UFR de Chimie et de Biologie
UNIVERSITÉ Grenoble Alpes

Master's degree in Biology – Chemistry-Biology Department

Internship project Master 2
Year 2018-2019

Laboratory/Institute: Institut de Biologie Structurale **Director:** Winfried Weissenhorn
Team: DNA Damage & Repair Team (VIC Group) **Head of the team:** Joanna Timmins

Name and status of the scientist in charge of the project: **HDR: yes ☒ no ☐**
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Program of the Master's degree in Biology:

☐ Neurosciences and Neurobiology ☐ Immunology, Microbiology, Infectious Diseases
☒ Integrative Structural Biology ☒ Physiology, Epigenetics, Differentiation, Cancer

Title of the project: Development of a new therapeutic strategy for the treatment of drug-resistant tumours

Objectives (up to 3 lines):

The objectives of this project is to use a recently developed FRET-based biosensor to identify and characterize small molecule inhibitors of a complex formed between a DNA repair enzyme and a transcriptional regulator that is involved in the resistance to anti-cancer drugs.

Abstract (up to 10 lines):

DNA repair enzymes play an important role in the mechanisms of resistance to anti-cancer treatments. Human endonuclease III, or hNTH1, is responsible for the repair of oxidized pyrimidine bases and is involved in the development of cisplatin resistance used in the treatment of solid tumors. In these cells, hNTH1 interacts with YB1, a transcription factor involved in the genotoxic stress response, which stimulates hNTH1 repair activity. We have recently developed a FRET-based biosensor that allows us to reliably detect the interaction between hNTH1 and YB1 in vitro. With this tool we have performed preliminary screens of two chemical libraries in order to identify potential inhibitors of the hNTH1-YB1 complex. Several compounds of interest have been identified with IC50 around 5-10 µM. The project will involve the production of a large amount of biosensor in order to screen a large chemical library (10,000 compounds) and the validation of the initial hits using *in vitro* and *in vivo* interaction (FRET) and DNA repair assays.

Methods (up to 3 lines):

Large-scale protein expression in *E. coli* and purification; *In vitro* Fluorescence Resonance Energy Transfer (FRET) measurements; Cytotoxicity assays; Protein-protein interaction assays (Alpha-Screen technology); DNA repair assays.

Up to 3 relevant publications of the team:

The manuscript describing the biosensor is in preparation…

Sarre A, Ökvist M, Klar T, Hall DR, Smålas A, McSweeney S, Moe E and Timmins J. Structural and functional characterization of two unusual endonuclease III enzymes from Deinococcus radiodurans. Journal of Structural Biology (2015) 191 (2) p. 87-99.

Timmins J and Moe E. A decade of biochemical and structural studies of the DNA repair

machinery of *Deinococcus radiodurans.* Review article. Comput Struct Biotechnol J. (2016) 14 p. 168-176.

Requested domains of expertise (up to 5 keywords):

Biochemistry; Fluorescence imaging; DNA repair; Chemical library screening; Structural Biology;