

Sujet de stage de Master 2 (1 page max.)

Laboratoire : Institut de Biologie Structurale

Directeur : Winfried Weissenhorn

Intitulé de l'équipe : Pathogénie Bactérienne Responsable : Andréa Dessen

Nom et Qualité du Responsable du Stage : Pauline Macheboeuf, chercheure CNRS HDR oui

Adresse : 71 avenue Jules Horowitz – CS 10090 – 38044 Grenoble

Tél : 04 57 42 87 53

email : pauline.macheboeuf@ibs.fr

Parcours de Master 2 (*Rayer la/les mention(s) inutile(s)*) :

Chemistry for Life Sciences (CLS)

~~Polymers for Advanced Technologies (PTA)~~

~~Organic Synthesis (SOIPA)~~

Titre du sujet :

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

Objectifs visés du stage (5 lignes max) :

The work will be dealing with a very complex protein machinery that is responsible for the biosynthesis of a genotoxin in *E. coli* named colibactin. The structural characterization of members of this complex will help our understanding of the colibactin biosynthesis pathway and will also allow us to envisage combinatorial chemistry in order to modify these enzymes and create new bioactive molecules.

Intérêts pédagogiques et compétences visées (5 lignes max) :

This project is at the interface of biology, chemistry and physics and is located in an excellent environment for structural biology since the IBS is part of the partnership for structural biology (PSB), including the IBS, the EMBL, the ILL neutron source and the ESRF X-ray source. The multiple techniques and instruments employed in our project offers a great opportunity for students to learn multiple techniques applied to structural biology.

Résumé :

Escherichia coli strains that are members of the human intestinal flora have been 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. In addition, the structural knowledge on these enzymes will pave the way for combinatorial chemistry experiments in order to modify the enzymatic pathway and create new bioactive molecules.

Approches & matériels utilisés (5 lignes max) :

Molecular biology, Biochemistry, X-ray crystallography and electron microscopy

Domaines de compétences souhaitées du candidat (3 lignes max):

A basic knowledge of protein biochemistry and an interest in protein structural biology is needed.

Dates du stage : January to June 2024