**Master 2 internship project**

**Year 2024-2025**

**Laboratory/Institute:** Institute for Advanced Biosciences **Director:** P. HAINAUT

**Team:** Protein methylation dynamics in cancer **Head of the team:** N. REYNOIRD

**Name and status of the scientist in charge of the project:** N. REYNOIRD

**HDR: yes**

**Address:** site santé, allée des Alpes 38700 la Tronche

**Phone:** 0476549576 **e-mail:** Nicolas.reynoird@univ-grenoble-alpes.fr

**Program of the Master’s degree in Biology:** Physiology, Epigenetics, Differentiation, Cancer

**Title of the project: Characterization of RNF113A ubiquitin ligase in lung cancer**

Objectives (up to 3 lines):

- To identify substrates of the ubiquitin ligase RNF113A involved in small cell lung cancer chemoresistance

- To validate and characterize its interaction candidate partners with previously identified by the lab

Abstract (up to 10 lines):

Our lab recently identified the SMYD3-RNF113A pathway involved in small cell lung cancer resistance to alkylating chemotherapy. We notably found that the SMYD3 methyltransferase methylates the ligase RNF113A, exacerbating its functions in DNA alkylation damage repair (Lukinovic *et al*., Cancer Discovery 2024). However, the direct activity of RNF113A remains unknown and the objective of this internship is to characterize the molecular signaling linking RNF113A to DNA damage repair. Notably, follow up studies in the lab identified a potential partner complex of RNF113A that the candidate will validate and study in depth. Additionally, the M2 candidate will develop a new tool to identify for the first-time genuine substrates ubiquitinated by the RNF113A ligase, to provide key insights into the molecular pathway and the functional consequence of its ubiquitin activity for DNA damage repair.

Methods (up to 3 lines):

The M2 candidate will perform cloning, cell culture and co-immunoprecipitation of RNF113A and subunit of the interacting complex. Finally, the candidate will use state-of-the art proximity labeling and mass spectrometry approaches to discover novel RNF113A substrates.

Up to 3 relevant publications of the team:

G. Casanova, G. S. Roth, S. Hausmann, X. Lu, L. J. M. Bischoff, E. M. Froeliger, L. Belmudes, E. Bourova-Flin, N. M. Flores, A. M. Benitez, T. Chasan, M. Caporicci, J. Vayr, S. Blanchet, F. Ielasi, S. Rousseaux, P. Hainaut, O. Gozani, M. Le Romancer, Y. Couté, A. Palencia, P. K. Mazur\*, N. Reynoird\*, Cytoskeleton remodeling induced by SMYD2 methyltransferase drives breast cancer metastasis. Cell Discov. 10, 12 (2024)

V. Lukinović, S. Hausmann, G. S. Roth, C. Oyeniran, T. Ahmad, N. Tsao, J. R. Brickner, A. G. Casanova, F. Chuffart, A. M. Benitez, J. Vayr, R. Rodell, M. Tardif, P. W. T. C. Jansen, Y. Couté, M. Vermeulen, P. Hainaut, P. K. Mazur\*, N. Mosammaparast\*, N. Reynoird\*, SMYD3 Impedes Small Cell Lung Cancer Sensitivity to Alkylation Damage through RNF113A Methylation-Phosphorylation Cross-talk. Cancer Discov. 12, 2158–2179 (2022).

N. Tsao, J. R. Brickner, R. Rodell, A. Ganguly, M. Wood, C. Oyeniran, T. Ahmad, H. Sun, A. Bacolla, L. Zhang, V. Lukinović, J. M. Soll, B. A. Townley, A. G. Casanova, J. A. Tainer, C. He, A. Vindigni, N. Reynoird, N. Mosammaparast, Aberrant RNA methylation triggers recruitment of an alkylation repair complex. Mol. Cell 81, 4228-4242.e8 (2021).

Requested domains of expertise (up to 5 keywords):

Cell signaling; cancer; protein post-translational modification