**Master 2 internship project**

**Year 2023-2024**

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

**Team:** Cancer target and experimental therapeutics **Head of the team:** Jean-Luc Coll

**Name and status of the scientist in charge of the project:** Amandine HURBIN **HDR: yes**  **no ☐**

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

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

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

**Title of the project: Study of the role of alternative splicing in the resistance of melanoma cells to targeted therapies**

Objectives (up to 3 lines):

Our aim is to determine whether alternative splicing can be regulated by signals from the tumor microenvironment, such as extracellular matrix remodeling, IGF1/IGF1R and/or integrin pathways, and thus modulate the response of melanoma cells to targeted therapies.

Abstract (up to 10 lines):

Cutaneous melanoma is the most aggressive of all skin cancers. Targeted therapies (BRAF and MEK inhibitors, BRAFi/MEKi) prolong patient survival, but resistance mechanisms rapidly render these molecules ineffective. Disruption of alternative splicing can lead to uncontrolled proliferation, acquisition of migration and invasion properties, and resistance to treatment. Increased extracellular matrix rigidity, growth factors, or activation of survival pathways lead to splicing modifications.

Our preliminary data indicate that IGF1R, integrins, and kinases regulating alternative splicing are deregulated in melanoma cells resistant to BRAFi/MEKi. We will study the signaling pathways leading to overexpression of splicing kinases in BRAFi/MEKi-resistant cells, and their link to the tumor microenvironment. This project will allow the identification of therapeutic targets to counteract resistance to targeted therapies in melanoma.

Methods (up to 3 lines):

Human melanoma cells culture (2D and 3D-spheroids); cytotoxicity assays; confocal microscopy; flow cytometry; invasion assays; western-blotting.

Up to 3 relevant publications of the team:

- Castillo-Ferrer et al., Journal of Investigative Dermatology (in revision)

- Jeannot V *et al.*, Journal of Controlled Release (2018) 275:117-128.

- Guerard M *et al.,* Cancer Lett. 2018 Apr 28;420:146-155.

Requested domains of expertise (up to 5 keywords):

Melanoma; targeted therapies; cell culture; alternative splicing; survival signaling pathways