Antimicrobial peptide – metal interactions – understanding the relationship between coordination chemistry, structure, thermodynamics and mode of action

The inspiration for choosing our topic is an exponential increase of antimicrobial resistance in the last three decades. Drugs which we currently rely on stop working, as bacteria and fungi get resistant to their actions. Abnormally high percentages of hospital-acquired infections caused by highly resistant microbes pose serious threats to human health. According to the European Commission, if nothing is done to prevent the increase of resistance, by 2050, in Europe, 390 thousand deaths annually will be caused by the invasion of drug resistant microbes. Novel, effective treatments for antibiotic resistant bacteria and to drug resistant invasive mycoses are being actively sought.

Antimicrobial peptides are a big hope in the fight of drug-resistant pathogens. They are small molecules that form part of the innate immune response shared by all classes of life. Different AMPs are active against fungi, bacteria, viruses, protozoa, and even cancer cells. Presumably, bacteria have been exposed to AMPs for millions of years and, with the exception of a few species, widespread resistance has not been reported, making them a potential 'treasure trove' of starting points for rational, focused antimicrobial drug design.
There are more than 2800 experimentally reported AMPs produced by living organisms listed in specialized AMP databases. More than 100 new AMPs are being reported annually. Although this class of compounds is being intensively studied, their mode of action is still very far from being clear – AMPs may interact with pathogens via membrane disruption, production of reactive oxygen species, inhibition of cell wall, nucleic acid and protein synthesis, or by the withdrawal of essential metal ions. Biologically indispensable metal ions, such as Zn(II) and Cu(II), which are the key players of this project, have a dual effect on the activity of antimicrobial peptides: (i) AMPs bind them, so that microbes cannot get enough metals essential for their life and virulence (removal of metal ions) or (ii) AMPs need the given metal ion to boost their antimicrobial activity

In the scope of our project, we will define the thermodynamics, structure and coordination chemistry of 38 AMPs with Zn(II) and/or Cu(II) and compare these data to the outcome of biological growth studies on bacterial and fungal strains. This way, we will draw conclusions about the relationship between the metal-antimicrobial peptide complex structure, stability, mode of action and efficacy. In the second step of the project, the most efficient complexes will serve as templates for the design of novel, more potent AMP-based therapeutics – we will design novel AMPs or AMP complexes with enhanced features which contribute to their antimicrobial efficacy and chimeric compounds, e.g. based on AMPs bound to conventional antibiotics or antifungal drugs and again check the correlation between their thermodynamical and structural properties and their biological activity.
This knowledge will allow us to understand the inorganic biochemistry of antimicrobial peptides and will be a massive stepping stone towards finding new, specific antibacterial and antifungal treatments.