



MÁSTER EN INVESTIGACIÓN BIOMÉDICA

Research Project Proposal

Academic year 2022-2023

Project Nº 03

Title: *Redesigning the impact of radiotherapy in breast cancer with new players: Role of Circulating Tumor Cells (CTCs) and Enpp1-based vulnerabilities*

Department/ Laboratory *Solid Tumors Program CIMA 2.01*

Director 1 *Rafael Martínez-Monge*

Contact: *rmartinezm@unav.es*

Codirector: *Fernando Lecanda*

Contact: *flecanda@unav.es*

Summary

In spite of multimodality treatment triple negative or HER2+ subtypes of breast cancer not achieving a pathological complete response after neoadjuvant treatment present exceedingly high locoregional failure (LRF) rates in about 10 to 25% of the cases. LRF portends a poor prognosis since it is frequently accompanied by subclinical or overt distant metastases. LRF represents an unmet clinical need in the field of Radiation Oncology. Yet, the lack of mechanistic insights in this process have been translated to the difficulty to identify novel vulnerabilities that could be turned into innovative treatments.

Using novel preclinical models, we have recently identified Enpp1/CD203a (Ruiz Fernández de Córdoba, Cancer Discovery 2022) participating in the adenosinergic pathway as a novel therapeutic target associated with LRF. Initial mechanistic dissection indicates that Enpp1 triggers a strong immunosuppressed landscape, favoring infiltration of Treg and PMN-MDSC subpopulations, which is reversed by Enpp1 inhibitor.

Based on these preliminary findings, we hypothesize that targeting Enpp1 together with current state-of-the-art radiotherapy, we will diminish LRF and tackle an unmet clinical need.

To validate this hypothesis we envision reaching the following specific aims:

Aim 1) Mechanistic dissection of the Enpp1 pathway including its contribution to radioresistance, its effect on mobilized immune subpopulations and its impact in global LRF.

Aim 2) Clinical assessment of new biomarker of LRF co-modulated with Enpp1 in breast cancer patients.

Aim 3) Development of an investigator-initiated phase II trial aimed to evaluate the combination of Enpp1 inhibitor and radiotherapy in high-risk triple-negative and HER2+ breast cancer patients.

yes	YES
no	

Does the project include the possibility of supervised animal manipulation to complete the training for animal manipulator?