Structural and functional investigation of a molecular regulator involved in bacterial silver resistance using NMR

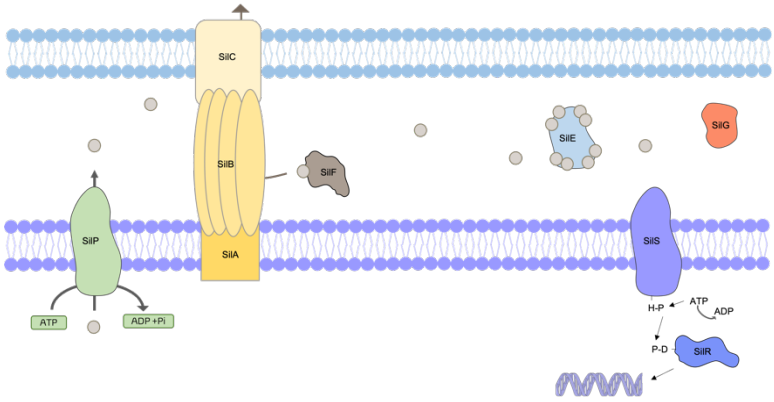

Figure 1 : Composition of the sil system

Like werewolves and vampires, bacteria have a weakness: silver. The antimicrobial properties of this precious metal have extensively been used for thousands of years. Despite this long-standing history and its demonstrated activity against Gram-negative bacteria, the complete bactericidal mode of action of silver remains unclear. Nevertheless, silver misuse can damage the cells and a note of caution is mandatory about its potential toxicity. To counteract the toxic effect of silver, Gram-negative bacteria have developed different resistance mechanisms, including the efficient efflux of the metal out of the cell. The first silver-resistant plasmid pMG101 was isolated from *Salmonella* strain after the death of patients in the burn ward at the Massachusetts General Hospital. The silver-resistant gene cluster is composed of nine genes: a chemiosmotic efflux pump (SilCBA), an ATPase efflux pump (SilP), a responder and membrane sensor performing two-component transcription regulation (SilRS) and three periplasmic silver-binding proteins SilE, SilF and SilG.

Our group is interested into the understanding of the complete mechanism of silver ions eviction through the efflux pump system *sil*. Until now, we tried to decipher how the interplay between SilB, SilF and SilE proteins contribute to the silver efflux pump mechanism. The next challenge will be the understanding of the role of SilG. This small protein was the last discovered and the only homologous protein is found in the *cop* system, namely CopG (identity 44%). The role of CopG is to interconvert Cu(I) and Cu(II) to minimize toxic effects and facilitate export by the efflux pump. In our case, we wonder if SilG has also a role of an oxidoreductase for Ag(I). The structures in the free and complexed with silver ions forms must be resolved and we would like to understand the interaction with the other periplasmic proteins. To reach our goal, we first produce and purify the different periplasmic proteins and then, we combine biophysical methods, namely Nuclear Magnetic Resonance (NMR), Circular Dichroism (CD) and Small Angle X-Ray Scaterring (SAXS) with hybrid molecular dynamics to completely describe the mechanism of the eviction of silver ions through the efflux pump.

The project will be hosted by the analytical science institute located in Lyon/Villeurbanne (France). This new institute comprise around 150 researchers and is among the largest analytical science center in Europe. The thesis project will be developed inside the Biosys group and will mainly make use of NMR and will benefit from the expertise of the group members. A part of the project will be dedicated to the production of isotope labeled proteins.

Hiring profile - The successful candidate should have completed (or in stage of completion) M.Sc. degree either in biochemistry, structural biology, biology, physical chemistry or related fields. Willingness to learn NMR will be strongly appreciated.

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Main ArchiFun theme involved:

- ☐ Host-pathogen interactions;
- ☑ Mechanisms of bacterial resistance and cancer onsets;
- ☐ Neurodegenerative and autoimmune diseases;
- ☐ Translational research in prevalent diseases;
- ☐ Physiology and ecology;
- ☐ Neurosciences and cognition.