Funded PhD project in Integrated Structural & Cell Biology in Grenoble, France (2025-2028)

Title of the PhD project:
Deciphering the dynamics of DNA repair complexes in the context of chromatin in response to DNA damage.

PhD supervisor(s):
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Host laboratory (UMR):
Institute of Structural Biology (IBS) - UMR5075 CNRS, Univ. Grenoble Alpes, IRIG institute – CEA

Host team/group:
I2SR Group – GenOM Team

Project summary:
The stability of our genome is ensured by the action of DNA repair pathways, including the base excision repair (BER) pathway that localizes and eliminates damaged DNA bases caused notably by exposure to oxidizing or alkylating agents, but also several chemotherapeutic drugs used in cancer therapy. Repair of this type of damage requires the activity of DNA glycosylases (including NTH1) that remove the damaged bases and create a single-strand break at the site of the lesion. This in turn leads to the recruitment of PARP1 and the stimulation of its PARylation activity, which regulate downstream events and notably de novo DNA synthesis. DNA repair processes are highly regulated in time and space, to ensure a timely, step-by-step processing of DNA damage and to minimize the accumulation of toxic byproducts. Numerous studies have revealed the importance of PTMs and PPIs for the repair of DNA double-strand breaks and UV-induced pyrimidine dimers, but little is known so far regarding the post-translational regulation of repair factors involved in the BER pathway. To better characterize the events regulating the initial and intermediate steps of the BER pathway, our first objective is to use mass spectrometry-based proteomics to identify and map the PTMs and interacting partners of key enzymes from this pathway in response to oxidative stress. Secondly, we will use functional assays to characterize the role of the identified partners and PTMs in regulating the BER activity. This work will provide deeper insights into the regulation of the BER pathway and, we hope, contribute to the identification of novel targets for cancer therapy.

Keywords:
BER, Biotin-ID, Chromatin, Mass spectrometry, Post-translational modifications, Protein-Protein interactions

Relevant publications:
- Moe E, Silveira CM, et al., Human Endonuclease III/NTH1: Focusing on the [4Fe-4S] cluster and the N-terminal domain. Chem Comm (2022) 58 p. 12568-12571. DOI: 10.1039/D2CC03643F.
- Hans F, Senarisoy M, Bhaskar Naidu C and Timmins J. Focus on DNA glycosylases – A set of tightly regulated enzymes with high potential as anticancer drug targets. (Review) Int. J. Mol. Sci., (2020). 21 (23), 9226. DOI: 10.3390/ijms21239226.
- Senarisoy M, et al., A FRET-based biosensor for targeting the hNTH1-YB1 interface as a potential anticancer drug target. ACS Chemical Biology (2020) 15, 4, 990-1003. DOI: 10.1021/acschembio.9b01023.
- Caron, P., Pankotai, T., Wiegant, W. W., Tollenaere, M. A. X., Furst, A., Bonhomme, C., et al. (2019). WWP2 ubiquitylates RNA polymerase II for DNA-PK-dependent transcription arrest and repair at DNA breaks. Genes Dev. 33, 684–704. doi:10.1101/gad.321943.118.
- Caron, P., van der Linden, J., and van Attikum, H. (2019b). Bon voyage: A transcriptional journey around DNA breaks. DNA Repair (Amst.) 82, 102686. doi:10.1016/j.dnarep.2019.102686.

Student role:
The PhD student will employ molecular and cell biology techniques to analyze cellular processes. Protein biochemistry approaches, such as western-blots, pulldowns, biochemical assays, and mass spectrometry, will be essential to the study. The student will also utilize advanced imaging methods, including confocal and super-resolution microscopy, to investigate cellular processes. In addition, large-scale data analysis and bioinformatics tools will be applied.

Skills & Qualifications:
Candidates should be highly motivated, hold a **Master's degree,** and have an excellent academic record. A basic training in biology is required, along with experience in a laboratory environment.
Expertise in molecular and cell biology techniques, protein biochemistry, or advanced imaging methods would be an asset. Additionally, knowledge of DNA repair mechanisms and genome stability is highly desirable.