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

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Title of the M2 research internship:
Biosynthesis of post-translationally modified peptides by radical chemistry

Project summary:
The context of this proposal is the threat to public health that represent the increasing tolerance of pathogenic bacteria to existent antibiotics. To offer a solution to the need of new antibiotics, we study the mechanisms of biosynthesis of peptides, with bactericidal activity, carried out by enzymes belonging to the family of radical S-adenosyl methionine (SAM) proteins.
Thus, the overall goal of this M2 internship proposal is to disentangle the mechanism of biosynthesis of three-amino acid cyclophanes, a family of ribosomally-produced and postranslationally-modified peptides (RiPPs). RiPPs are a major class of natural compounds with antibiotic, antiviral or anticancer properties. RiPPs are ubiquitous in nature and are characterised by their vast structural diversity and chemical functionality. The modified peptides are produced from ribosomally-synthesized propeptides of 20-110 amino acids with the following linear structure: a signal sequence followed by a leader, a core, and a follower. The general mechanism of post-translational modifications and maturation is conserved among different classes of RiPPs: peptides are synthesized and transported through their signal sequence to their dedicated tailoring protein(s), that recognize them through either one or both sequences flanking the core (leader and follower). Recognition and binding to their modifying protein triggers its activity causing specific modifications over the core sequence. The mature peptide is finally obtained upon the action of either broad range or specific cellular proteases. Modified peptides are converted from flexible substrates into rigid and stable compounds with increased affinity and specificity for their biological targets.
The M2 student will carry out biochemical characterizations of radical SAM proteins that will comprise, purification, enzyme kinetics and sample preparation for liquid chromatography-mass spectrometry (LC/MS) and for structural studies (X-ray crystallography and cryo-electron microscopy (CryoEM)).

Keywords:
RiPPs, radical chemistry, antibiotics

Relevant publications of the team:
Montalban-Lopez, M.; Scott, T. A.; Ramesh, S.; Rahman, I. R.; van Heel, A. J.; Viel, J. H.; Bandarian, V.; Dittmann, E.; Genilloud, O.; Goto, Y.; Grande Burgos, M. J.; Hill, C.; Kim, S.; Koehnke, J.; Latham, J. A.; Link, A. J.; Martinez, B.; Nair, S. K.; Nicolet, Y.; Rebuffat, S.; Sahl, H.-G.; Sareen, D.; Schmidt, E. W.; Schmitt, L.; Severinov, K.; Suessmuth, R. D.; Truman, A. W.; Wang, H.; Weng, J.-K.; van Wezel, G. P.; Zhang, Q.; Zhong, J.; Piel, J.; Mitchell, D. A.; Kuipers, O. P.; van der Donk, W. A. New Developments in RiPP Discovery, Enzymology and Engineering. Nat. Prod. Rep. 2021, 38 (1), 130–239.

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