



**MASTER'S DEGREE IN BIOMEDICAL RESEARCH**  
**Research Project Proposal**  
Academic year 2024-2025

<b>Project Nº 24</b>
<b>Title: Novel strategies to overcome immunotherapy resistance in NSCLC</b>
<b>Department/ Laboratory</b> <i>Laboratory where the project will be carried out indicating Department, Area, Faculty, CUN, CIMA etc.</i> <b>Program in Solid Tumors, CIMA, Laboratory 202</b>
<b>Director 1</b> <i>Name and surname of the director (If there will be two co-directors indicate both)</i> <b>Contact:</b> <i>Alfonso Calvo González (acalvo@unav.es)</i> <b>Codirector:</b> <b>Contact:</b> <i>Diego Serrano Tejero (dserrano@unav.es)</i>
<b>Summary</b> <i>Short summary of the project with a maximum extension of 250 words, including the goals and the methodology that will be used</i> <p>Non-small Cell Lung Cancer (NSCLC) accounts for 85% of all lung cancer patients and is usually diagnosed at late stages. Survival rates are still below 20%, which shows the need of investigating novel therapeutic strategies. Immunotherapy has changed dramatically the management of NSCLC patients, with pembrolizumab, nivolumab and atezolizumab as approved antibodies that block the PD-1/PD-L1 axis, for the treatment of patients with advanced disease. However, resistance to this therapy eventually occurs. Different mechanisms have proven to confer primary or acquired resistance, such as mutations in <i>B2M</i>, the loss of HLA, the coexistence of <i>KRAS</i> and <i>STK11</i> (LKB1) mutations, the gain in <i>MYC</i> expression, etc.</p> <p>Using CRISPR/Cas9 technology we have developed NSCLC models with resistance to anti-PD-1 therapy by targeting <i>B2M</i> or <i>PTEN</i> in cancer cells. These mutations are found in NSCLC patients and are associated to lack of response to immunotherapy. These two publications from our group provide more information about these topics: DOI: 10.1158/0008-5472.CAN-22-3023; DOI: 10.3390/cancers15123076.</p> <p><u>The master's project will consist of investigating the molecular and cellular mechanisms leading to this resistance and how to overcome it. We are using specific drugs targeting key pathways leading to immunotherapy resistance. Our preliminary results show an impressive antitumor response, with cures in a high percentage of animals.</u></p> <p>Specifically, the goals of the project are as follows: 1) to perform 3D co-culture experiments between these cancer cells with <i>B2M</i> or <i>PTEN</i> mutations and immune cells, in the presence or absence of drugs, and to determine cytotoxicity; 2) To characterize the immune microenvironment of tumors from animals treated with the drugs (or untreated) by flow cytometry; 3) to analyze by multiplex immunofluorescence the modification of the immune landscape upon treatment with the drugs.</p> <p>The candidate will learn numerous molecular and cellular techniques, such as cell culture, western blot, PCR, flow cytometry, multiplex immunofluorescence and immunohistochemistry. He/she will participate in animal work related to immunotherapy treatments. The project will be carried out with help of members of the laboratory and results will be discussed in group meetings.</p>



Universidad  
de Navarra

Facultad de Ciencias

yes	X
no	

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