UFR de Chimie et de Biologie
UNIVERSITÉ Grenoble Alpes

Master's degree in Biology – Chemistry-Biology Department

Master 2 internship project
Year 2021-2022

Laboratory/Institute: IBS
Director: Dr Winfried Weissenhorn
Team: GenOM
Head of the team: Dr Joanna Timmins

Name and status of the scientist in charge of the project: Fabienne Hans **HDR: yes X☐**
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Program of the Master's degree in Biology:

☐ Immunology, Microbiology, Infectious Diseases ☐ Structural Biology of Pathogens
X☐ Physiology, Epigenetics, Differentiation, Cancer ☐ Neurosciences and Neurobiology

Title of the project: Inhibition of the hNTH1-YB1 complex: a new strategy to counter cisplatin resistance in solid cancers.

Objectives (up to 3 lines):

The objective of this internship is to select and validate inhibitors of the hNTH1-YB1 interaction, with sub-micromolar IC50 values, that promote death by apoptosis in tumor cells resistant to genotoxic agents, and that can enter preclinical testing phases.

Abstract (up to 10 lines):

Most cancer therapies create irreversible DNA damage, resulting in cell death. However, many cases of resistance to these genotoxic therapies appear over time, mostly related to the reactivation of certain DNA repair pathways. This is the case for some cisplatin chemoresistant cancer cells, for which the DNA repair activity of hNTH1, a DNA glycosylase belonging to the base excision repair pathway, has been shown to be overstimulated, as a result of its interaction with the YB1 protein. Thus, the hNTH1-YB1 interface appears to be a relevant target for the development of new anti-tumor molecules. In the lab, High Throughput Screening of chemical libraries specifically targeting protein-protein interactions led to the identification of several compounds that inhibit the hNTH1-YB1 interaction, some of them partially restoring the sensitivity of cisplatin chemoresistant cancer cells. The aim of the project is to further validate, characterize and optimize these new inhibitors *in vitro* and *in cellulo*.

Methods (up to 3 lines):

The methods used in this project are biochemical, molecular biological and cell biological methods. The biochemistry methods are based on protein-protein interaction measurements. The cell biology methods are based on assays measuring cell viability, induction of apoptosis and phagocytosis.

Up to 3 relevant publications of the team:

1- 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., Special issue: Recognition of DNA lesions. (2020). 21 (23), 9226. DOI: 10.3390/ijms21239226.
2- 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) 15, 4, 990-1003. DOI: 10.1021/acschembio.9b01023.
3- Sarre A., Stelter M., Rollo F., De Bonis S., Seck A., Hognon C., Ravanat J.L., Monari A., Dehez F., Moe E. and Timmins J. (2019) The three Endonuclease III variants of Deinococcus radiodurans possess distinct and complementary DNA repair activities. DNA Repair 78 p. 45-59

Requested domains of expertise (up to 5 keywords):

The candidates should have a solid background in Molecular Biology, Biochemistry or Cellular Biology. Having previous experience in protein purification would be appreciated.
The candidates should have knowledge and be interested in DNA repair and cancer.