

**Master 2 internship project  
Year 2021-2022**

**Laboratory/Institute:** Institut de Biologie Structurale  
**Team:** Bacterial Pathogenesis

**Director:** Winfried Weissenhorn  
**Head of the team:** Andréa Dessen

**Name and status of the scientist in charge of the project:** Pauline Macheboeuf, CNRS staff  
**HDR:** no

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**Program of the Master's degree in Biology:**

- Immunology, Microbiology, Infectious Diseases     Structural Biology of Pathogens  
 Physiology, Epigenetics, Differentiation, Cancer     Neurosciences and Neurobiology

**Title of the project:**

**Characterization of the megacomplex involved in the biosynthesis of the genotoxin colibactin in *E. coli***

**Objectives (up to 3 lines):**

The objective of this project is to provide mechanistic insight into the synthesis of colibactin, a small molecule synthesized by the *E. coli* NRPS-PKS machinery, in order to better understand the link between colibactin synthesis and colorectal cancer development.

**Abstract (up to 10 lines):**

Recently, *Escherichia coli* strains that are members of the human intestinal flora were shown to be involved in the development of colorectal tumors in animal models of cancer. *E. coli* strains responsible for this effect express a multi-protein machinery, a nonribosomal peptide synthase-polyketide synthase (NRPS-PKS) assembly line. NRPS-PKS assemblies, whose masses can reach up to 2 megadaltons, catalyze linear reactions leading to the synthesis of chemically diverse natural products. In this case, the machinery synthesizes colibactin, a small molecule that, when secreted, leads to targeted DNA destruction and apoptosis, genomic instability and colorectal tumor progression.

The objective of this project is to provide mechanistic insight into colibactin synthesis through the structural characterization of NRPS-PKS assemblies.

**Methods (up to 3 lines):**

We will use biochemistry, X-ray crystallography and electron microscopy techniques in order to characterize different NRPS-PKS complexes.

**Up to 3 relevant publications of the team:**

Silva YRO, Contreras-Martel C, Macheboeuf P, Dessen A (2020). Bacterial secretins : Mechanisms of assembly and membrane targeting. *Protein Science* 29, 893.

Howard SP, Estrozi LF, Bertrand Q, Contreras-Martel C, Strozen T, Job V, Martins A, Fenel D, Schoehn G, Dessen A (2019). Structure and assembly of pilotin-dependent and -independent secretins of the type II secretion system. *PLoS Pathogens* 15.

Laddomada F, Miyachiro MM, Jessop M, Patin D, Job V, Mengin-Lecreux D, Le Roy A, Ebel C, Breyton C,

Gutsche I, Dessen A (2019). The MurG glycosyltransferase provides an oligomeric scaffold for the cytoplasmic steps of peptidoglycan biosynthesis in the human pathogen *Bordetella pertussis*. *Scientific Reports* 9, 4656.

Requested domains of expertise (up to 5 keywords):

Recombinant protein expression  
Protein purification  
Structural biology interest