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Host laboratory:

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Title of the M2 research internship:

Exploring the link between the human microbiome and cancer development

Project summary:

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.

We will use biochemistry, X-ray crystallography and electron microscopy techniques in order to characterize different NRPS-PKS complexes and unravel the link between colibactin and colorectal cancer development.

Keywords:

integrative structural biology, crystallography, electron microscopy

Relevant publications of the team:

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

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.