Metallophores – understanding (and lighting up) metal transport in pathogens to help the host trick the invaders

Antimicrobial resistance is the ability of a microorganism (like bacteria or fungi) to stop an antimicrobial drug (such as antibiotics and antifungals) from working against it. As a result, standard treatments become ineffective, infections persist and may spread to others (http://www.who.int/antimicrobial-resistance/).

Drug resistance in a wide range of bacterial and fungal microbes is on the rise worldwide, becoming an increasingly serious threat to global public health that requires action across all government sectors and society. Abnormally high percentages of hospital-acquired infections caused by highly resistant bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA), and multidrug-resistant Gram-negative bacteria pose serious threats to human health. Also the incidence of drug resistant invasive fungi has increased dramatically, in both immunosuppressed and non- immunosuppressed patients. New resistance mechanisms emerge and spread globally, making common infectious diseases untreatable, resulting in death or disability of patients. As a result, the development of novel, highly specific agents that will not become drug resistant are now keenly sought. One of the biggest obstacles in finding such effective, pathogen-specific therapeutics that will not cause severe side-effects in patients arises from the fact that bacteria and fungi share essential metabolic pathways with humans (especially fungi, since they are both eukaryotes). In order to design a highly specific antifungal drug, it is crucial to **understand and aim at differences in the metabolism of humans and pathogens**. Although pathogen-selective targets are scarce, there is at least one significant difference between the bacterial, fungal and mammalian cells: **the transport system of transition metal ions.**

Transition metal ions are crucial for the survival of all living organisms, and b**oth pathogens and hosts are aware of the importance of their acquisition**. Bacteria and fungi have developed highly efficient transport systems, which rely on **metallophores** – metal chelating molecules which are excreted outside the pathogen in order to efficiently bind a given metal ion. This can serve either as metal acquisition systems (metal-bound metallophores are transported back to the pathogen) or as a way of protecting themselves against the toxic excess of metal ions in their surroundings. On the other hand, vertebrate hosts have developed mechanisms which restrict the bioavailability of metal ions for pathogens via a process called **nutritional immunity**. This process describes the competition between the pathogen and the host for an important resource (in this case a metal ion), during which both the pathogen and the host make huge efforts to control its availability. In the scope of the **Metallophores** project, we focus on four of these metals — Fe(III), Cu(II), Zn(II) and Ni(II), trying to understand their roles at the pathogen–host interface. and **providing insight into the thermodynamics and coordination chemistry of their interactions with specific metallophores and metal transporters**.

The aim of the **Metallophores** project is to obtain a full understanding of metal transport in pathogens and to enhance the nutritional immunity of the host. The **Metallophores** team will focus on the thermodynamics and coordination chemistry of metallophores, metal transporters, and their interactions with appropriate metal ions to understand and 'light-up' their in vivo transport. We will use both natural metallophores, transporters, and their synthetic analogues (biomimetics) to follow the process of metal binding *in vitro* and in microbes. Moreover, the realization of the project will allow the development of novel, non-invasive, *in vivo* imaging agents and drugs, which can be based on a traditional signaling tool/drug coupled to a part of the metallophore which is specifically recognized by the bacterial or fungal transporter, and will be smuggled via 'Trojan Horse' strategy providing more sensitive and specific methods to diagnose and distinguish between invasive fungal/bacterial infections.