

Exploring the link between the human microbiome and cancer development

Context:

Escherichia coli is both a commensal of the normal human gut, and the most common causative agent of infectious disease brought about by a Gram-negative organism. This versatility is linked to the fact that it is able to produce a vast array of virulence factors and effectors that manipulate different host cell functions. Recently, *E. 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 employ biochemistry, X-ray crystallography, and electron microscopy techniques in order to characterize different NRPS-PKS complexes.

Project localization:

This project will take place at the Structural Biology Institute (IBS) in Grenoble (France) which is part of the Partnership for Structural Biology, providing access to different platforms including X-ray crystallography facilities, electron microscopy, NMR, confocal microscopy among others. This project is also supported by a collaboration with the EM group at the IBS (G. Schoehn) and the University of Clermont-Ferrand (R. Bonnet).

Candidate requirement

The candidate should have experience in recombinant protein expression, protein purification and an interest in structural biology. The candidate will be required to apply to the French doctoral school system in order to obtain a scholarship for the 3-year PhD program.

Please send CV and master grades and rankings to andrea.dessen@ibs.fr
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