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

Supervisor(s):
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Host laboratory:
IBS, https://www.ibs.fr/

Host group/team:
Metalloproteins

Title of the M2 research internship:
Modular enzymes for synthetic chemistry

Project summary:
Background: Natural products are an endless source of bioactive compounds, including antimicrobial and anticancer drugs. The increasing availability of genomes and the development of improved tools to mine into genomic and proteomic data has revealed the existence of proteins involved in the synthesis of unknown bioactive products. Among the most abundant, several members of the family of ribosomally synthesized and post-translationally modified peptides (RiPPs) have been discovered carrying out unexpected reactions such as ether-mediated cross links, N to C cyclizations, epimerisations or thioether formation. The general mechanism of post-translational modifications is conserved among different classes of RiPPs: peptides are synthesized and transported through their signal sequence to their dedicated tailoring proteins, 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. Because the RiPP synthesis machinery works in a modular way, RiPPs have emerged as a promise to set the basis for modular synthesis of bioactive peptides that could be used as drugs.
Aim: The aim of the M2 internship is to understand how ribosomally synthesized substrates are recognized by their modifying protein and how the complex reactions take place in their active sites. To solve these questions, the M2 student will characterise complexes of modifying protein-substrate and their respective reactions by mass spectrometry, and will subsequently crystallise them to solve solid structures of reaction intermediates that will allow engineering of both, the active site of the protein and the substrate, to allow the synthesis of desired products.

Keywords:
structural biology, synthetic chemistry, ribosomally synthesized and post-translationally modified peptides (RiPPs)

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.

Nicolet, Y. Structure-Function Relationships of Radical SAM Enzymes. Nat. Catal. 2020, 3 (4), 337–350.

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