Defining a new paradigm in bacterial copper homeostasis: distinct cytosolic and periplasmic copper storage proteins

All organisms, from bacteria to humans, require small quantities of metals as micronutrients. These metals, such as iron, zinc or copper, perform essential functions in biology. Copper, in particular, is an important cofactor used by enzymes to catalyse chemical reactions that cannot be achieved by organic molecules alone. On the other hand, too much of these metals is toxic. Therefore, organisms must acquire sufficient metals for their needs, while minimising toxicity that would be caused by excess. This is exploited by the immune system, which actively starves invading bacteria of essential iron while using high concentrations of copper to induce toxicity in the pathogen.

In 2015, with collaborators in the UK, I described a novel family of proteins in bacteria that act as copper storage proteins (Csp). We identified and characterised the first members of this protein family in important environmental bacteria, but Csps are widespread among bacteria. We showed that these Csps played a role in provision of copper to copper-requiring enzymes in that bacterium, but it is unclear what the function of the Csp proteins is more broadly. In particular, no studies have tested the function of a Csp in a pathogenic bacterium.

In this project, we will perform detailed characterisation of the structure and function of two unstudied Csp proteins from two pathogenic bacterial species, Neisseria gonorrhoeae and Salmonella enterica sv. Typhimurium. We will use biochemistry, biophysics and structural biology to determine how each protein functions at the molecular level and how these functions differ between these two Csps. These two proteins are localised in distinct compartments of their bacterial cell (periplasm and cytosol, respectively). We hypothesise that these two proteins perform distinct roles within these different species due to their different locations, which we will test within this project. Furthermore, we will study the wider Csp protein family and its evolution. Using bioinformatic and biochemical approaches, we will assess the diversity of Csp proteins across the whole tree of life. We will systematically test the function of a diverse set of Csps from different organisms across the tree to determine how the Csp proteins vary and how they are evolving.