Towards the design of effective antibacterial agents

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Pathogenic infections represent a persistent threat to human health. The overuse of antibiotics in human, medicine and agriculture including food production contributes to the rise of antibiotic-resistant infections that are difficult to treat. The World Health Organization 2014 report states, "this serious threat is no longer a prediction for the future, it is happening right now in every region of the world and has the potential to affect anyone, of any age, in any country". Another major concern in this field is the phenomenon of bacterial persistence. Persistent cells are the small fraction of a bacterial population that tolerates antibiotics by entering a state of dormancy, thus creating a challenge to develop compounds that will target them. There is an urgent need to design novel antimicrobial agents.

Our research goal is to develop and explore peptides-based tools as novel antimicrobial compounds. The broad molecular diversity among natural antimicrobial peptides suggests that their activity is not tightly coupled to specific features of amino acid sequence or peptide conformation. This situation has inspired us to develop a novel approach to generate random cationic peptide mixture. We have previously shown that random peptide mixture of hydrophobic and cationic a-amino acids, such as phenylalanine and lysine, display strong antimicrobial activity. In the current proposal we will investigate the mechanism of action of these peptides mixture, aiming at the design of effective compounds.

Another peptides based tool that we will develop in the current proposal is the design of vital protein-protein interaction peptide-like inhibitors in bacteria. We will design novel and selective antibiotic agents by studying the Toxin-antitoxin (TA) system in bacteria, an unexplored and novel basis for drug development. One of the types of TA systems consists of an antitoxin protein that binds to and inactivates a toxin protein. Upon degradation of the antitoxin, the toxin is released to induce bacterial cell death. TA systems play important role in the development of persistent cells, by inducing cell growth arrest that leads to antibiotic tolerance. Inhibiting TA interactions offers a good opportunity for development of novel antibacterial compounds because there are no known mammalian homologs of TA pairs. We will discover and explore TA peptidic inhibitors using phage display to identify short polypeptides that binds the antitoxin protein. We will characterize their ability to penetrate bacterial cell and to induce bacterial cell death. The novel techniques and concepts developed in the proposed interdisciplinary research program will lead to the design of selective and effective antimicrobial agents. These antimicrobial agents may find wide applications in biomedical or food science fields.