The accelerating emergence of multidrug resistant (MDR) pathogens poses a great threat to public health and creates a demand for new antibiotics. With antibiotics being increasingly ineffective, the treatment of even common infectious diseases is becoming increasingly 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 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 exhibit 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 selective electrostatic interactions with negatively charged bacterial membranes over neutral mammalian membranes. As a result, AMPs have broad-spectrum antibacterial activity and low toxicity.

The basis of the selectivity and mechanism of action of AMPs is different from that of classical antibiotics. Classical antibiotics exert their activity through the inhibition of specific enzymes or processes, which increases susceptibility to bacterial resistance. Furthermore, classical antibiotics target fast-dividing cells, which decreases their effectiveness against biofilm-forming dormant bacteria. The selectivity of AMPs is based on the distinct compositions of bacterial and mammalian membranes, and a membranolytic mode of action ensures the rapid killing of bacterial cells and prevents bacteria from developing resistance to AMPs. However, natural AMPs have 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.

The main aim of this project is to obtain metallacarborane-containing ultrashort cationic peptides with potent activity against gram-negative bacteria and good biocompatibility. The peptides will have an amphipathic structure and activity similar to AMPs. In this project, we plan to synthesize a library of metallacarborane-containing peptides and determine their antibacterial activity, mechanism of action, biocompatibility, immunomodulatory activity, and ability to self-assemble into nanostructures. As a result of this project, we expect to identify peptides with high antibacterial activity and good selectivity, as well as increase our knowledge of the molecular principles of the activity of metallacarboranes and metallacarborane-containing peptides in biological systems.