Universidad de Navarra

Máster en Investigación Biomédica
Facultad de Ciencias

Research Project Proposal
Academic year 2017-2018

Project Nº 37

Title:
Inhibitory strategies to target key effectors in epithelial tumors driven by the KRAS oncogene

Department/ Laboratory
Oncogenes and Target Effectors lab
Program in Solid Tumors and Biomarkers
Center for Applied Medical Research (CIMA).

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Summary
KRAS represents a dominant oncogene driving human tumorogenesis in 30% of human tumors. Mutations in KRAS are found in epithelial cancer types including lung, pancreas and colorectal carcinomas, which are among the deadliest tumors. Given the unique features of KRAS as a target, it has remained refractory to therapeutic inhibition. Thus, a paradigm switch of this trend remains imperative to develop strategies designed to reach this unmet clinical need.
The current proposal stems from our recently published work aimed to identify KRAS-regulated genes across a diverse range of mutant KRAS tumors, through an integrative gene-expression approach. This study identified a cross-tumors KRAS gene signature that included genes whose inhibition represents a vulnerability in mutant KRAS tumors (2). The goal of this proposal is to test the clinical and functional relevance of other candidates of this signature in KRAS-driven epithelial tumors, with a special focus on lung and pancreatic cancer.
The project will focus around the following specific goals:
1. To dissect the implication of gene modulation of candidate genes in mutant KRAS tumors using loss- and gain-of-function strategies in vitro through 2D and 3D culture systems (3).
2. To define the role of candidate genes as potential therapeutic targets in mutant KRAS tumors in human and mouse in vivo models.
3. To investigate the effect of inhibitory pharmacological combinations in mutant KRAS tumors.

References
1. Stephen et al., Dragging Ras back in the ring. Cancer Cell. 2014 Mar17; 25 (3):272-81
2. Vallejo et al. An integrative approach unveils FOSL1 as an oncogene vulnerability in KRAS-driven lung and pancreatic cancer. Nature Communications. 2017, Feb 2; 8:14294
3. Boj SF et al, Organoid models of human and mouse ductal pancreatic cancer. Cell. 2015, Jan 15; 160 (1-2): 324-38