2-years post-doctoral fellowship – Open position

Inhibition of bacterial conjugation to control antibioresistance spread

Context and general objectives of the project

Antibiotic resistance genes spread through horizontal gene transfers, mainly via bacterial conjugation. Importantly, several multiresistant Gram+ strains have emerged recently, leading to severe public health threats. This project is part of a larger research work aiming at deciphering the molecular mechanisms of Gram+ conjugation, and at opening new routes to control it. Especially, we focus on the DNA processing steps of bacterial conjugation orchestrated by relaxase enzymes encoded by ICEs.

Previous studies provided biochemical and structural information on MOB_T relaxases (Soler *et al*, 2019, Laroussi *et al*, 2022), a family of enzymes widespread in Firmicutes but not well characterized until now. The catalytic active site of one MOB_T protein, named RelSt3, was studied. Thanks to our multidisciplinary consortium of laboratories at the Université de Lorraine, a first promising inhibitory molecule was identified, which partly inhibits the endonuclease activity of RelSt3. However, this molecule has to be optimized because of its low solubility and high cellular toxicity.

With this project, we plan to obtain 3D experimental data by X-ray crystallography and use these 3D data to optimize this current inhibitory molecule, and perhaps to find new molecules that could better fit the active site of RelSt3. We will also extend our study to other relaxases distantly related to RelSt3. This would allow comparisons to be made between these relaxases, with respect to their specificity against the different inhibitory molecules found to successfully inhibit RelSt3.

Laboratory framework

The recruited researcher will work in two neighboring laboratories located at the faculty of sciences of the Université de Lorraine, Nancy, France. Genetic constructs, protein expression and purification, and enzymatic assays (including inhibition tests) will be held in the DynAMic laboratory, supervised by Dr Nicolas Soler. Crystallogenesis and X-ray structure determination of protein/inhibitor complexes will be performed in the CRM2 laboratory, supervised by Dr Frédérique Favier. The two laboratories possess or have access to all equipment required for molecular cloning, protein purification, biophysical analysis (*eg* circular dichroism, SEC-MALS), cristallogenesis and X-ray structure determination. This work will also involve the COSSBA team at the ICBMS institute in Lyon, which will provide us with the inhibiting chemical compounds.

Terms and tenure

This post-doctoral fellowship is for a period of 2 years. The contract is reserved for PhD in protein biochemistry/structural biology who have defended their thesis less than 3 years before the start of the contract. The target start date is October 1st, 2023, with some flexibility on the exact start date. The gross salary will be, depending on experience, between 2700 and 2900 euros per month.

Candidate profile – How to apply

We are looking for an experienced, motivated and dynamic researcher. Candidate should have solid experience in protein biochemistry and biocrystallography methods. The candidate is expected to contribute both experimentally and intellectually to the performance and development of the project. The candidate should be proficient in English both in writing and speaking.

Candidates should send their complete application to Dr Soler (nicolas.soler@univ-lorraine.fr) and Dr Favier (frederique.favier@univ-lorraine.fr): full CV including list of publications, and at least 1 contact referee, cover letter. The deadline for application is July 1st, 2023. Candidates will be selected for an interview during which they will have to show their motivation and their suitability for the proposed position.