

**Internship project Master 2
Year 2018-2019**

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

HDR: no

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Program of the Master's degree in Biology:

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

Title of the project: Exploring the link between the human microbiome and cancer development

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:

Dortet L, Lombardi C, Cretin F, Dessen A, and Filloux A (2018) The type III secretion system uses the translocon as a "pore-forming toxin" to manipulate the host epigenome. *Nature Microbiol*, 3,378.

Contreras-Martel C, Martins A, Ecobichon C, Maragno Trindade D, Mattei PJ, Hicham S, Hardouin P, El Ghachi M, Boneca IG, Dessen A (2017) Molecular architecture of the PBP2:MreC core bacterial cell wall synthesis complex. *Nature Commun.* 8, 776.

Bisson-Filho AW, Discola KF, Castellen P, Blasios V, Martins A, Sforça M, Garcia W, Zeri AC, Erickson HP,

Dessen A, and Gueiros-Filho FJ (2015) FtsZ filament capping by MciZ, a developmental regulator of bacterial division. Proc. Natl. Acad. Sci. USA, 112, e2130-e2138.

Requested domains of expertise (up to 5 keywords):

Recombinant protein expression
Protein purification
Structural biology interest