Universidad de Navarra
Facultad de Ciencias

MASTER'S DEGREE IN BIOMEDICAL RESEARCH
Research Project Proposal
Academic year 2023-2024

Project Nº 10

Title: *Unravelling the complexity of drug resistance development in ovarian cancer: analysis of cellular and molecular mechanisms involved in acquired PARP inhibitors resistance in syngeneic animal models*

Department/ Laboratory *Solid Tumors Department, Laboratory 2.04, Cancer Division*

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Summary

Ovarian cancer is one of the most lethal gynecological cancers. Current therapeutic strategies based on PARP inhibitors (PARPi) allow temporary control of the disease, but most patients develop resistance. Therefore, the development of new therapies to improve the overall survival of ovarian cancer patients is an urgent clinical need. There are several key factors linked to the development of drug resistance in cancer therapy, including, tumoral mutation burden, tumor heterogeneity, size and growth, physical barriers, the immune system, and the tumor microenvironment (TME). The interaction between genetic alterations and the role that TME plays in the development of resistance to PARPi has hardly been studied, being one of the most interesting fields of research due to the valuable information that will be obtained increasing the chances of predicting the appearance of future resistance. Due to the relevance of genomic alterations and the TME in ovarian cancer tumorigenesis, our aim is to characterize the cellular changes and identify new molecular pathways associated with acquired PARPi resistance in preclinical models of ovarian cancer using different molecular and cellular technologies including qPCR, Western blot, shRNA o plasmid overexpression to assess their functional implication in resistance mechanisms to PARPi. Firstly, in-vitro ID-8 VEGF p53-/-luc resistant cell lines will be intraperitoneally injected in C57BL6 mice ($7*10^6$ cells) and tumor growth will be monitored by bioluminescence. After this time, animals from different arms will be euthanized and the peritoneum and the reproductive system (ovaries and uterus) will be biopsied for the performance of multiple fluorescence immunohistochemistry (multispectral imaging by Vectra). We will evaluate the frequency and distribution of CD4+, CD8+, CD4+Treg, CD68+ as immune cells, PanCK (tumor) and DAPI (nuclei). Blood and ascitic fluid will be collected at least one per week to analyze potential changes in the TME during treatment. Multiple cytokine secretion analysis by Luminex (e.g ProcartaPlex 20-plex panel) and flow cytometry with CytoFLEX for several markers.

yes	x
no	

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