Master 2 research internship in Integrated Structural & Cell Biology in Grenoble

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Host laboratory:
Lab : Biosciences and bioenGineering for hEalth (BGE), IRIG, CEA Grenoble.

Host group/team:
IMAC2 : Ingénierie et Médecine personnalisée Appliquées au Cancer et aux pathologies Cutanées
Engineering and Personalized Medicine Applied to Cancer and Skin Diseases

Title of the M2 research internship:

Impact of Aberrant Wnt/β-Catenin Signaling on Small Extracellular Vesicles Function in Adrenocortical Carcinoma – Immunological Implications and Clinical Perspectives

Project summary:
Adrenocortical carcinoma (ACC) is an aggressive endocrine tumor that arises in the cortex of the adrenal gland. ACC is classified as an immunologically 'cold' tumor with low immune infiltration and resistance to immunotherapies. Gain of function (GOF) mutations in CTNNB1 gene encoding β-Catenin are found in 40 % of ACC and are associated with aggressiveness and poor prognosis. These mutations lead to the constitutive activation of the **Wnt/β-Catenin signaling pathway**, a well-known driver of tumor progression and suppression of tumor immune infiltration. Our recent findings show that the aberrant activation of Wnt/β-Catenin signaling pathway markedly alters the biogenesis and molecular cargo of **small extracellular vesicles** (sEVs) released by ACC cells (Bangoura et al, manuscript in preparation). sEVs are central mediators of intercellular communication between cancer cells and the tumor microenvironment, particularly immune cells. They may contribute to **tumor immune evasion**. The internship project aims to elucidate the role of sEVs secreted by adrenocortical carcinoma cells harbouring constitutive activation of the Wnt/β-catenin pathway in immune escape. We have already developed several cellular and molecular tools (sEVs isolation and characterization, cell lines expressing an inducible shRNA to repress mutant β-catenin, 3D cellular models, reporter genes, fluorescent sEVs, and co-culture systems) that will be immediately available for this program. The project has two main objectives: **(1)** To define the impact of sEVs derived from ACC cells expressing (β-Cat$^+$) or not (β-Cat$^-$) β-catenin on immune cell phenotype, using either addition of exogenous sEVs to Peripheral Blood Mononuclear Cells (PBMC) or co-cultures of PBMC and ACC cells in vitro. Expression of PBMC specific markers, transcriptome and gene networks analyses will be performed. **(2)** To determine the function of (β-Cat$^+$) and (β-Cat$^-$) sEVs in immune cell recruitment in a 3D cell co-culture model including ACC cells and PBMC. We expect from this study a first characterization of the impact of aberrant Wnt/β-Catenin signaling in the regulation of sEVs dynamics and function in immune cell recruitment, a process that could lead to ACC resistance to immunotherapies. Understanding the functional role of sEVs derived from β-catenin-mutated tumors may open new avenues for precision medicine by enabling the development of personalized diagnostic biomarkers and targeted therapeutic strategies.

Keywords:
Extracellular vesicles, Wnt/β-Catenin signaling pathway, adrenocortical cancer, immune evasion

Relevant publications of the team:

1. Velut L, Fancello L, Cherradi N, Guyon L. Single-cell microRNA-mRNA co-sequencing techniques convey large potential for understanding microRNA regulations but require careful and systemic approaches. Nat. Communications 2025. 16(1), 5255. https://doi.org/10.1038/s41467-025-60274-7

2. Hut M, Denis J, Bottausci F, Cubizolles M, Laurent P, Kaal J, Benessalah M, Boizot F, Cherradi N, Fouillet Y, Agache V. Automated Microfluidic Platform for Single Spheroid Culture and Extracellular Vesicle Isolation: Application to Spheroid Transcriptomic Profiling. Small. 2025 Dec;21(48):e08115. doi: 10.1002/smll.202508115. Epub 2025 Oct 14.

3. Cristante J, Reda El Sayed S, Denis J, Ragazzon B, Hantel C, Chabre O, Guyon L, Cherradi N. Aberrant activation of Wnt/β-Catenin signaling pathway drives the expression of poor prognosis-associated microRNAs in adrenocortical cancer with a major impact on miR-139-5p and its host gene PDE2A. bioRxiv. 2023:2023.02.10.527992.

4. Agosta C, Laugier J, Guyon L, Denis J, Bertherat J, Libé R, Boisson B., Sturm N., Feige JJ., Chabre O., Cherradi N. MiR-483-5p and miR-139-5p promote aggressiveness by targeting N-Myc Downstream-Regulated Gene family members in adrenocortical cancer. Int. J. Cancer. 2018. 143(4):944-957. doi: 10.1002/ijc.31363.4.

5. Justine Cristante, Reda El Sayed S, Josiane Denis, Walid Bertal, Catherine Pillet, Bruno Ragazzon, Constanze Hantel, Olivier Chabre, Laura Fancello, Laurent Guyon, Nadia Cherradi. A β-Catenin–miR-139-5p/PDE2A Axis Drives Tumor Progression in Adrenocortical Carcinoma and Reveals LEF1 as a Robust Activity and Prognostic Marker. Submitted.

6. Mohamed Bangoura, Soha Reda El Sayed, Josiane Denis, Olivier Chabre, Laura Fancello, Justine Cristante, Laurent Guyon, Nadia Cherradi. Constitutively active Wnt/β-Catenin signaling controls small extracellular vesicle biogenesis, composition and secretion in adrenocortical cancer. In preparation.