Grenoble Alliance for Integrated Structural & Cell Biology

INTERNSHIP PROPOSAL

Institute and Group: IBS group M&P

Supervisor: **Email**: corinne.deniaud@ibs.fr

Deniaud Corinne/Fieschi Franck

Phone: 33 4 57 42 85 41

Research project title:

Resistance to HOCl: a new enzyme system involved in bacterial pathogenicity

5 Keywords to describe the project: Methionine sulfoxyde resistance, Hypochlorous acid stress, electron transfer, pathogenic bacteria, Antibacterial molecules

Description of the project (aims, experimental techniques, recommended background):

Reactive chlorine species are extremely toxic for bacteria. Indeed, methionine oxidation of the proteins leads to a loss of structure and function and ultimately to the pathogen death. A novel enzymatic system with a methionine sulfoxide reductase (Msr) activity has recently been identified in some bacteria. It comprises a membrane protein (MsrQ1) and a periplasmic protein (MsrP1) encoded by the same operon and is proposed to enable resistance to moderate HOCl doses by reducing altered methionines and restoring periplasmic protein integrity. Interestingly, some intracellular pathogen bacteria such as *Brucella* able to colonize macrophages and resist to their high HOCl concentration present a duplication of this operon (MsrP2-MsrQ2) in pathogenicity islands. This second operon, also observed in some uropathogenic bacteria contains a small methionine rich periplasmic protein, MrpX, that could act as a sink for HOCl and be subsequently regenerated by the MsrP2-MsrQ2 system. In our laboratory, we have in hands *E.coli* MsrP1/MsrQ1 and Mrpx from a uropathogenic strain. We want to express both independently and as an operon MsrP2/MsrQ2 to undertake a molecular and functional characterization of this system and demonstrate its functional redundant Msr activity and its role in virulence. The long-term objective is the design of inhibitors of these proteins

Recommended background: bacterial recombinant expression, protein purification and characterization

Justification that the internship's subject fits with the general theme of GRAL:

Deciphering the molecular mechanism of an enzymatic system that seems to be involved in resistance to inflammation processes and thus potentially in the virulence of some highly pathogenic bacteria. This could lead to the development of alternative anti-bacterial therapeutics to face the problem of antibiotic multi-resistance.

Relevant publications of the team:

Juillan-Binard C, Picciocchi A, Andrieu JP, Dupuy J, Petit-Hartlein I, Caux-Thang C, Vivès C, Nivière V, Fieschi F (2017) A Two component NADPH Oxidase (NOX)-like System in Bacteria Is Involved in the Electron Transfer Chain to the Methionine Sulfoxide Reductase MsrP. J. Biol. Chem. 292(6):2485-2494.

Hajjar C, Cherrier MV, Dias Mirandela G, Petit-Hartlein I, Stasia MJ,3, Fontecilla-Camps JC, Fieschi F, Dupuy J (2017) The NOX Family of Proteins Is Also Present in Bacteria. MBio. Nov 7;8(6). pii: e01487-17. doi: 10.1128/mBio.01487-17.