The **oral cavity** has the second largest and diverse microbiota in the human body, housing **more than 700 bacterial strains and also fungi, viruses and protozoa**. The oral microbiome plays a crucial role in the maintenance of homeostasis in the mouth. The imbalance between bacteria and the host's defensive ability may lead not only to periodontal diseases, but also to other oral and systemic diseases, such as respiratory illnesses (by direct aspiration through the lower respiratory tract) or heart disease, psoriasis, psoriatic arthritis, carcinogenesis at various sites (via the transfer of pathogens through the bloodstream). Respiratory diseases are responsible for significant morbidity and mortality in the human population. Increasing **difficulties in the effective prevention and treatment of many infections** are related to the increasing resistance of bacteria, parasites and fungi to commonly used antibiotics. **Antibiotic resistance is the main problem of the 21st century** and a global threat to human life, especially now, in the current crisis related to the novel SARS-CoV-2 coronavirus, where a large number of co-infections with other viruses, fungi and bacteria are recorded, many of which originate in the oral cavity.

Due to the frighteningly rapid growth rate of antibiotic-resistant bacteria, new strategies to combat pathogenic microorganisms must be developed. **Saliva is the first line of defense** against pathogenic microbes in the oral cavity. In this body fluid, a **unique set of antimicrobial peptides** (AMPs) **fights pathogens in the defense of the host**. **Metal ions** are often necessary for their biological functions, playing an important role as co-factors of salivary enzymes, and causing conformational changes in salivary proteins that eventually lead to important modulation of their functionality, such as *e.g*. **enhancement** of their **antimicrobial activity**. However, one of the major drawbacks of antimicrobial peptides (and also AMP-based drugs), which seriously limits their use in the clinic, is their poor proteolytic stability.

The most reasonable solution of this problem, and also **the aim of this project, is the design of AMP-based, metabolically stable, non-toxic, metal-enhanced peptidomimetics to eradicate pathogenic microorganisms from the oral cavity**. **Incorporation** of **unnatural occurring building blocks** to native peptides (*e.g*. in the sites most prone to metabolic degradation) **can alter their physicochemical properties without impairing the antimicrobial activity**, what is a crucial in the design of novel, more effective peptidomimetics.

In order to achieve the best results, a number of studies will be carried out on (from **design** of **peptidomimetics** through **synthesis** to **characterization of their structural and thermodynamic properties**). DFT calculations will complete the characteristics of the complexes formed with metal ions and **biological tests** on selected bacterial strains will verify whether the antimicrobial effects have been kept (or, preferably, improved).

The outcome of this work will be novel, proteolytically stable and potent antimicrobial derivatives of selected salivary peptides and their Zn(II) and Cu(II) complexes.

The results will allow us to draw conclusions whether "arming" naturally occurring peptides from saliva with a perfect "ammunition": D-, β-, γ- and unnatural amino acids, and zinc or copper ions, will be able to fight antibiotic-resistant pathogenic microorganisms. This approach will allow us to **obtain novel classes of metal-based antimicrobial agents** with higher metabolic stability and possibly improved efficacy against pathogenic microbes.