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

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**Host laboratory:**
BioSanté, https://biosante-lab.fr/en

**Host group/team:**
IMAC: Invasion Mechanisms in Angiogenesis and Cancer

## Title of the M2 research internship:

Impact of aberrant Wnt/beta-catenin signaling pathway on extracellular vesicles secretion and function in adrenocortical cancer

**Project summary:**
Adrenocortical carcinoma (ACC) is an endocrine tumor that originates in the cortex of the adrenal gland. Gain of function (GOF) mutations in CTNNB1 gene encoding β-Catenin are frequent in ACC and are associated with their aggressive phenotype. These mutations lead to the constitutive activation of Wnt/β-Catenin signaling pathway, with the induction of an oncogenic program and upregulation of pro-tumorigenic genes. We have previously shown that adrenocortical cancer cells release extracellular vesicles (EVs) that contain oncogenic microRNAs and proteins. EVs are emerging as a new class of cancer biomarkers with a major role in tumor microenvironment remodeling and in metastasis. The aims of the internship are: (1) to investigate the impact of constitutive activation of Wnt/β-Catenin signaling on the release of EVs by ACC cells, (2) to determine whether the signaling pathway drives the molecular content of the EVs (microRNAs and proteins) and (3) to examine the effect of ACC cells-derived EVs on key components of the tumor microenvironment, here the vascular endothelial cells. To this end, the student will use ACC cell lines expressing inducible shRNAs to silence β-Catenin (already available in the team). Evs will be prepared using protocols established in the team. The molecular content of EVs released by ACC cells expressing β-catenin (β-Cat+) will be compared to the one of EVs from ACC cells without β-catenin (β-Cat-) using RNA-Sequencing (Helixio company) and proteomics (EDYP platform, BGE Lab). Finally, vascular endothelial cells will be treated with EVs from β-Cat- or β-Cat+ ACC cells to determine their effects on endothelial cell migration and organization in 2D and 3D cultures. We expect from this study a first characterization of the role of β-Catenin in the regulation of EVs dynamics and function in endothelial cell reprogramming, a process that could lead to tumor progression and dissemination.

**Keywords:**
extracellular vesicles, Wnt/Beta-Catenin signaling pathway, adrenocortical cancer

**Relevant publications of the team:**

Justine Cristante, Soha Reda El Sayed, Josiane Denis, Bruno Ragazzon, Constanze Hantel, Olivier Chabre, Laurent Guyon, Nadia Cherradi. 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 Phosphodiesterase 2A. BioRxiv 2023 doi:https://doi.org/10.1101/2023.02.10.527992

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Giroux P, Bhajun R, Segard S, Picquenot C, Charavay C, Desquilles L, Pinna G, Ginestier C, Denis J, Cherradi N, Guyon L. miRViz: a novel webserver application to visualize and interpret microRNA datasets [published online ahead of print, 2020 Apr 22]. Nucleic Acids Res. 2020;gkaa259. doi:10.1093/nar/gkaa259.

Oreglia M, Sbiera S, Fassnacht M, Guyon L, Denis J, Cristante J, Chabre O, Cherradi N. Early Postoperative Circulating miR-483-5p Is a Prognosis Marker for Adrenocortical Cancer. Cancers. 2020;12(3):724. doi:10.3390/cancers12030724.

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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 Aug 15;143(4):944-957. doi: 10.1002/ijc.31363.