Significance of the project and Objectives

During infection pathogens must acquire a broad array of essential nutrients such as metal ions from the host. Especially the first –row transition metals iron, manganese and zinc are essential for life due to their roles in in facilitating the structure and function of proteins. Pathogenic bacteria acquire transition metals for cell viability and persistence of infection on competition with host nutritional defence. Vertebrates take advantage of this fact to combat invading microorganisms by restricting their ability to acquire these essential nutrients, a defense known as nutritional immunity. The most well appreciated aspect of nutritional immunity is the sequestration of Fe. However, recently it has become apparent that the host also restricts access to other essential metals such as Mn. The requirement for manganese by pathogenic bacteria necessitates the acquisition of this metal ion from the host environment, making manganese acquisition a potential therapeutic target at the host−pathogen interface. As a consequence, the transport components for manganese uptake are known virulence determinants for a range of human pathogens that cause a variety of life-threatening infections of significant clinical concern, such as *Borrelia burgdorferi*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Staphylococcus aureus Salmonella typhimurium* and *Yersinia pestis*. The treatment of these organisms is increasingly challenging due to the rise of antibiotic resistance. Both the Centres for Disease Control and Prevention (CDC) and the World Health Organization (WHO) have identified them as a serious threat to human health, stating that there is a critical need to develop novel therapeutics to treat antibiotic-resistant infections. One approach to solve this challenge is targeting the mechanisms that pathogens utilize to subvert or evade host defences. Elucidating how the bacterial manganese uptake systems and manganese-sequestering host-defence protein, calprotectin, that restricts Mn(II) from extracellular space compete for the same metal ions is an important avenue for future work.

The aim of the project is to understand and fully characterize the bioinorganic chemistry of manganese transporters in bacteria and fungi – to elucidate different binding sites, thermodynamic features and structural details. A large input into insufficiently explored to date, general knowledge of the beautiful, basic bioinorganic chemistry of Mn(II) will bring us closer to understanding the mechanism of Mn(II) acquisition and its homeostasis at the host-pathogen interface. It will also give an insight into the impact of other transition metals, such as Fe(II) and Zn(II), on Mn(II) acquisition and homeostasis. To achieve the main goal we will focus on basic bioinorganic chemistry of (i) manganese ions and model peptide ligands and (ii) manganese ions and peptide fragments of unstructured regions of manganese binding proteins – their thermodynamics, structure and coordination chemistry. In the last step of the project we will focus on the search for effective Mn(II) ions chelators able to sequester Mn(II) from its metal binding sites, thus limiting its availability to pathogenic bacteria. The search and design of a stable and selective Mn(II) chelator with potential applications, used as the new therapeutic strategies for treating bacterial pathogens, such as *S. aureus* - one of the most frequently isolated pathogens in both community and hospital practices, responsible for burn wound infections, may be the first step to develop this topic in the future. Due to the antibiotic resistance of bacteria and the emergence and transmission of methicillin-resistant *S. aureus* (MRSA) in burn centers resulting in some poor outcomes such as prolonged hospitalization, bacteremia or sepsis, even death, which require further prevention and treatment efforts, the search of alternative therapies is urgently needed. But before I let my imagination run wild I have to start from the beginning – learn a little bit more about the beautiful, basic bioinorganic chemistry of Mn(II) ions.

Methodology

In order to achieve the best results, a number of studies will be carried out (from design through synthesis to characterization of their structural and thermodynamic properties) with the use of several methods including mass spectrometry, potentiometric titration, isothermal titration calorimetry, electron paramagnetic resonance, nuclear magnetic resonance, UV-Vis and CD.

Expected impact

The impact of the results of this project will be a large input into the general knowledge of the fascinating, and not yet well explored bioinorganic chemistry of Mn(II) complexes, and what is even more important, it might really be a stepping stone towards finding new, specific antimicrobial therapies. Results of this project will be published in peer-reviewed journals and presented on international conferences.