The "NER-Specificity" project, described below, was selected as part of the UGA (University Grenoble Alps) IDEX "Strategic Research Initiative" call and was awarded a PhD grant (2017-2020). We are therefore looking for an excellent candidate to carry out this project.

Summary of the projet IDEX-IRS 2017 "NER Specificity"

Title: Nucleotide Excision Repair – New approaches to investigate its exceptionally broad substrate specificity

The project will focus on the nucleotide excision repair (NER) pathway, a versatile pathway, capable of removing a very wide range of bulky DNA lesions, including adducts caused by smoking or generated by chemotherapy and UV-induced lesions. Bacterial NER requires the sequential action of 3 proteins: UvrA, UvrB and UvrC. Despite three decades of studies of the prokaryotic NER pathway, the processes enabling the Uvr proteins to repair a broad range of structurally and chemically diverse DNA lesions remain largely enigmatic and so far, due to difficulties in expressing and purifying these proteins, incision activity assays have relied on the use of Uvr proteins from different sources and notably from thermophilic bacteria. Also, due to limitations in the synthesis of lesion-containing DNA oligonucleotides, most studies have so far focused on a small sub-set of DNA lesions.

The objectives of the project are (i) to reconstitute *in vitro* a functional NER system using UvrA, UvrB and UvrC proteins from a single, mesophilic organism, namely *D. radiodurans* and (ii) to determine the nature and common features of the DNA lesions that are processed by this pathway by evaluating the repair of a wide range of DNA lesions introduced into genomic DNA using an approach relying on HPLC coupled to tandem mass spectrometry. This project will rely on the complementary expertise of J. Timmins' team (biochemistry and structural biology of *D. radiodurans* Uvr proteins) from IBS and J. L. Ravanat's team (characterisation, quantification, chemical synthesis and repair of DNA lesions) from SyMMES. Their joined skills to produce and purify NER enzymes and to monitor the repair of a broad range of DNA lesions are unique, not only in France, but also worldwide.

Student profile

The candidates should hold a Master's degree in Biology, Biochemistry or Chemistry obtained, should possess excellent academic records and ideally should have a dual training in Biology and Chemistry. The candidates should be highly motivated and have experience in recombinant protein expression and protein chromatography techniques. Additional experience in analytical chemistry (in particular HPLC-MS) would be a bonus.

PhD supervisors

PhD supervisor: Joanna Timmins (HDR) ; IBS Grenoble ; joanna.timmins@ibs.fr

PhD co-supervisor: Jean-Luc Ravanat (HDR) ; CEA Grenoble ; jean-luc.ravanat@cea.fr

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Laboratories

IBS: The Institute of Structural Biology (IBS; UMR5075) is a research center for integrated Structural Biology funded by the CEA, the CNRS and the University Grenoble Alpes (www.ibs.fr). The institute performs interdisciplinary research at the interface of biology, physics and chemistry. The thesis project will be carried out in the Viral Infection and Cancer (VIC) group, within the 'DNA Damage and Repair' team led by Joanna Timmins (http://www.ibs.fr/research/research-groups/viral-infection-and-cancer-group-c-petosa/timmins-team/). The team studies the molecular mechanisms involved in the recognition and repair of DNA damage in humans and in the radiation-resistant bacterium *Deinococcus radiodurans*. This is achieved using a multidisciplinary approach combining structural biology, biophysical and biochemical methods with fluorescence microscopy (conventional and super-resolution) in order to decipher these complex molecular processes.

SyMMES: The SyMMES laboratory is a mixed unit between CEA, UGA and CEA (regrouping about 50 researchers), developing basic research on themes with strong societal issue: zero-carbon energy, information and communications technology (ICT), biotechnology and human health. Chemists and biologist of the CIBEST team develop complementary tools to better estimate the cyto- and genotoxicity of several stresses. In particular this laboratory has developed highly powerful methods to monitor the formation and repair of several DNA lesions at the cellular level following exposure of cells to exogenous genotoxic agents (UV, HAPs, ionizing radiation...).
More info here: http://inac.cea.fr/Phocea/Pisp/index.php?nom=jean-luc.ravanat

Applications including detailed CV, cover letter and 2 reference letters should be sent to Joanna Timmins (joanna.timmins@ibs.fr) or Jean-Luc Ravanat (jean-luc.ravanat@cea.fr).

Deadline for sending applications: 31st May 2017