The overuse and careless use of antibiotics by humans and in animal husbandry have enabled bacteria to develop several resistance mechanisms against known antibiotics. To make matters worse, in recent years, the World Health Organization has announced a list of six multi-drug resistant strains of bacteria. These bacteria pose a massive danger because no antibiotics are effective against them. What's even worse, the development of new antibiotics has practically stalled since 1987. However, scientists see hope in peptide antibiotics. They have been increasingly considered as a future alternative to conventional antibiotics. According to the reports, more than 10% of all compounds in the preclinical phase are peptides.

Peptides are found in all living organisms. They are short polymers made of amino acids that perform various biological functions. Most often, peptides interact with other molecules, thereby regulating physiological processes. Some peptides are a crucial element of the defense system due to their antimicrobial potential. This is why, in recent years, peptides have filled a niche in medicinal chemistry research and are appreciated as possible, new, and more effective therapeutic agents. However, not even 1% of the compounds approved by the Food and Drug Administration as new drugs are peptides.

The main goal of this project is to design a computational method allowing for the effective prediction of new peptide antibiotics. This aim can help scientists fight the problem of antibiotic resistance. In addition, I will develop concepts of peptide stabilization. Stabilization of peptide structures will allow me to increase their antibacterial potential and eliminate undesirable properties. These properties include the susceptibility of peptides to rapid digestion by proteolytic enzymes, hemolytic activity, cytotoxicity, and possible immunogenicity. Due to these limitations, most peptides are not being approved by the Food and Drug Administration as novel antibiotics.

There are various strategies to overcome the above limitations of peptides. Primarily these include peptide modifications. For this reason, the central part of the project will be the optimization of theoretical models from computational biophysics. These models will be used to scan the peptide sequence to find the amino acid whose mutation would increase its biostability. Recent studies indicated that better biostability increases antibacterial potential. Interestingly, some peptide stabilization methods also enhance the therapeutic potential, increase the helicity and eliminate some or even all undesirable properties. In the project, it is also principal to introduce non-standard amino acids into the peptide sequence, the properties of which can also increase the peptide biostability.

An equally important part of the project will be experimental validation. To prove the reliability of the computational models, I will synthesize the designed mutants and determine whether they inhibit the growth of bacteria. The antibacterial activity of the mutants will be determined for standard and drug-resistant strains. However, a peptide with antibacterial activity may still not be considered an effective antibiotic. That is why, at the end of the project, I will select the most promising peptide. I will check if it has the features to become an effective antibiotic by experimentally checking if it is not hemolytic, digested by the trypsin enzyme, and cytotoxic.

To sum up, the recent information received from the World Health Organization is worrying. Despite intensive research, many compounds are not being approved as new drugs. The implementation of the project will provide an innovative approach to automate the process of finding novel and effective antibacterial peptides. I will computationally propose an synthetically introduce a single-point mutation that can lead me to enhance peptide biostability. In addition, according to recent studies, the original amino acids substitution for non-standard ones can dramatically alter the antibacterial activity. Such mixed compounds are highly desired.

In the future, my proposed protocol may help researches design new peptides and allow the Food and Drug Administration to finally approve new antibiotics. It will be a significant step in the fight against highly resistant bacterial strains.