

PhD position available at IBS Grenoble: Super-resolution microscopy studies of mechanisms of chemo-resistance.

Project title: Cellular dynamics of the NTH1 DNA glycosylase and its partner YB1 by super-resolution microscopy

Laboratory: Institut de Biologie Structurale (IBS) in Grenoble, France - Integrated Imaging of Stress Response (I2SR) Group / Genome Organisation & Maintenance (GenOM) Team.

Web site: <https://www.ibs.fr/research/research-groups/integrated-imaging-of-stress-response-group/genome-organisation-maintenance-genom-team/>

PhD supervisor: Dr. Fabienne Hans (MCF Univ. Grenoble Alps)

PhD co-supervisor: Dr. Joanna Timmins (Head of GenOM team)

Funding: 3-year position starting October 1st 2022 (IDEX UGA grant)

Doctoral school: [Chemistry & Life Sciences Doctoral School of the University Grenoble Alps](#)

Project summary:

The strategy of most cancer therapies is to create irreversible DNA damage, resulting in cell death. However, many cases of resistance to these initially effective cytotoxic therapies have been reported and are related to the reactivation of certain DNA repair pathways. Thus, there are growing interests in investigating the molecular mechanisms underlying the regulation of genome maintenance to better understand cancer cells etiology and evolution and to develop personalized anticancer therapeutic approaches. In our research team, we are particularly interested in the human bifunctional DNA glycosylase NTH1, an enzyme of the base excision repair (BER) pathway, and its partner YB1, an oncoprotein, now recognized as a metastatic marker. YB1 has been shown to interact directly with NTH1 *in vivo* and *in vitro*, and to stimulate its catalytic DNA repair activity. Interestingly, in some tumors, escape from chemotherapies can be explained, in part, by the increased catalytic activity of hNTH1 induced by YB1. To shed light on the cellular and molecular mechanisms underlying the functions of NTH1 and YB1 in chemoresistance, we wish to develop a new research axis in the team to explore the cellular localization and dynamics of NTH1 and YB1 in response to DNA damage caused by chemotherapeutic agents. Our objective is to determine whether these factors localize to specific regions or structures of the cytoplasm and/or nucleus in relation to their functions. To achieve this, we propose to use single-molecule localization microscopy that allows cellular studies at the highest possible spatial resolution (down to 10nm). This project will also allow us to identify putative chromatin nanodomains associated with NTH1 and, more broadly, BER activity, and to evaluate the influence of YB1 on the recruitment of NTH1 and other BER proteins to the chromatin and in particular to sites of oxidative DNA damage. Collectively, this work will shed light on fundamental mechanisms of DNA repair and their regulation that are at play in chemo-resistant cancer cells. We expect our work to also contribute to translational research in the area of drug-resistant tumors by characterizing the cellular determinants of formation of the NTH1-YB1 complex, which our team has recently shown to constitute a promising target for new anti-cancer drugs. Interface inhibitors could indeed serve as the basis for the development of new drugs which could significantly improve the efficacy of treatment of tumors resistant to the drugs already on the market.

Keywords: Super-resolution microscopy; Cancer; DNA repair; Base excision repair; DNA glycosylase; Drug resistance.

Methodology: Molecular biology; Mammalian cell culture; Single-molecule localization microscopy (STORM, PALM and single-particle tracking PALM).

Candidate profile: The candidates should be highly motivated, hold a Master's degree in physics, biophysics or structural biology with a marked interest for advanced optical microscopy and data processing, should possess excellent academic records and should have at least a basic training in biology. The candidates should be highly motivated. Previous experience in super-resolution microscopy techniques would be a clear asset.

Application: To apply, please send your curriculum vitae, along with your Master degree transcripts (including grades and ranking), a letter of motivation and two recommendation letters to Fabienne Hans (fabienne.hans@ibs.fr) and Joanna Timmins (joanna.timmins@ibs.fr) by June 3rd 2022.