



**Research Project Proposal**  
Academic year 2021-2022  
**Máster en Investigación Biomédica**

<b>Project Nº 27</b>		
Title: Drug combinations to potentiate the antitumor activity of KRAS inhibitors in cancers with distinct mutational landscape		
Department/ Laboratory Laboratory where the project will be carried out indicating Department, Area, Faculty, CUN, CIMA etc. Oncogenes and Effector Targets (OnTarget) lab Program in Solid Tumors CIMA		
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<p>Summary:</p> <p>Since the discovery of the KRAS oncogene 40 years ago, large efforts from academia and industry attempted to inhibit KRAS oncogenic activity with no success. Thus, KRAS was perceived as an undruggable target. Recently, a new family of direct KRAS inhibitors (KRASi) has entered clinical trials with great expectations. Promising results have been reported in lung cancer patients, with half of patients displaying tumor regression or stable disease. Nonetheless, the antitumor effect is still limited (overall survival ~10-12 months), indicating that combinatorial approaches are required to maximize the effect of KRAS. Furthermore, mutant KRAS lung cancer patients with distinct mutational spectrum in tumor suppressor genes (TSGs) display different level of response to KRASi.</p> <p>One strategy to enhance the efficacy of KRASi is through combined administration of targeted therapies or immune checkpoint inhibitors. The current project aims to identify new combinatorial approaches for mutant KRAS lung cancer that are tailored to the different subgroups co-expressing mutations in either P53, LKB1 or KEAP1.</p> <p>To do this, we will perform an integrative approach involving 1) the use of CRISPR/Cas9 technology to incorporate mutations in mutant KRAS cell lines of the most prevalent TSGs, 2) the development of 2D and 3D co-culture experiments, 3) the generation of syngeneic mouse models, and 4) the implementation of metabolomics and single cell immune-phenotyping, to assess the contribution of TSGs to the activity of KRASi in mutant KRAS lung cancer.</p>		
yes	<input checked="" type="checkbox"/>	Does the project include the possibility of supervised animal manipulation to complete the training for animal manipulator?
no	<input type="checkbox"/>	