# Master 2 research internship in Integrated Structural & Cell Biology in Grenoble

**Supervisor(s):**
Pierre Caron, pierre.caron@ibs.fr
Joanna Timmins, joanna.timmins@ibs.fr

**Host laboratory:**
IBS www.ibs.fr

**Host group/team:**
I2SR / GenOM

## Title of the M2 research internship:
Regulation of the Base Excision Repair pathway in the context of chromatin

**Project summary:**
Repairing DNA damage is essential for maintaining genome integrity and preventing the onset of serious diseases such as cancer. Every day, the genome of our cells undergoes a considerable amount of DNA damage caused by endogenous or exogenous genotoxic stresses. In particular, oxygen free radicals and alkylating agents can cause damage to DNA bases, which are eliminated by a repair mechanism called Base Excision Repair (BER). Although the various repair factors involved in this pathway and the different molecular steps are well characterized, many of the mechanisms that regulate this pathway in the context of chromatin and within the nuclear space remain to be explored and characterized.
The aim of the research project will be to identify new partners of the human BER repair factors PARP1, NTH1 and its cellular partner, YB-1.
To this end, co-immunoprecipitation and pulldown experiments against YB-1, NTH1 and PARP1 or their tagged versions will be performed on cells treated with genotoxic agents soliciting the BER pathway. Then, protein extracts will be analyzed by western-blot to monitor the interaction between YB-1/NTH1, YB-1/PARP1 and NTH1/PARP1 and evaluate whether these interactions are modulated in response to DNA damage. In addition, the aim of these experiments will be to establish a protocol compatible with a mass spectrometry analysis to be carried out in collaboration with the EdyP platform at CEA.
Finally, in the light of recent findings in the literature, the impact of YB-1 in regulating PARP1 activity following DNA damage will be explored. To this end, cells depleted or not for YB-1 will be treated with DNA genotoxic agents and parylation levels will be monitored by immunofluorescence and western-blot.
The completion of this project will shed light on the role of YB-1 during BER, and help to understand its impact on the activity of crucial repair factors.

**Keywords:**
base excision repair, DNA repair complex, cancer

**Relevant publications of the team:**

. Elin Moe, Célia M Silveira, Lidia Zuccarello, Filipe Rollo, Meike Stelter, Salvatore De Bonis, Catharina Kulka-Peschke, Sagie Katz, Peter Hildebrandt, Ingo Zebger, Joanna Timmins, Smilja Todorovic. Human endonuclease III/NTH1: focusing on the [4Fe-4S] cluster and the N-terminal domain. Chem Commun., 2022

. 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

. Senarisoy M, Barette C, Lacroix F, De Bonis S, Stelter M, Hans F, Kleman JP, Fauvarque M-O and Timmins J. Förster resonance energy transfer-based biosensor for targeting the hNTH1-YB1 interface as a potential anti-cancer drug target. ACS Chemical Biology, 2020

. Pierre Caron, Tibor Pankotai, Wouter W. Wiegant, Maxim A.X. Tollenaere, Audrey Furst, Celine Bonhomme, Angela Helfricht, Anton de Groot, Albert Pastink, Alfred C.O. Vertegaal, Martijn S. Luijsterburg, Evi Soutoglou, Haico van Attikum. WWP2 ubiquitylates RNA polymerase II for DNA-PK-dependent transcription arrest and repair at DNA breaks. Genes & Dev, 2019

. Sarre A, Stelter M, Rollo F, De Bonis S, Seck A, Hognon C, Ravanat JL, Monari A, Dehez F, Moe E and Timmins J. The three Endonuclease III variants of Deinococcus radiodurans possess distinct and complementary DNA repair activities. DNA Repair, 2019