**Master 2 internship project**

**Year 2023-2024**

**Laboratory/Institute:** Institute for Advanced Biosciences **Director:** Pierre Hainaut

**Team:** RNA splicing, Cell Signaling and Response to Therapies **Head of the team:** Béatrice Eymin

**Name and status of the scientist in charge of the project:** Béatrice Eymin **HDR: yes X no ☐**

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**Program of the Master’s degree in Biology:**

**☐** Microbiology, Infectious Diseases and Immunology **☐** Structural Biology of Pathogens

**X** Physiology, Epigenetics, Differentiation, Cancer **☐** Neurosciences and Neurobiology

Title of the project:

Tackling anticancer resistance in lung tumors by targeting the DNA repair and splicing machineries

Objectives (up to 3 lines):

With the aim of identifying the sources of resistance to anti-cancer treatments in lung cancer cells, we will study the impact of the DNA repair pathways in connection with the spliceosome machinery on the sensitivity of lung cancer cells to Osimertinib, a therapeutic inhibitor targeting mutated EGFR receptor.

Abstract (up to 10 lines):

Lung cancer is the most lethal cancer worldwide and therefore a major health problem. Advances in basic and clinical research have led to the development of drugs that target dysregulated receptors. These inhibitors show high therapeutic efficacy. However, some cells escape treatment and lead to the development of secondary tumors resistant to these inhibitors. With the aim of counteracting the appearance of secondary tumors, we are interested in factors that promote genome instability and the dysregulation of the DNA damage response. Indeed, recent findings argue that resistance to anti-cancer treatments arises from increase in genome instability. Remarkably, recent findings from the lab show that overexpression of the splicing factor SRSF2 increases endogenous DNA damage levels and alters DNA double-strand breaks repair pathway choice. Thus, we aim to assess whether modulating SRSF2 protein levels and the DNA double-strand break repair pathways activity may have an impact on the sensitivity of lung cancer cells to EGFR receptor inhibitors.

Methods (up to 3 lines):

The candidate will subject cancer cells to treatment with Osimertinib, combined or not with inhibitors of DNA repair factors or modification of SRSF2 splicing factor expression levels. This will be followed by monitoring the impact of these treatments on cell survival and on the DNA damage response dynamics.

Up to 3 relevant publications of the team:

1. Hatat AS, Benoit-Pilven C, Pucciarelli A, de Fraipont F, Lamothe L, Perron P, Rey A, Levra MG, Toffart AC, Auboeuf D, Eymin B, Gazzeri S. Altered splicing of ATG16-L1 mediates acquired resistance to tyrosine kinase inhibitors of EGFR by blocking autophagy in non small cell lung cancer. Mol Oncol. 2022; 16(19):3490-3508.

2. Jia T, Jacquet T, Dalonneau F, Coudert P, Vaganay E, Exbrayat-Héritier C, Vollaire J, Josserand V, Ruggiero F, Coll JL, Eymin B. FGF-2 promotes angiogenesis through a SRSF1/SRSF3/SRPK1-dependent axis that controls VEGFR1 splicing in endothelial cells. BMC Biol. 2021; 19(1) :173.

3. Boudria A, Abou Faycal C, Jia T, Gout S, Keramidas M, Didier C, Lemaître N, Manet S, Coll JL, Toffart AC, Moro-Sibilot D, Albiges-Rizo C, Josserand V, Faurobert E, Brambilla C, Brambilla E, Gazzeri S, Eymin B. VEGF165b, a splice variant of VEGF-A, promotes lung tumor progression and escape from anti-angiogenic therapies through a b1 integrin/VEGFR autocrine loop. Oncogene 2019 38(7):1050-1066.

Requested domains of expertise (up to 5 keywords):

. Cell Culture experiments

. Cell survival and viability assays

. Biochemistry (Western-blot)

. Epifluorescence microscopy

. Knowledge on genome stability and splicing machinery