OUR OVERVIEW

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 showed the utility of immunological parameters with prognostic value in PPGL, showed that DLST mutations remodel cellular succinytoma — being a promising therapeutic target — and defined novel RCC drug response predictive markers.”
**RESEARCH HIGHLIGHTS**

**DLST mutations in pheochromocytoma and paraganglioma (PPGL) cause pro tease hyposuccinylation and metabolic remodelling**

PPGLs are the most heritable tumours. One of the most recently identified PPGL susceptibility genes is DLST, a component of the OGDH complex that catalyses the conversion of alpha-ketoglutarate to succinyl-CoA in the tricarboxylic acid (TCA) cycle. In addition, DLST plays an understudied role in protein succinylation, a post-translational modification (PTM) that causes transcriptional shift from oxidative phosphorylation to a hypoxic cellular state. We concluded that global protein succinylation levels depend strongly on DLST, and proposed DLST as a promising therapeutic target for treating diseases linked to dysregulated succinylation.

**Immunogenomics as a theranostic tool in the immunotherapy context of metastatic PPGL**

The mechanisms triggering metastasis in PPGL are unknown, hindering therapeutic options for patients with metastatic tumours (mPPGL). Genomic profiling of a large cohort of mPPGL allowed us to conclude that high metastatic load, microsatellite instability, and somatic copy number alteration mutations are suitable genomic markers. Transcriptomic analysis defined signaling networks involved in the acquisition of metastatic competence and established a gene signature related to mPPGL, highlighting CDK8 as an additional mPPGL marker. Immunogenomics coupled with immunohistochemistry enabled us to identify a heterogeneous ecosystem at the level of the tumour microenvironment, linked to genomic subtype and tumour behaviour. Specifically, we identified a general immunosuppressive microenvironment in mPPGLs, the exception being MAML3-related tumours expressing PD-L1. We have discovered canonical markers of metastatic risk and suggested the utility of including immune parameters in clinical management for PPGL prognosis and identification of patients who might benefit from immunotherapy (FIGURE 1).

**Novel predictive biomarkers for renal cancer therapy**

Targeted therapy has improved the survival of patients with metastatic renal cell carcinoma (RCC). However, the large inter-patient variability in drug response stresses the urgent need to define novel predictive biomarkers. Here we provide two examples:

1. During clear cell RCC (cRCC) tumour evolution, VHL inactivation is followed by secondary mutations linked to tumour progression. The mutation screening and transcriptomic analysis of large series of cRCC showed that mutation of the chromatin remodeler genes PBRM1 and IDHMC increases tumour angiogenesis and leads to higher benefit from antiangiogenic drug treatment. These modifications can mutate the tumour microenvironment and might serve as predictors of antiangiogenic response.

2. mTOR inhibitors are used to treat RCC. Whole exome sequencing in a large number of patients with exceptional mTOR inhibitor sensitivity revealed that the deubiquitinase USP9X was the only shared mutated gene. Increased drug sensitivity in mutant cells was verified using cell line models. Proteome analyses and immunofluorescence assays demonstrated a p62-mediated deregulation of autophagy in USP9X-depleted cells that has a synergistic effect with mTOR inhibitors. Thus, we defined USP9X as a potential novel marker of sensitivity to mTOR inhibitors and a target for cancer.

**FIGURE 1** Immunogenomics as a theranostic tool in the immunotherapy context of metastatic PPGL. (A) Heatmap of 267 PPGLs profiled by RNA-Seq and classified into 4 distinct TME subtypes. Genomic and clinical features are depicted in the legend. (B) Kaplan-Meier plot of time to progression in patients according to the primary tumour TME subtype (n=33 for IE, n=55 for F, n=24 for IF and n=62 for D). Only primary tumours from non-metastatic and metastatic patients are included. P-value was calculated using a log-rank test.

**PUBLICATIONS**


**HUMAN CANCER GENETICS PROGRAMME | DESCARTES ENDOCRINE CANCER GROUP**

**ANNUAL REPORT 2023**

**SPANISH NATIONAL CANCER RESEARCH CENTRE, CNIO**