Melanomas are a prime example of how basic and translational research has been translated into improved prognosis for affected patients. Nevertheless, clinical responses are still incomplete. The long-term goals of our Group are to identify new progression biomarkers and therapeutic agents. Focusing on stress response programmes involving apoptosis, autophagy and endosome mobilisation, we have discovered lineage-specific oncogenes that define the melanoma ‘fingerprint’. Transcriptomic and proteomic analyses of the melanoma secretome have enabled us to define how tumour cells remodel the (lymph)angiogenic vasculature and avoid immune recognition. Moreover, we have generated a unique set of animal models for non-invasive imaging of melanoma progression \textit{in vivo}. 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.

‘Combining a series of –omic studies with \textit{in vivo} imaging in mouse models, we have identified a melanoma-associated signature of prometastatic genes that make this tumour uniquely aggressive.’
**CNIO Melanoma Group: objectives and model systems**

Melanomas are aggressive solid tumours and provide a prime example of how integrated basic and clinical research has significantly improved patient prognosis. Nevertheless, despite great successes achieved with targeted and immune-based therapies, sustained clinical responses are still limited. Moreover, the field lacks molecular markers of diagnosis, and the knowledge on how melanomas progress and metastasise is largely incomplete. In addition, one of the main hurdles to advance in this disease is the lack of animal models to monitor melanoma initiation and progression in vivo. To this end, our Group focuses on 3 main objectives (FIGURE 1):

- **Aim 1. Oncogenic pathways selectively deregulated in melanoma that may represent new diagnostic indicators.**
- **Aim 2. Risk factors and prognostic markers.**
- **Aim 3. Animal models that allow for non-invasive monitoring of pre-metastatic niches.**

**Lineage-specific oncoenic dependencies in melanoma**

One of the long-term objectives of the Melanoma Group is to discover new melanoma drivers. We have previously identified an 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 (ATG5) 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 because they are largely absent in melanoma tissues, and their expression levels in metastatic cells are higher than in melanomas. We have now identified additional RBPs in a screen for modulators of melanoma progression. Specifically, we discovered a set of RBPs as unexpected binding partners of p62/SQSTM1, a factor we had selected for analysis based on previous reports in the literature linking this protein to autophagy.

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**Figure 1** Main objectives of the CNIO Melanoma Group aim to identify new progression biomarkers and validate more efficient anticancer agents. Indicated are main experimental systems and representative publications.

**Figure 2** New functions for pro-metastatic drivers in melanoma. Schematic representation of a set of pro-tumourigenic factors with no previous links to melanomas identified by addressing the expression and functional requirement of p62/SQSTM1 in this disease. Different from roles of p62 in autophagy described in a broad spectrum of types, this protein was found in melanoma to bind a selected set of RNA binding proteins (RBPs), here exemplified by CUGBP1. **Aim** 2 studies in cell lines combined with histopathological studies in genetically modified mouse models (GEMM) and histopathological validation in clinical biopsies identified the survival factor FERM2 as a downstream target of the p62/CUGBP1 axis. Both p62 and FERM2 were found overexpressed in advanced melanomas, representing new indicators of poor prognosis.