MSc project / (Potentially also BSc)

Structural characterisation and design of antibiotics

NMR spectroscopy Group, Bijvoet Center for Biomolecular research
m.h.weingarth@uu.nl *see also: weingarth-group.org*

Antibiotics are the bedrock of modern medicine, and the world is running out of these magic bullets at a dramatic pace. To date, resistance has been observed against all clinically used antibiotics, which is a major factor of mortality worldwide, including in developed countries, and which is soon expected to cause more human deaths than cancer. To make things worse, the industry's drug-discovery pipeline for antibiotics is almost empty. It is hence of pressing need to develop novel antibiotics that operate via unexploited mechanisms and that are robust to resistance development.

Ideal templates for such magic bullets could be **peptide-antibiotics** that specifically target the membrane-anchored cell wall precursor *lipid II*. These peptides kill even the most refractory pathogens without detectable resistance and without showing cytotoxicity. However, due to the challenge of studying small drug–receptor complexes in membranes, structural knowledge on peptide–lipid II binding is limited and totally absent in native-like media. In consequence, peptide-binding modes such as pores that require physiological conditions could never be visualized. Moreover, while the structure of lipid II and of the entire cell membrane vary across bacteria, how this modulates peptide–lipid II binding cannot be studied with current high-resolution methods. Altogether, this lack of knowledge critically limits the use of lipid II binding peptides for antibiotic design.

In Utrecht, in the Bijvoet Center for Biomolecular research, we are working on the structural characterisation of peptide-antibiotic **plectasin-type** (Schneider et al., Science 2010) in order to develop novel and improved antibiotics. We offer MSc projects on the structural characterisation of these promising antibiotics; and also on the design and testing of improved antibiotics.