Internship project Master 2
Year 2017-2018

Laboratory/Institute: Institut de Biologie Structurale **Director:** Winfried Weissenhorn
Team: Pneumococcus Group **Head of the team:** Thierry Vernet

Name and status of the scientist in charge of the project: André Zapun **HDR: yes** ☒ **no** ☐
Address: IBS 71 av. des Martyrs 38044 Grenoble France
Phone: +33 (0)4 57 42 85 43 **e-mail:** andre.zapun@ibs.fr

Program the Master's degree in Biology:

☐ Neurosciences and Neurobiology ☒ Immunology, Microbiology, Infectious Diseases
☐ Integrative Structural Biology ☐ Physiology, Epigenetics, Development, Differentiation

Title of the project:

Interaction of beta-lactam antibiotics with penicillin-binding proteins from *Streptococcus pneumoniae*

Objectives (up to 3 lines):

To determine the affinity of the non-covalent binding of different beta-lactams to their target enzymes from *S. pneumoniae* to better understand the mechanism of resistance.

Abstract (up to 10 lines):

Streptococcus pneumoniae is a major human pathogen that causes otitis, pneumoniae and meningitis and kills over 1.5 million persons per year. Beta-lactams, such as penicillin, form a covalent adduct within the active site of essential enzymes called penicillin-binding proteins (PBPs). The pneumococcus is now commonly resistant to beta-lactams, by expressing altered PBPs that react extremely slowly with the drugs. The reaction between beta-lactams and PBPs comprises two steps: the formation of a non-covalent complex, followed by the formation of a covalent bond. To help the design of novel antibiotics, we want to determine the relative importance of the alterations of the PBPs that cause resistance on the formation of the non-covalent complex with the beta-lactams or the formation of the covalent linkage.
We will compare the interaction of various beta-lactams with PBPs from susceptible and resistant strains. Mutant PBPs that cannot form the covalent linkage will be used to investigate the affinity of the non-covalent complex.

Methods (up to 3 lines):

Recombinant protein purification, fluorescence spectroscopy, thermal and chemical protein denaturation.

Up to 3 relevant publications of the team:

Calvez, P., et al. (2017) Substitutions in PBP2b from β-lactam resistant Streptococcus pneumoniae have different effects on enzymatic activity and drug reactivity. J. Biol. Chem. 292, 2854-65.
Philippe, J., et al. (2015) Mechanism of β-lactam action in Streptococcus pneumoniae: the piperacillin paradox. Antimicrob. Agents Chemother. 59, 609-21.
Zapun, A., et al. (2013) In vitro reconstitution of peptidoglycan assembly from the Gram-positive pathogen Streptococcus pneumoniae. ACS Chem. Biol. 8, 2688-96.

Requested domains of expertise (up to 5 keywords):

Interest in biochemistry and microbiology.