

INTERNSHIP PROPOSAL

Institute and Group: IBS, BACTERIAL PATHOGENESIS (PATBAC)

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Research project title: Development of new antimicrobials by targeting the bacterial cell wall formation pathway

5 Keywords to describe the project: crystallization, antibiotics, protein interactions, screening, protein complexes

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

The widespread resistance to antibiotics developed by bacterial pathogens that cause diseases ranging from meningitis to tuberculosis calls for a major effort towards the identification of new antimicrobial development approaches. The bacterial cell wall is the validated target of mainstream antimicrobials such as penicillin and other β -lactams, which act by targeting Penicillin-Binding Proteins (PBPs), enzymes that play key roles in its biosynthesis. The objective of this project is to structurally characterize complexes between PBPs and small molecules/fragments that bind to protein interaction regions. The techniques employed will include protein expression, purification, high throughput screening, and X-ray crystallography. Candidates with experience in biochemistry and an interest in learning structural biology are encouraged to apply.

Justification that the internship's subject fits with the general theme of GRAL (3 lines):

This project views the identification and characterization of small molecules that block the recognition between two proteins that are essential for formation of the bacterial cell wall. We will use major structural biology platforms of the PSB, and we also count on a fruitful collaboration with the Attree lab (BIG).

Relevant publications of the team:

Dortet L, Lombardi C, Cretin F, Dessen A, and Filloux A (2018) The type III secretion system uses the translocon as a "pore-forming toxin" to manipulate the host epigenome. **Nature Microbiol.** 3, 378-386.

Contreras-Martel C, Martins A, Ecobichon C, Maragno Trindade D, Mattei PJ, Hicham S, Hardouin P, El Ghachi M, Boneca IG, Dessen A (2017) Molecular architecture of the PBP2: MreC core bacterial cell wall synthesis complex. **Nature Commun.** 8, 776.

Wong SG and Dessen A (2014) Structure of a bacterial α 2-macroglobulin reveals mimicry of eukaryotic innate immunity. **Nature Commun.** 5, 4917