UFR CHIMIE & BIOLOGIE Université Grenoble Alpes

Master's degree in Biology – Chemistry-Biology Department

Master 2 internship project
Year 2026-2027

Laboratory/Institute: Institut de Biologie Structurale (IBS) **Director:** W. Weissenhorn
Team: I2SR **Head of the team:** J. Timmins

Name and status of the scientist in charge of the project: M. Noirclerc-Savoye

HDR: yes X **no** ☐

Address: 71, avenue des Martyrs, CS 10090, 38000 Grenoble, France
Phone: +33 (0)4 57 42 86 38 **e-mail:** marjolaine.noirclerc@ibs.fr

Program of the Master's degree in Biology:

☐ Microbiology, Infectious Diseases and Immunology X Biochemistry & Structure
☐ Physiology, Epigenetics, Differentiation, Cancer ☐ Neurosciences and Neurobiology

Title of the project: Characterizing NPM1-APE1 Protein Complex Using Integrative Structural Biology Approaches

Objectives (up to 3 lines):

The goal of this M2 internship project is to identify and characterize NPM1-associated protein complexes involved in Base Excision Repair (BER) pathway using biochemical, biophysical and structural approaches.

Abstract (up to 10 lines):

Nucleophosmin 1 (NPM1) is a multifunctional human protein and a major nucleolar component. NPM1 has been identified as a regulator of the base excision repair (BER) pathway, used by cells to restore the integrity of their genome following exposure to oxidative stress, or chemotherapeutic agents. NPM1 modulates the stability, activity, and nucleolar localization of key BER proteins, including AP endonuclease 1 (APE1), which recognizes and processes apurinic/apyrimidinic (AP) sites generated under oxidative stress. The NPM1/APE1 interface represents a promising therapeutic target, as both proteins are overexpressed in multiple cancers with poor prognosis and their interaction drives chemoresistance.
Preliminary biochemical and biophysical analyses have begun to elucidate the interaction between NPM1 domains and APE1, revealing the stoichiometry of the complex. Cryo-electron microscopy (cryo-EM) data suggest that the NPM1/APE1 complex is amenable to single-particle analysis, while NMR experiments have identified the protein domains mediating this interaction. To further characterize the functional impact of NPM1 on APE1, in vitro assays will assess how NPM1 domains influence APE1 nuclease activity. Additionally, pulldown experiments using NPM1 or APE1 will be employed to identify novel interaction partners, which will be structurally characterized using complementary approaches.

Methods (up to 3 lines):

The intern will produce and purify proteins, enabling the reconstitution of protein complexes for structural studies, and their characterization using in vitro experiments using biochemical and

biophysical methods.

Up to 3 relevant publications of the team:

Seck A, De Bonis S, Stelter M, Ökvist M, Senarisoy M, Hayek MR, Le Roy A, Martin L, Saint-Pierre C, Silveira CM, Gasparutto D, Todorovic S, Ravanat JL & Timmins J. Structural and functional insights into the activation of the dual incision activity of UvrC, a key player in bacterial NER. *Nucleic Acids Research* (2023) 51 (6). DOI: 10.1038/s42003-022-03064-x

Spittler, D., Indorato, R. L., Boeri Erba, E., Delaforge, E., Signor, L., Harris, S. J., Garcia-Saez, I., Palencia, A., Gabel, F., Blackledge, M., Noirclerc-Savoye, M.*& Petosa, C*. Binding stoichiometry and structural model of the HIV-1 Rev/importin β complex. Life Sci Alliance 5 (2022). DOI : 10.26508/lsa.202201431

Senarisoy M, Barette C, Lacroix F, De Bonis S, Stelter M, Hans F, Kleman J.P., Fauvarque M.O., and Timmins J (2020). Förster Resonance Energy Transfer Based Biosensor for Targeting the hNTH1–YB1 Interface as a Potential Anticancer Drug Target. ACS Chem. Biol (2020). DOI : 10.1021/acschembio.9b01023

Requested domains of expertise (up to 5 keywords):

Molecular biology, protein purification, protein complex characterization, structural biology