**Master 2 2023-2024**

Protein Maturation, Cell fate and Therapeutics

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**Challenging deadly virulence mechanisms causing dysentery in the course of *Shigella* infection**

In the course of their pathogenic interaction with their host, many human bacteria deliver effector proteins that divert specific cell processes to induce the disease. Among these, IpaJ orthologs are major virulence factors expressed in *Shigella*, Salmonella, Vibrio, Pseudomonas, Bordetella, or Burkholderia pathogenic species. These bacteria are main vectors of human infectious diseases. To achieve hijacking of the target cell, bacterial effectors modify a number of cell pathways. *Shigella* IpaJ removes Myristoylation (MYR) from proteins. MYR is one of the main protein modification classes. N-myristoyltransferases (NMTs) are responsible for MYR addition and are universally-conserved enzymes of eukaryotes. MYR is involved in a range of major physio-pathological processes, and represents a promising drug target. However, both complex MYR biology and NMT biochemistry have hampered fundamental advance as well as the development of selective inhibitors, with existing compounds failing in practice. For instance, several issues have made challenging the characterization of the pool of proteins undergoing MYR. In addition, N-termini and relative modifications such as MYR and N-acetylation (NTA) are poorly identified in conventional shotgun proteomics experiments. As a result, only very partial subsets of N-terminal protein modifications are identified to date.

The ambition and originality of the present project is to obtain a multiscale description of the dynamics of the human MYRed targets taking advantage of IpaJ-driven effect, in vitro, in cellulo and upon infection by two different pathogenic enterobacteria (*Shigella flexneri* and *Salmonella enterica*). The overarching aim of this project is to understand the regulation of MYR, its role in cellular processes and pathological consequences of its deregulation. This project will take advantage of the already set collaborations.

The M2 student will participate to the development and use of new approaches to overcome bottlenecks inherent to the characterization of MYRed proteins. A key original feature of the project will be the use of the deMyristoylase activity of *Shigella* IpaJ in a new workflow allowing to study the MYR at proteomic level and shed light on the Gly- and Lys-Myristoylomes and N-terminal Acetylome dynamics. Hence, the student will participate in performing an exhaustive quantitative characterization of all these proteomes and we will study their variations and dialogues following (i) cellular expression of *S. flexneri* IpaJ and (ii) *S. flexneri* infection. Finally, as we have highlighted the existence of IpaJ orthologs in other bacterial pathogens, this project will be a springboard to initiate the characterization of IpaJ deMyristoylase activity and its implications in *S. enterica*, another major human pathogen.

The student will be involved in a larger national project supported by ANR, ARC and in tight collaboration with a world-leading chemist group.

This opportunity offers a serious and intellectually stimulating environment for Master's students who are passionate about molecular biology, proteomics, and infectious diseases. By unraveling the proteomic intricacies of protein demyristoylation, you will contribute to our understanding of host-pathogen interactions and pave the way for potential therapeutic interventions.