Melanomas are inherently aggressive cancers for which basic and translational research have significantly improved patient prognosis. Nevertheless, clinical responses are still incomplete. The long-term goals of our Group are to identify new tumour biomarkers and to validate more effective therapeutic agents. We are particularly interested in mechanisms of cellular stress that, being selectively deregulated in melanoma, define lineage-specific vulnerabilities (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. Our ultimate objective is to improve the management of patients with otherwise refractory metastatic melanomas.

“*We have visualised and targeted (pre)metastatic niches in melanoma and defined mechanisms of immune suppression with clinical implications for cancer patients.*”
An increasing number of (epi)genetic alterations and mechanisms of immune evasion have been identified in malignant melanomas. Nevertheless, no molecular biomarker has been approved as a bona fide prognostic indicator. The field is also in need of improved treatments, as a significant fraction of patients is resistant to targeted and immune-based therapies. The long-term goal of our Group is to define and target drivers of this aggressive behaviour. Our main aims are:

→ To define when and how melanomas act “at a distance” beyond tumour cell dissemination.
→ To determine how melanoma cells evade the immune system, and whether distinct mechanisms may be activated at different anatomical sites.
→ To develop anticancer agents to prevent and eliminate metastatic sites.

New immune suppressors that favour melanoma progression

One of the long-term objectives of the Melanoma Group is to discover new melanoma drivers. We previously identified a cluster of endobiosomal-associated genes that distinguish melanoma from over 30 additional malignancies (Alonso-Curbelo et al., Cancer Cell 2014). Further analyses of lysosomal-dependent pathways also revealed distinctive features of autophagy genes (ATGs) and RNA binding proteins (CEBP4, CILP1 and Igf2rBP3) with selective roles in melanoma progression (García-Fernández et al., Autophagy 2016; Perez-Guijarro et al., Nat Commun 2016; Cifadas et al., Nat Commun 2017; Karras et al. Cancer Cell, 2019). In addition, we have pursued melanoma-secreted factors that could exert long-range activities at visceral organs, particularly in the generation of premetastatic niches. Our Group pioneered the analysis of such systemic effects in vivo by exploiting melanoma MetAlert mice, which have the unique feature of visualising tumour-activated lymphatic vasculature (Olmeda et al., Nature 2017).

MetAlert animals, in combination with human tissue specimens, have revealed the growth factor MDK (MDK) as a new driver of melanoma metastasis. Further functional studies in animal models and expression analyses in large patient cohorts have shown yet another function of MDK in immune suppression. Specifically, we found that MDK promoted an immunotolerant microenvironment whereby macrophages are recruited to tumours, but instead of attacking the cancer cells, promote a dysfunctional state in CD8+ T cells, ultimately favouring immune escape (Wallis et al., Nature Medicine 2020). More recently, we have demonstrated a broader impact of MDK on the immune system in other immune cell types, with global implications for antigen presentation. MetAlert mice is part of large collaborative efforts in the melanoma community to develop better models for gene discovery and testing of pharmacological agents (Patton et al., Cancer Cell 2021).

We have now exploited the MetAlert mice to screen for anticancer agents. First, we demonstrated that these MetAlert mice could recapitulate partial antitumoural effects of compounds in clinical testing in patients (i.e., inhibitors of BRAF and of the immune checkpoint blocker PD-L1). We then used these mice to identify more potent therapeutic agents. Specifically, we tested nanoplastesis of RNA (BO-110), which we had previously found to exert long-term antimelanoma effects in vivo (Tormo et al., Cancer Cell 2009). Using the MetAlert mice, we uncovered potent systemic anti-lymphangiogenic blockers, with activity observed just after a single administration. Mechanistically, dsRNA nanoplastesis were found to exert a rapid dual action in tumour cells and in their associated lymphatic vasculature, involving the transcriptional repression of the lymphatic drivers Midkine and Vegfr3, respectively (FIGURE 2). This suppressive function was mediated by cell-autonomous type I interferon signalling and was not shared by FDA-approved anti-melanoma treatments. These results reveal an alternative strategy for targeting tumour cell-lymphatic crosstalk and underscore the power of Vegfr3-lymphoreporters for pharmacological testing in otherwise aggressive cancers (Olmeda et al., EMBO Mol Med. 2021). The results of these studies contributed to María Soengas being nominated to the Real Academia Nacional de Farmacia and the Real Academia de Ciencias de la Ciencia. She also received the prestigious Pezcoller-Marina Larcher Foundation EACR Women in Cancer Research Award.

MetAlert mice for the discovery of drivers of (pre)metastatic sites

FIGURE 1 Pharmacological analyses in the MetAlert lymphoprobe model. The upper schematic summarises the knock-in model used, which reports neolymphangiogenesis by means of Vegfr3-coupled emission of bioluminescence. Shown are images pre- and post-treatment with BO-110 in melanoma mice treated in vivo. Reproduced with permission from (Olmeda, EMBO Mol Med. 2021).—FIGURE 2. Vegfr3+ “MetAlert” lymphoprobe mice for gene discovery and pharmacological testing of anticancer agents. Analyses in untreated mice had revealed the growth factor Midkine (MDK) as a new prolymphangiogenic and prometastatic factor. Using these mice, BO-110 is now found as a new blocker of neolymphangiogenesis, acting by an IFN-associated dual repression of MDK and VEGFR3.

<FIGURE 1>

<FIGURE 2>

—> PUBLICATIONS


—> AWARDS AND RECOGNITION

→ Carmen y Severo Ochoa Award for Research in Molecular Biology, Fundacion Carmen y Severo Ochoa, Spain.
→ Academia de las Ciencias del Real patronato de la Farmacia, Spain.
→ Top50 Influential Women in Cancer, Comas Gallego.
→ Nominated Top100 Women Leaders in Spain, Mujeres & Co.
→ Elected Member, Real Academia de Ciencias de España, Spain.