



MASTER'S DEGREE IN BIOMEDICAL RESEARCH

Research Project Proposal

Academic year 2023-2024

Project Nº 20

Title: OPTIMIZATION OF CO-TREATMENT WITH SMALL-MOLECULE VEGFR3 INHIBITORS AND IMMUNOTHERAPY FOR THE TREATMENT OF AGGRESSIVE BREAST CANCER

Department/ Laboratory *Bioquímica y Genética/ Inmunoterapia CIMA*

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Summary

Breast cancer (BC) a highly heterogeneous cancer with complex biology and is the most common cancer affecting women worldwide. These tumors produce the lymphangiogenic molecule VEGF-C that signals through VEGFR3 receptors. In breast cancer, excessive VEGFR3 signalling associates with lymphatic metastases, impaired immune cell migration and an incremented immune suppression.

Treatment of breast cancer is based on chemotherapy, radiotherapy and surgery with discrete results if the tumor is diagnosed with lymphatic extension. Immunotherapy with inhibitors of the immune checkpoint (IChPI) has offered discrete results in advanced cancer patients. Resistance to therapy results mostly from stroma-derived immune-suppression.

To tackle this limitation, in this project, we propose targeting the VEGFR3 pathway concomitantly to immunotherapy to alleviate stroma derived immune-suppression.

To this aim, we will explore the efficacy of combinations of treatments with IChPI: PD-L1 and the VEGFR small molecule inhibitor fruquintinib in an orthotopic model of breast cancer in mice. We will compare its efficacy with that obtained with chemotherapy (Capecitabine) or the anti-angiogenic agent bevacizumab.

Concretely, the Master student herein will explore:

- a) **Maximun tolerated doses** of fruquintinib.
- b) **Survival, tumor growth** and onset of lymph node and distal **metastases** after combined therapy.
- c) Modulation of the **tumor immune phenotype** and cytotoxic activity.
- d) **Migration of myeloid cells** to adjacent lymph nodes.
- e) Study of **in vivo migration** of immune cells by use of kikume photoconvertible-mice.

yes	X
no	

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