



Grenoble Alliance for Integrated  
Structural & Cell Biology

## GRAL MSc RESEARCH SCHOLARSHIP 2020-2021

### RESEARCH INTERNSHIP PROPOSAL

#### Institute / Group

IRIG / IBS - PATBAC

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#### Research Project Title

Exploring the link between the human microbiome and cancer development

#### Description of the project

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, anti-cancer drugs, NRPS-PKS enzymes

#### Relevant publications of the team

Singh S, Nazabal A, Kanniyappan S, Pellequer J-L, Wolberg AS, Imhof D, Oldenburg J and Biswas A (2019) The plasma Factor XIII heterotetrameric complex structure: unexpected unequal pairing within a symmetric complex. *Biomolecules*.

Chaves RC, Dahmane S, Odorico M, Nicolaes GAF and Pellequer J-L (2014) Factor Va alternative conformation reconstruction using Atomic Force Microscopy. *Thromb. Haemost.* 112: 1167-1173.

Trinh M-H, Odorico M, Pique ME, Teulon J-M, Roberts VA, Ten Eyck LF, Getzoff ED, Parot P, Chen S-wW and Pellequer J-L (2012) Computational reconstruction of multidomain proteins using atomic force microscopy data. *Structure* 20: 113-120.

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