

Group name: Developmental and cognitive disorders

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Group web: <https://in.umh-csic.es/es/grupos/trastornos-cognitivos-y-del-neurodesarrollo/>

Title of the MRP/TFM: Unravelling the role of the peripheral nervous system in breast cancer therapy resistance.

Summary of the Project:

Emerging evidence has identified tumor innervation as a pivotal contributor to cancer progression and therapeutic resistance. In particular, interactions between the peripheral nervous system (PNS) and the tumor microenvironment are increasingly recognized as modulators of malignancy. Building on these findings, our preliminary data suggest that targeting PNS-mediated signaling may represent a promising strategy to overcome drug resistance in metastatic breast cancer.

This TFM project aims to advance our understanding of how neurotransmitter signalling and its downstream molecular pathways influence the development of therapy resistance in breast cancer. To this end, we will employ both *in vitro* and *in vivo* models that faithfully recapitulate innervated, drug-resistant breast tumors. Using these systems, we will evaluate the effects of pharmacological and genetic interventions targeting neurotransmitter pathways on the emergence of adaptive, drug-resistant cancer cell subpopulations.

Molecular analyses will focus on identifying resistance mechanisms involving evasion of apoptosis and senescence, as well as dysregulation of DNA damage response (DDR) and repair processes. We will also conduct bulk RNA sequencing of adaptive-resistant sublines, enabling unbiased transcriptomic profiling. These data will be compared with transcriptomic datasets generated from our *in vivo* metastatic breast cancer models to uncover conserved gene regulatory networks and signalling pathways associated with PNS-mediated drug resistance.

Finally, selected candidate genes and pathways will be functionally validated using established molecular biology techniques. This work is expected to provide mechanistic insights into neuro-cancer interactions and identify novel therapeutic targets to counteract drug resistance in metastatic breast cancer.

Methods and technology involved in the MRP/TFM Project:

The proposed work will provide the TFM candidate with theoretical knowledge and technical skills in cell culture, imaging, and molecular biology techniques relevant to the field of neuro-oncology research.

The TFM training will include the following key components:

- 2D and 3D cell culture of breast cancer cell lines (e.g., MCF7, MDA-MB-231, MDA-MB-436).
- Drug dose-response analysis (chemotherapy agents and drug inhibitors), performed in the presence or absence of neurotransmitter receptor antagonists.
- Proliferation kinetics, cell survival, and resistance emergence analysis using fluorescence-based cell tracking and time-lapse imaging (e.g., Incucyte Live-Cell Imaging System).
- RNA extraction and quantitative gene expression analysis by RT-qPCR.
- Protein extraction and quantitative protein expression analysis by Western blot.

Proposal of Master Research Project / Proyecto fin de Master for the academic year 2025-26

- Specific gene targeting (Short-herpin or CRISPR/Cas9 gene editing) for in vitro functional validation.
- Handling and immunohistochemistry on samples from mouse models of breast cancer.

Member/s of the lab who will act as tutor/co-tutor of the project (if different from the group IP; PhD required to be tutor / co-tutor):

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