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 new major susceptibility gene for paraganglioma, a gene-net regulated by methylation in medullary thyroid carcinoma, and germline variants and tumour microRNAs that predict outcomes in cancer therapies.”
Remarkably, the inhibition of STAT3 increased the sensitivity of M918T genetic studies with MTC cell models pointed to a to the malignant behaviour of by methylation, such as DKK4, target in RETM918T tumours identifies the STAT3 pathway as a potential therapeutic predisposition. a DNA methyl transferase gene involved in cancer PGL susceptibility genes, but also represents, to the best of our mutations affecting the same residue in six additional PGLs, Targeted deep sequencing revealed the presence of subclonal (FDR<0.15) hypermethylation of homeobox-containing genes, affecting a DNA methyl transferase gene involved in cancer predisposition. MultilayerOMIC data in Medullary Thyroid carcinoma identifies the STAT3 pathway as a potential therapeutic target in RETM918T tumours Medullary thyroid carcinoma (MTC) is a rare disease with few genetic drivers that, when diagnosed at an advanced stage, remains incurable. Due to its rarity, its genomic dissection has not been comprehensively explored. Exploiting multilayer genomic data, considering the transcriptome, miRNAome and methylation, it is possible to uncover genes negatively regulated by methylation, such as JAK1, PCLCR, MMP20, miR-10a, miR-30a and miR-200c, using ME-CHIC-1 and CT cell lines. Moreover, hypomethylation may induce activation of key pathways related to the malignant behaviour of RETM918T-related MTCs. Functional annotation enrichment analysis identified the JAK-Stat pathway as a specific hallmark of RETM918T, harbouring MTCs. In vitro studies with MTC cell models pointed to a RETM918T genetic class-specific proliferative dependence on STAT3 activity. Remarkably, the inhibition of STAT3 increased the sensitivity of RETM918T-bearing MTC cells to the FDA-approved RET inhibitor Vandetanib. This combinational treatment could potentially overcome the adverse effects encountered in clinical practice when Vandetanib monotherapy is applied. Identification of germline genetic variants and tumour microRNAs to predict outcomes in cancer therapies Personalised cancer treatment is of enormous clinical and social relevance since it can lead to safer and more efficient therapies. This year we focused our efforts on applying next generation sequencing to: i) understand how low frequency genetic variants impact paclitaxel-induced neurotoxicity, and ii) identify microRNAs predictive of the antiangiogenic drug response in renal cancer patients. Peripheral neuropathy diminishes the quality of life of many cancer patients, sometimes permanently, and limits the dose and efficacy of many cancer drugs. We found that low frequency variants in EPHA6, EPHA5 and EPHA4 genes contribute to the susceptibility to paclitaxel-induced neurotoxicity. Furthermore, EPHA5 neuronal injury repair function suggests that these genes might constitute important neurotoxicity markers for many neurotoxic drugs. Regarding antiangiogenic therapies, these have drastically improved the survival of kidney cancer patients; however, a fraction of the patients are refractory to these drugs. The first miRNA deep-seq study on an exceptional series of patients treated with sunitinib revealed microRNAs predictive of sunitinib response. Furthermore, a two microRNA-based classifier discriminated individuals with progressive disease upon sunitinib treatment (P=1.3x10-4) with better predictive value than the commonly used clinicopathological risk factors. Thus, we provide new relevant markers that can help rationalise cancer treatment. • PUBLICATIONS • Moncada V, Montoro-Conde C, Perea-Palob P, Santacana M, Jodkowska K, Ingala-Pérez L, Castellano-B, Ermogi E, Soriano M, Matías-Guiu X, Franqu I, Pérez-Rubio M (2016). 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