Internship project Master 2
Year 2017-2018

Laboratory/Institute: METALLO/IBS **Director:** W. Weissenhorn
Team: METALLO **Head of the team:** Yvain Nicolet
Scientist in charge of the project: Y. NICOLET (Group Leader) **HDR: yes** ☐ **no** ☐
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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: Radical chemistry and Natural compounds

Objectives (up to 3 lines):

Structure/function relationships of radical SAM enzymes involved in the synthesis of natural products such as antibiotics. The main goal is to solve X-ray structures of these proteins in complex with their substrate, product and when possible intermediates or analogues and to combine these structural data with in vitro functional analyses (enzymology and spectroscopy).

Abstract (up to 10 lines):

Radical SAM enzymes correspond to one of the widest superfamily of enzymes (over 110,000 members) that use radical-based chemistry to perform over 70 different types of chemical reactions. These enzymes are found at key steps in the biosynthetic pathways of many cofactors and vitamins, in post-translationnal modifications of proteins, modification of tRNAs and in DNA repair. Over the last few years, increasing numbers of radical SAM enzymes have been identified in the biosynthetic routes of natural compounds, with many of them having antibiotic properties. Understanding the chemical mechanisms at play in these enzymes have dual benefits: i) developing new routes for organic synthesis using radical-based chemistry and ii) developing new tools for the production of such compounds of pharmaceutical interest. This work is part of an international collaboration.

Methods (up to 3 lines):

Anaerobic glove boxes, functional analyses (HPLC-MS). Biochemistry (expression, purification…). X-ray crystallography and molecular docking, theoretical chemistry (QM/MM). EPR and NMR spectroscopies (collaborations in Grenoble)

Up to 3 relevant publications of the team:

Rohac R., Amara P., Benjdia A., Martin L., Ruffié P., Favier A., Berteau O., Mouesca J.M., Fontecilla-Camps J.C. and Nicolet Y. (**2016**) "Carbon-sulfur bond-forming reaction catalysed by the radical SAM enzyme HydE" *Nat. Chem. 8* 491-500
Sicoli G., Mouesca J.M., Zeppieri L., Amara P., Martin L., Barra A.L., Fontecilla-Camps J.C., Gambarelli S. and Nicolet Y. (**2016**) "Fine-tuning of a radical-based reaction by radical *S*-adenosyl-L-methionine tryptophan lyase" *Science 351* 1320-3
Pagnier A., Martin L., Zeppieri L., Nicolet Y. and Fontecilla-Camps J.C. (**2016**) "CO and CN- syntheses by [FeFe]-hydrogenase maturase HydG are catalytically differenciated events" *Proc Natl Acad Sci* U S A. *113* 104-9

Requested domains of expertise (up to 5 keywords):

Basic biochemistry techniques, knowledge in organic chemistry (reactivity), knowledge in structural biology (X-ray crystallography).