
**2-year Postdoctoral position : Bacterial Molecular Physiology and Pathogenesis (Unit on Genetics of Bacterial Genomes, Institut Pasteur, Paris, France)**

**ref:PTR 256**

***Open as from february 1rst 2008***

We have characterized the three main regulators of sulfur metabolism in *Bacillus subtilis*. They include two LysR-type regulators, CysL and YtlI, and a pleiotropic Rrf2-type repressor, CymR. Interestingly, the signaling pathway controlling CymR activity in response to cysteine availability involves the formation of a complex with a key enzyme of the cysteine biosynthetic pathway, CysK (synthesis of cysteine from sulfur and OAS). We now seek to analyze in detail **the signaling pathway modulating the CymR-CysK complex activity** and the regulatory network controlled by this complex *in vivo*. Using molecular genetic, biochemical and physiological studies, we will identify effectors (*O*-acetylserine (OAS), other precursors of cysteine) participating in signal transduction. An *in vitro* quantitative characterization of interactions involved in the CymR-dependent regulation (surface plasmon resonance, analytical ultracentrifugation, fluorescence anisotropy) and the determination of the structure of the CymR repressor and of the CymR-CysK complex (crystallization, X-ray diffraction) will also be performed. These various approaches coupled with a modeling strategy will allow us to construct an integrated model of the cellular physiology controlling sulfur metabolism in *B. subtilis*. Based on the results obtained with the model organism *B. subtilis*, we would like to unravel the sulfur metabolism pathway and its regulation in related, pathogenic bacteria, such as *Staphylococcus aureus*, *Clostridium difficile* and *Clostridium perfringens*. Our preliminary results indicate that the regulation of cysteine metabolism is related to the sensitivity of *S. aureus* to various stresses. In addition, the synthesis of toxins by *C. difficile* and *C. perfringens* is repressed in the presence of cysteine. Thus, we will test the potential **involvement of cysteine and CymR-like regulators in the control of stress responses and/or virulence** in these pathogenic bacteria. We will first construct *cymR* mutants and/or strains overproducing CymR. Using global (transcriptome) and more specific molecular approaches (fusions, q-RT-PCR, protein-DNA interactions), we plan to obtain new insights about CymR-dependent and/or the cysteine-dependent regulation in these microorganisms. Animal and cellular models of infection will also be tested. This research will be carried out in collaboration with several groups from the Pasteur Institute.

Specific role of the Postdoctoral fellow:
The Fellow, under the supervision of I. Martin-Verstraete, will characterize the interaction between the molecular partners involved in the regulation by the CymR-CysK complex in *B. subtilis* in collaboration with P. England and carry out expression profiling experiments in *C. difficile* and *C. perfringens* in collaboration with B. Dupuy.

Scientific expertise : Molecular biology and biochemistry of bacterial proteins, with special focus on production and purification techniques. Experience in microbiology is desirable. Experience with DNA arrays would be useful.

Research teams involved in this project:
I. Martin-Verstraete (Genetics of Bacterial Genomes, Institut Pasteur)
T. Msadek (Biology of Gram-positive Pathogenic Bacteria, Institut Pasteur)
B. Dupuy (Toxins and Bacterial Pathogenesis, Institut Pasteur)
P. England (Biophysics of Macromolecules and their Interactions, Institut Pasteur)
A. Haouz (Crystallization and X-ray diffraction, Institut Pasteur)
V. Fromion (Mathematic Computing and Genome Analysis, INRA, Jouy en Josas)

Contact: Isabelle Martin-Verstraete (iverstra@...; Tel: 01 40 61 35 61)