



Grenoble Alliance for Integrated  
Structural & Cell Biology

## GRAL MSc RESEARCH SCHOLARSHIP 2020-2021

### RESEARCH INTERNSHIP PROPOSAL

#### Institute / Group

IRIG / IBS – METALLO

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#### Research Project Title

Mechanism of radical SAM enzymes involved in the maturation of ribosomally-synthesized and post-translationally modified peptides with antibiotic properties

#### Description of the project

Ribosomally-synthesized and post-translationally modified peptides (RiPPs) are a promising source for the development of new antibiotics. They contain unusual modifications performed by a superfamily of metalloenzymes, namely radical SAM enzymes, which use radical-based chemistry to catalyze oxidations, methylations, epimerizations, or amino acid residue crosslinks. The resulting RiPPs usually correspond to macrocycles with increased stability and new properties. The goal of this project is to study a few radical SAM enzymes involved in the production of such macrocycles to understand both the chemical reaction involved and the factors that control substrate recognition, in order to develop new enzymes suitable for future biotechnological applications. The project is a partnership between the METALLO group at IBS, Serge Gambarelli SYMMES at IRIG and ChemSyBio at INRA. The candidate will be in charge of the structural characterization of variants of a selected enzyme using X-ray crystallography, as well as protein sample preparation for spectroscopic analyses. The goal is to decipher the chemical mechanism and to modify the protein to use it as a tool for biotechnological applications for the future development of new antibiotics.

#### Keywords

Radical-based chemistry, iron-sulfur cluster, X-ray crystallography, anaerobic conditions, EPR spectroscopy

#### Relevant publications of the team

Amara P., Mouesca J.M., Bella M., Martin L., Saragaglia C., Gambarelli S., Nicolet Y. (2018) "Radical S-Adenosyl-L-methionine Tryptophan Lyase (NosL): How the Protein Controls the Carboxyl Radical •CO<sub>2</sub>- Migration" *J. Am. Chem. Soc.* 140 16661-8.

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.

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