The main objective of our Group is to identify and validate new drivers and therapeutic targets in melanoma, the most aggressive form of skin cancer. We are particularly interested in mechanisms that, being selectively deregulated in melanoma, may account for the unique ability of this tumour type to bypass immune recognition and generate metastases already from lesions barely over one millimetre in depth (publications in *Nature*, *Cancer Cell*, *Nature Cell Biology*, *Nature Communications*, among others). Our laboratory has also reported the first-in-class lymphoreporter (*MetAlert*) mice for non-invasive imaging of pre-metastatic niches in melanoma (*Nature*). These systems led to the identification of new mechanisms of immune resistance (*Nature Medicine*) and the generation of nanoparticle-based treatments (*Cancer Cell, EMBO Mol Med*), with derivatives now being tested in clinical trials. These studies are performed in the context of large cohorts of patient-associated datasets, with the ultimate goal of defining physiological relevance.

“Performing single cell analyses, we have identified different cellular states and new mechanisms of immune suppression in melanoma that will pave the way for potential diagnostic markers and therapeutic targets.”
RESEARCH HIGHLIGHTS

The long-term goals of our Group are to:
1. Define the “fingerprint” that distinguishes melanomas from other cancer types.
2. Visualise and target melanoma progression at the whole-body level in vivo.
3. Determine and target signalling cascades that turn immunologically “hot” melanomas into “cold” and refractory tumours.
4. Develop new therapeutic strategies to overcome immune suppression and immune tolerance in melanoma.

New drivers of melanoma progression

A main objective of our Group is to understand and target mechanisms that define the inherent aggressiveness of malignant melanoma. We address this unmet need through genetic and functional studies in melanocytic cell lines, mouse models, and tissue specimens, but also by performing cross-cancer type analyses. We previously identified mechanisms of vesicular trafficking, autophagy, and RNA-associated metabolism with protumorigenic functions in this disease that are not shared by over 25 malignancies (Alonso-Curbelo et al., Cancer Cell 2014; García-Fernández et al., Autophagy 2016; Pérez-Guijarro et al., Nat Commun 2016; Cidhalo et al., Nat 2017; Karra et al., Cancer Cell, 2019). In addition, in collaboration with Sagrario Ortega at CNIO, we developed the first ‘Melanoma-MetAlert’ murine strain for spatio-temporal analyses of premetastatic niches in vivo and the first ‘Melanoma-MetAlert’ murine strain for spatio-temporal analyses of premetastatic niches in vivo (Olmeda et al., Nature 2017). ‘MetAlert’ animals, in combination with human tissue specimens, revealed the growth factor MIDKINE (MDK) as a tumour-secreted pro-metastatic factor with a broad spectrum of action of the immune suppressive functions of MDK. First, we reported that MDK rewrites macrophages, which instead of recognising and eliminating malignant cells, act as tumour promoters via the induction of dysfunctional CD8+ T cells (Cerezo-Wallis et al., Nat Medicine 2020). More recently, we discovered an additional novel role of MDK as a potent suppressor of antigen presentation, namely by inhibiting the differentiation and function of dendritic cells (DCs), specifically those that are conventional types 1 (CD8+). Furthermore, we uncovered an MDK-associated signature in DCs that defines bad prognosis and resistance to immune checkpoint blockers actively used in human patients (Catena et al., BioRxiv 2022; Catena et al., submitted). In light of the tumour-promoting and immune-suppressive roles of MDK, we are now actively pursuing this protein as a therapeutic target.

Single cell analyses of tumour and immune compartments in melanoma

One of the challenges in the rational design of new therapies in melanoma is the marked inter- and intra-tumoural heterogeneity of these lesions. Recent studies have identified various cellular states in melanoma, but the underlying drivers are not well understood. Using scRNAseq, we recently addressed the impact of MDK at the cellular level, both in cutaneous lesions and at premetastatic sites in lymph nodes and the lungs (FIGURE 2). This approach revealed the existence of distinct clusters in tumour implants driven by aggressive melanoma cells. Of these, MDK depletion was found to impinge particularly on a population linked to antigen presentation and interferon response. Importantly, we identified distinct effects of MDK on the transcriptome of macrophages, DCs, and T cells, among others. These data provide new insight into how the secretome of tumour cells can impact at distal sites through a coordinated reprogramming of the expression profile of multiple immune cell types. Our expertise in immune suppression has also helped in collaborative studies to describe the tumour-to-lung systemic effects of yet other immune modulators (i.e., IL22) in aggressive cancers (Briukhovetska et al., Immunity 2023).

FIGURE 1 Identification of tumour drivers and immune modulators in melanoma. Combination of MetAlert mice and functional studies in patient biopsies for the discovery of lymphangiogenic factors, with roles in tumour cell metastasis and immune suppression, here illustrated for the growth factor Midkine.

FIGURE 2 scRNAseq for a comprehensive analysis of the impact of MDK at primary vs premetastatic sites. (A-C) UMAP plots of scRNAseq data in tumour lymph nodes, and lungs (A), with the corresponding separation of malignant cells (B) and immune cells (C). (D) Differential expression profile of MDK-associated tumour cellular states.