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 progression biomarkers and 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 generated the first-in-class lymphoreporter mice for non-invasive imaging of pre-metastatic niches in melanoma (*Nature*). These systems have led to the validation of nanoparticle-based treatments that are currently being tested in clinical trials. Our ultimate objective is to improve the management of patients with otherwise refractory metastatic melanomas.

“The long-term goal of the Soengas Laboratory is to translate basic research in melanoma into the clinic, by identifying novel tumour markers and drug targets.”
CNIo Melanoma Group: objectives and model systems

Melanomas are aggressive solid tumours and a paradigm of how basic and clinical research have significantly improved patient prognosis. Nevertheless, despite great success achieved with targeted and immune-based therapies, sustained clinical responses are still limited. Moreover, the field lacks molecular markers of diagnosis, and the knowledge about how melanomas progress is largely incomplete. These are main unmet needs, as melanomas are the only tumours where lesions barely over one millimetre in depth can be at risk for metastasis. One of the main objectives of our Group is to define drivers of this lineage-specific behaviour. In addition, we are interested in imaging and targeting (pre)metastatic niches in vivo. Specifically, we have elected to visualise the tumour-induced expansion of the lymphangiogenic vasculature (neo-lymphangiogenesis), as this is a process that is activated at early stages of melanoma initiation. However, the specific contribution of lymphatic endothelial cells (LECs) to melanoma is unclear. LECs can secrete a variety of cytokines, which, depending on the context, may favour or inhibit immune surveillance. Moreover, sentinel lymph node removal does not necessarily extend the overall survival of melanoma patients, suggesting that melanoma cells ‘escape’ very early to distal (pre)metastatic niches, but how this occurs remains poorly defined.

The main aims of our Group are (FIGURE 1):
1. To define when and how melanomas act ‘at a distance’ (on stromal and immune compartments) before tumour dissemination
2. To determine how melanoma cells evade the immune system, and whether distinct mechanisms may be activated at different anatomical sites
3. To dissect the impact of the microenvironment, particularly alarmins and bacterial response factors
4. To develop anticanic agents to prevent and eliminate metastatic sites.

Lineage-specific oncogenic dependencies in melanoma

One of the long-term objectives of the Melanoma Group is to discover new melanoma drivers. We previously identified a cluster of endolysosomal-associated genes that distinguish melanoma from over 35 additional malignancies (Alonso-Curbelo et al., Cancer Cell 2014). Further analyses of lysosomal-dependent pathways also revealed unique features of autophagy genes (ATGs) in melanoma (García-Fernández et al., Autophagy 2016).

Other melanoma-enriched regulatory mechanisms were identified by focusing on RNA binding proteins (RBPs). We selected RBPs (a family of over 1500 members) because they are largely unexplored in melanoma, although this is a tumour characteristically associated with a plethora of changes in mRNA gene expression profiles. Performing a series of genome-wide studies (i.e. genomic, transcriptomic, proteomic and interactomic analyses), we uncovered new roles of the RBPs CPEB4 and CUGBP1 in the modulation of mRNA stability, with unexpected targets involving master specifiers of the melanoctye lineage (Pérez-Guijarro et al., Nat Commun 2016; Cifuentes et al., Nat Commun 2017). We have now identified new roles of the RNA binding protein IGF2BP1 in the control of the half-life of a large set of pro-metastatic factors. These included FERTM2 and a series of tumour drivers with no previous links to melanoma. Transcriptomic, proteomic and interactomic analyses, combined with mouse models, identified p62/SQSTM1 as a key binding partner of IGF2BP1. This was unexpected, as p62 was considered a key modulator of autophagy or oxidative stress, but had not been reported as an RBP-binding factor. The relevance of these data was emphasized by clinical analyses of patient prognosis revealing p62 and FERTM2 as adverse determinants of disease-free survival (Karras et al., Cancer Cell 2019, with the cover highlighting the new signalling cascades identified).

‘MetAlert’ mice for the visualisation of premetastatic niches in melanoma and as a platform for gene discovery and target validation

We previously published lymphoreporter melanoma models to visualise metastatic niches before their colonisation (Olmeda et al., Nature 2017). We have now exploited the MetAlert mice to further define immunomodulatory roles of MDK, and to screen for anticanic agents. In particular, we identified an unexpected ability of dsRNA-based mimic BC-101 to blunt neolymphangiogenesis and the associated melanoma metastases (Olmeda et al., BioRxiv 2019; see comparative analyses with respect to targeted agents or immunomodulatory antibodies in FIGURE 2). The MetAlert and its potential for gene discovery and pharmacological testing of anticancer agents. Luciferase-based imaging of drug response in MetAlert mice that reestablish malignant melanoma driven by oncogenes. BioRxiv (in the context of Phen los (Vpgh-1); Tcr-Cre;D8I2; drug). (A) Representative examples of mice with no tumours (not induced), and mice with established melanomas were induced by tamoxifen, but were left either untreated or treated as indicated. (B) Growth curves of treatments as in (A).

- **PUBLICATIONS**

- **AWARDS AND RECOGNITION**
  - Fritz Anders Medal, European Society for Pigment Cell Research (ESPCR).
  - Seidman Award for Influential Women in Science and Innovation.
  - China-Rioja Foundation 2019 (Top 100 Influential Spanish Women).
  - Elected Member, Academia Galáctica de Farmacia.
  - Elected Treasurer, Confederación de Sociedades Científicas de España (COSE).
  - Special mention Ciencia y Mujer 2019.
  - WomenCEO, Jóvenes Investigadoras Gallegas en El Entorno Gallego.
  - Top100 Mujeres Líderes de España 2019 (Top 100 Women Leaders in Spain).
  - Muñoz E, O. A.

- **MAIN OBJECTIVES OF THE CNOI**
  - To define when and how melanomas act ‘at a distance’ (on stromal and immune compartments) before tumour dissemination
  - To determine how melanoma cells evade the immune system, and whether distinct mechanisms may be activated at different anatomical sites
  - To dissect the impact of the microenvironment, particularly alarmins and bacterial response factors
  - To develop anticanic agents to prevent and eliminate metastatic sites.

Figure 1

- **Main objectives of the CNOI melanoma Group**
  - To define new immunomodulatory roles of MDK, and to screen for anticanic agents.
  - To further define immunomodulatory roles of MDK, and to screen for anticanic agents.

Figure 2

- **MetAlert** mice for the visualisation of premetastatic niches in melanoma and as a platform for gene discovery and target validation.

- **ACTIONS**
  - Previous publication lymphoreporter melanoma models to visualise metastatic niches before their colonisation (Olmeda et al., Nature 2017). ‘MetAlert’ animals, in combination with human tissue specimens, revealed growth factor MDK in a new driver of lymphangiogenesis and melanoma metastasis. We have now exploited the MetAlert mice to further define immunomodulatory roles of MDK, and to screen for anticanic agents. In particular, we identified an unexpected ability of dsRNA-based mimic BC-101 to blunt neolymphangiogenesis and the associated melanoma metastases (Olmeda et al., BioRxiv 2019; see comparative analyses with respect to targeted agents or immunomodulatory antibodies in FIGURE 2). The MetAlert and its potential for gene discovery and pharmacological testing of anticancer agents. Luciferase-based imaging of drug response in MetAlert mice that reestablish malignant melanoma driven by oncogenes. BioRxiv (in the context of Phen los (Vpgh-1); Tcr-Cre;D8I2; drug). (A) Representative examples of mice with no tumours (not induced), and mice with established melanomas were induced by tamoxifen, but were left either untreated or treated as indicated. (B) Growth curves of treatments as in (A).