



MASTER'S DEGREE IN BIOMEDICAL RESEARCH

Research Project Proposal

Academic year 2023-2024

Project Nº 26 ASIGNADO	
Title: Unveiling new vulnerabilities in KRAS-driven cancers to design novel therapeutic strategies	
Department/ Laboratory Dept. of Molecular Biotechnology and Health Sciences Molecular Biotechnology Center(MBC), University of Torino Oncogenes and Effector Targets (OnTarget Group) CIMA, University of Navarra	
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Summary KRAS is one of the most frequently found oncogene in human cancer and the largest mutated in lung cancer. Recently, direct KRAS inhibitors have been developed. Despite their rapid progress to the clinic given their promising activity, intrinsic and adaptive resistance mechanisms arise which compromise their antitumor effect in patients. Thus, combinatorial approaches are required to obtain more potent and durable responses. Preliminary data from our lab has unveiled a metabolic switch upon pharmacological or genetic inhibition of KRAS. Whether this metabolic adaptation may be driving tumor resistance is yet to be defined and represents a topic of paramount interest to the field as it could provide the basis for new combinatorial therapeutic strategies. The project's goal is to investigate in depth this process under the following research aims : - To carry out an in vitro screen using inhibitors to different metabolic pathways to identify those ones supporting resistance. - To functionally validate in vitro the targets identified in the pharmacological screen across a panel of mutant KRAS cancer cell lines. - To dissect the molecular changes underlying the metabolic adaptation to KRAS inhibition and unveil master regulators of such changes - To investigate the impact of nominated candidates in in vivo models including their combined inhibition with KRAS inhibitors and immunotherapy To do this, we will integrate state-of-the-art approaches such as a CRISPR/Cas9 and pharmacological screen, in vitro assays (cytotoxicity, cell cycle, apoptosis, ...) and in vivo experiments (tumor growth, multiplex immunohistochemistry, multiparametric flow cytometry) and technologies such as bulk and single cell RNAseq, ATACseq, proteomics and metabolomics	
yes	X
no	
Does the project include the possibility of supervised animal manipulation to complete the training for animal manipulator?	