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:
PatBac: Bacterial pathogenesis

Title of the M2 research internship:

Architecture and reprogramming of the colibactin-producing complex for novel antibacterial development

Project summary:
The continuous development of novel antibiotics is crucial in the actual context of bacterial resistance to classical antibacterial molecules. We are focusing our research on natural molecules production from the Polyketide/Non-Ribosomal Peptide synthase (NRPS/PKS) family of enzymes that are often used by microorganisms to synthesize antibiotics or antifungal molecules for interspecies competitiveness. In particular we are interested in the pks operon present in several Enterobacteriaceae that is responsible for the production of colibactin, a multifaceted compound showing a mild inhibition against S. aureus and B. subtilis; however, its genotoxic effect on eukaryotic cells due to the presence of DNA binding motifs makes it difficult to be employed as an antibiotic. Therefore, the structural characterization of the enzymes present in the pks operon is essential to allow an understanding of its mechanism of action that will further facilitate its bioengineering to create novel antibacterial compounds.
Here we would like to combine multiple structural biology strategies including X-ray crystallography, small angle X-ray scattering (SAXS), biophysical approaches and electron microscopy (EM) in order to decipher the structural architecture of the colibactin assembly line. In a second step we will use our structural knowledge on the connection and interaction between the individual enzymes to reprogram the Clb assembly line in order to synthesize new biomolecules that will be extracted, chemically identified and tested on different bacterial strains for their antibacterial properties. A better understanding of this fascinating natural machinery will pave the way for the discovery of new antibacterial drugs.

Keywords:
structural biology, drug design, combinatorial chemistry

Relevant publications of the team:

Bonhomme, S., Dessen, A., Macheboeuf, P.* Architecture of a PKS-NRPS hybrid megaenzyme involved in the biosynthesis of the genotoxin colibactin. Manuscript iunder revision in Structure

Bonhomme, S. Dessen, A., Macheboeuf, P*. (2021) The inherent flexibility of type I non-ribosomal peptide synthetase multienzymes drives their catalytic activity. Open Biology, 11, 200386.