The accelerating emergence of multi-drug resistant (MDR) pathogens poses a great threat to public health and creates a demand for new antibiotics. With antibiotics being less and less effective, treatment of even common infectious diseases is more difficult or even impossible. Importantly, the spread of antibiotic resistance undermines all treatments that rely heavily on antibiotics, such as surgeries, organ transplants, or cancer therapies. Thus, bacterial infections are becoming a major threat to our modern health systems.

Antimicrobial peptides (AMPs) present an attractive alternative to conventional antibiotics. AMPs are naturally occurring molecules that provide the first line of defense against infections in all multicellular organisms. AMPs show great diversity in their amino acid sequence, but they all share a structural feature – an amphipathic structure with distinct positively charged and hydrophobic regions. This amphipathic structure facilitates a selective electrostatic interaction with the negatively charged bacterial membranes over neutral mammalian membranes. As a result, AMPs have broad-spectrum antibacterial activity and low toxicity.

The basis of selectivity and mechanism of action of AMPs is different from classical antibiotics. Classical antibiotics exert their activity through the inhibition of specific enzymes or processes, which makes them susceptible to bacterial resistance. Furthermore, classical antibiotics target fast-dividing cells, which makes them powerless against biofilm-forming dormant bacteria. On the contrary, the selectivity of AMPs is based on a distinct composition of bacterial and mammalian membranes; and a membranolytic mode of action ensures fast killing and hinders bacteria from developing resistance to AMPs. However, natural AMPs show many limitations in their use as antibacterial drugs, such as low stability due to rapid metabolism and proteolytic degradation, immunogenicity, and poor pharmacodynamic and pharmacokinetic properties.

Peptidomimetics have improved bioavailability and metabolic stability while retaining activity and selectivity profiles resembling those of AMPs. Also, they often exhibit lowered toxicity as compared to natural AMPs. In this project, our main goal is to obtain metallacarborane-containing peptidomimetics that have potent antibacterial activity, high selectivity, and immunity to resistance development by bacteria. The studies planned in this project will allow us to identify peptidomimetics with the best antibacterial activity and to understand the underlying molecular principles of the observed biological effects.