Master 2 research internship in Integrated Structural & Cell Biology in Grenoble

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Host laboratory:
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Host group/team:
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Title of the M2 research internship:

Structural studies on the peptidoglycan biosynthesis complex from Pseudomonas aeruginosa

Project summary:

The widespread resistance to antibiotics developed by bacterial pathogens calls for a concerted effort towards the identification of new treatments and strategies. One of the main pathogens signalled by the WHO as urgently necessitating novel treatment approaches is Pseudomonas aeruginosa, a Gram-negative organism that is the causative agent of hospital- and community-acquired infections, in addition to being a major threat for cystic fibrosis patients. Most antibiotics used today are part of the beta-lactam family that targets the bacterial cell wall biosynthetic machinery. The spread of resistant strains, however, has thwarted the usefulness of these drugs and calls for efforts towards the understanding of processes that could lead to innovative treatments.

Bacteria are surrounded by a complex cell wall that is instrumental for their survival, virulence, shape, and adaptability. One of the main components of the bacterial cell wall is the peptidoglycan (PG), a three-dimensional mesh that envelops the entire cell and is formed by polymerized chains of repeating disaccharide subunits cross-linked by short peptides. PG biosynthesis involves the sequential action of reactions that take place in three cellular compartments: the cytoplasm, membrane, and periplasm, often involving proteins that associate into complexes whose inhibition or deregulation (i.e., through antibiotic action) can lead to lysis and death. Despite the importance of interactions between proteins in the different compartments for PG biosynthesis, little is known about their structural characteristics and regulation, an issue partly related to challenges in complex isolation and stability.

In this project, we will use biochemistry, structural biology and bacterial genetic approaches to tackle the characterization of a central PG biosynthetic complex in P. aeruginosa including one key factor i.e. the penicillin-binding protein 2 (PBP2) in order to understand issues such as regulation of interactions, coordinated assembly, and the existence of a potential stable PG biosynthetic conduit involving proteins from the three different compartments.

Keywords:
structural biology, microbiology, peptidoglycan biosynthesis

Relevant publications of the team:

1. Contreras-Martel, C. et al. Molecular architecture of the PBP2-MreC core bacterial cell wall synthesis complex. Nat. Commun. 8 (2017).

2. Martins, A. et al. Self-association of MreC as a regulatory signal in bacterial cell wall elongation. Nat. Commun. 12, 2987. (2021).

3. Bonhomme, S. et al. The inherent flexibility of type I non-ribosomal peptide synthetase multienzymes drives their catalytic activities. Open Biology. 11 (2021).

4. Shirakawa, KT. et al. Architecture and genomic arrangement of the MurE-MurF bacterial call wall biosynthesis complex. PNAS. 120 (2023)

5. Bonhomme, S. et. al. Architecture of a PKS-NRPS hybrid megaenzyme involved in the biosynthesis of the genotoxin colibactin. Structure. 31 (2023)