wenzel M, Chiriac AI, Otto A, Zweytick D, May C, Schumacher C, Gust R, Albada HB, Penkova M, Krämer U, Erdmann R, Metzler-Nolte N, Straus SK, Bremer E, Becher D, Brötz-Oesterhelt H, Sahl HG, Bandow JE. 2014. Small cationic antimicrobial peptides delocalize peripheral membrane proteins. *Proc Natl Acad Sci USA* **111**:E1409–E1418.

Albada HB, Metzler-Nolte N. 2016. Organometallic–peptide bioconjugates: Synthetic strategies and medicinal applications. *Chem Rev* **116:**11797-1839.

Danne L, Aktas M, Gleichenhagen J, Grund N, Wagner D, Schwalbe H, Hoffknecht B, Metzler-Nolte N, Narberhaus F. 2015. Membrane-binding mechanism of a bacterial phospholipid *N*-methyltransferase. *Mol Microbiol* **95**:313-331.