Investigating the function of the incomplete heme biosynthesis pathway in human oral pathogen *Porphyromonas gingivalis*

Porphyromonas gingivalis, a Gram-negative anaerobic bacterium, is considered one of the main etiological agents and a key pathogen involved in the initiation and progression of chronic periodontitis. Heme is a ligand for many enzymes involved in key processes necessary for survival, however, *P. gingivalis* lacks a functional heme synthesis pathway. Therefore, *P. gingivalis* has developed many mechanisms involved in heme uptake from the external environment, including Hmu and Hus systems. However, as part of the oral microbiome, *P. gingivalis* must compete with other bacteria for nutrients and their availability varies with the severity of the infection. In addition, *P. gingivalis* can infect and survive inside epithelial and immune cells, so it experiences fluctuations in the availability of nutrients, including heme. Analysis shows that *P. gingivalis* has a partially conserved heme synthesis pathway - the last three enzymes of this pathway (HemN, HemG, and HemH protein homologs), therefore we believe that at certain stages of infection, *P. gingivalis* could acquire heme precursors present in the host organism and use them for the synthesis of heme using HemN, HemG, and HemH proteins. Our preliminary studies indicate that the Hus system could be involved in the uptake of heme precursors by *P. gingivalis*. Therefore, in this project we want to determine: How do heme precursors affect the metabolism of *P. gingivalis*? What is the activity of *P. gingivalis* HemH, HemG, and HemN homolog proteins? What is the role of HemH, HemG, and HemN homolog proteins, and how do they influence *P. gingivalis* phenotype and virulence?

We believe that this project, using *P. gingivalis* as a research model, will increase the knowledge of heme metabolism and homeostasis in pathogenic, anaerobic bacteria. Moreover, the proposed research will provide knowledge that can help to understand the mechanisms that allow *P. gingivalis* to adapt to the changing conditions of the external environment. In addition, we believe that the results of this project will be helpful in planning future academic and industrial research aimed at finding new targets for the prevention and treatment of chronic periodontitis and other diseases mediated by *P. gingivalis*.