Our Group is mainly interested in identifying genetic risk factors involved in endocrine tumour susceptibility. Through a comprehensive analysis of tumour genomic features, we have been able to propose diagnostic and prognostic markers, to identify altered pathways that could be therapeutically targeted, and to identify new major susceptibility genes.

We are also interested in defining markers associated with differences in anticancer drug response and toxicity. We are applying targeted and whole-exome next-generation sequencing to a large series of clinically well-characterised patients. The aim is to identify new therapeutic approaches to personalise cancer treatment. These efforts will collectively improve the diagnosis, prognosis and treatment of patients.

“We identified a miR-21-3p/TSC2/mTOR axis with predictive value for mTOR inhibitor sensitivity in pheochromocytoma and showed that PTEN expression and TSC1/TSC2/mTOR mutations predict response to rapalogs in renal cancer.”
Integrative multi-omics analysis identifies a prognostic miRNA signature and a targetable miR-21-3p/mTOR axis in metastatic pheochromocytoma

Metastatic pheochromocytoma and paraganglioma (mPGLG) represent major clinical challenges due to the limited accuracy in diagnosis and effective treatments. We aimed to identify reliable metastatic risk miRNAs for mPGLG, and to decipher their role in progression through an integrative multi-omics data analysis. For this purpose, we carried out a comprehensive analysis of miRNomes in 443 patients, the largest discovery cohort explored so far thanks to the participation of an International Consortium of Reference Centres with expertise on this disease.

First, we succeeded in identifying in tumour tissues a miRNA signature related to metastatic risk and to shorter time to progression. Higher than median miR-21-3p levels were also detected in mPGLG patients’ liquid biopsies compared with controls. Using a prognostic predictive model, we built a miRNA-based classifier, which was further studied in an in vitro model, concluding that the classifier’s miRNA overexpression induces aberrant levels of mesenchymal and neuroendocrine markers and enhances cell migration capacity.

The miRNA/mRNA data integration of the same tumours revealed a link between miR-21-3p and TSC2. Moreover, a pan-cancer TCGA integrative study, also including protumorigenic data, further elucidated TSC2 as a potential target for miR-21-3p, being able to uncover a non-previously identified regulatory nature and a targetable miR-21-3p/TSC2/FRB pathway.

PTEN expression and mTOR, TSC1 and TSC2 mutations predict response to rapalogs in renal cancer

The mammalian target of rapamycin (mTOR) pathway inhibitors, also known as rapalogs, are key drugs for the treatment of many tumour types; however, there are predictive biomarkers in clinical use. To address this challenge, we performed a molecular and immunohistochemical characterisation of key mTOR pathway components in a series of 105 renal cell carcinoma patients treated with rapalogs, and recruited by the Spanish Oncology Genitourinary Group (SOGUG) and the University Hospitals Leuven. We demonstrated that response to these drugs occurred more frequently in cases with mTOR pathway mutations than in those without mutations (p < 0.030). Negative PTEN immunohistochemistry staining was detected in 58% of the tumours, and it was more frequent in rapaplog responder patients (p < 0.0029). Furthermore, mutations and negative PTEN protein expression were not mutually exclusive events, and their combination improved response prediction (p < 0.008). In conclusion, our findings suggest that mTOR pathway mutations, negative PTEN immunohistochemistry staining, and their combination, are potential markers of rapalog response. These results provide a step forward with regard to guiding treatment with mTOR inhibitors and personalising renal cancer treatment.