Mechanisms involved in heme acquisition - potential targets for therapies directed towards reduction of *Porphyromonas gingivalis* virulence

The human body is colonized by thousands of bacterial species that form microbiomes. Usually, bacteria live in symbiosis with the host, but certain factors can lead to dysbiosis and excessive proliferation of pathogenic bacteria. The microbiome of the oral cavity is one of the most diverse in the human body. Dysbiosis disrupts mutualism between members of the oral cavity microbiome and may lead to the development of periodontal diseases. It is a group of multifactorial, infectious inflammatory diseases, characterized by the destruction of tooth-supporting tissues, eventually leading to gum bleeding and tooth loss. Moreover, there is emerging evidence linking periodontal diseases with many systemic diseases such as diabetes, rheumatoid arthritis, osteoporosis, cardiovascular and respiratory diseases, as well as some neurodegenerative diseases as Alzheimer's disease. One of the main etiological agents and key pathogens involved in the initiation and progression of chronic periodontitis is *Porphyromonas gingivalis*. This bacterium produces many virulence factors leading to dysbiosis in the oral microbiome and enabling this pathogen to spread to other tissues. *P. gingivalis* virulence depends on iron and heme availability, therefore our previous work was dedicated to the characterization of heme uptake system Hmu with the leading role played by the HmuY and HmuR proteins. Our studies demonstrated for the first time that HmuY is a unique protein in regard to the heme acquisition mechanism, protein structure, and immunogenic properties, classifying it as *P. gingivalis* one of the major virulence factors. However, *P. gingivalis* produces numerous iron and heme acquisition systems and at the same time, the systems involved in heme degradation and neutralization are not known in this bacterium. Therefore, this project proposes a logical continuation of our studies on heme acquisition systems produced by *P. gingivalis.* We want to focus on Hmu, Hus, and Iht systems involvement in heme uptake, neutralization of heme excess and heme storage leading to *P. gingivalis* virulence. We think that *P. gingivalis* heme acquisition systems may work in a cooperative manner increasing its virulence, and the ability to cause dysbiosis in the oral microbiome. We expect that results obtained in this study will not only be of interest from a basic science point of view but also significantly deepen our understanding of the engagement of heme acquisition mechanisms in *P. gingivalis* virulence. The outcomes of this project will be invaluable for informing future academic- and industrial-led studies focused on finding novel targets for new-generation prevention methods and for developing anti-infective agents to treat *P. gingivalis*-mediated chronic periodontitis.