The application of non-covalent and electrostatic interactions in the design of helical oligomers to disrupt bacterial cell membranes.

The discovery of penicillin in 1928 initiated extensive research into new drugs, antibiotics, capable of combating bacterial infections. However, by 1945, cases of bacterial resistance to penicillin had been already observed. Since then, bacterial resistance to commonly used antibiotics has been growing at an alarming rate. It is estimated that in 2019 alone, approximately 1.27 million people died from bacterial infections resistant to antibiotics. Recent reports predict that by 2050, the number of deaths associated with antimicrobial resistance could reach as high as 10 million annually. These figures are alarming, prompting the search for new drugs with mechanisms of action different from those of existing antibiotics. One promising discovery is that peptides with specific structures (AMPs - antimicrobial peptides) can exhibit antibacterial activity by disrupting bacterial membranes. However, due to chemical structure of peptides, which makes them susceptible to proteolytic enzymes, their use as drugs is problematic. This has spurred the search for new compounds, known as structural and functional peptidomimetics, which have similar mechanisms of action, but resistant to enzymatic degradation. In this project, we want to synthesize compounds belonging to the group of peptidomimetics but also foldamers, whose main chains contain urea bonds (oligourea). The sequences of these compounds will be based on peptides and oligoureas with confirmed antibacterial activity. Our goal is to obtain foldamers selective for Gram-negative bacteria, which cause numerous severe infections, including pneumonia, bloodstream infections, surgical site infections, and meningitis in healthcare settings.

The originality of this project lies in our plan to develop compounds - foldamers capable of destroying bacterial membranes by interacting with their specific building elements, such as phosphates, sugars, and magnesium ions, which are essential for maintaining the integrity of the outer layer. Structural modifications of oligoureas will be introduced one at a time. Subsequently, we will investigate the interactions of the obtained foldamers with model compounds mimicking the structural elements forming the outer membrane of Gram-negative bacteria, such as simple phosphates, sugars, and magnesium salts, and finally with model bacterial membranes. The selected peptidomimetics will be then tested for their antibacterial properties, as well as cytotoxicity towards eukaryotic cells. In the last stage of the project, we will try to introduce all the structural elements that are binding sites for bacterial membrane components into one molecule. This will be the biggest challenge of the project, consisting in optimizing the structure of this new molecule (e.g. extending the foldamer sequence so that the binding sites are at the right distance or connecting several helices with an appropriate linker) in order to achieve synergy of action of individual building units. In this way, we hope to obtain the so-called "super-foldamer", capable of combating Gram-negative bacteria through in multiple ways.

The results obtained during the project should contribute to a better understanding of the mechanisms of action of antibacterial peptides and peptidomimetics, thereby facilitating the development of new active compounds to counteract bacterial resistance.