



**Research Project Proposal**  
Academic year 2018-2019

**Project Nº 38**

**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  
Center for Applied Medical Research (CIMA).*

**Director:** *Silvestre Vicent*

**Contact:** *silvevicent@unav.es*

**Codirector:** *Karmele Valencia*

**Summary**

*KRAS represents the dominant oncogene driving human lung cancer, in around 30% of cases. However, it has remained refractory to therapeutic intervention and its inhibition is regarded to as the Holy Grail of Oncology (1, 2). Thus, a paradigm switch 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 dependencies (3-5). The goal of this proposal is to test the clinical and functional relevance of some of these candidates in the context of conventional treatments (chemotherapy) and targeted therapies (immunotherapy, RAS effectors' inhibitors), with a special focus on lung and pancreatic cancer. The project will focus around the following general goals:*

- 1. To dissect the influence of gene modulation of candidate genes in mutant KRAS tumors via loss-of-function strategies in vitro using CRISPR/Cas9 technology and deploying 2D and 3D culture systems (3).*
- 2. To define the role of candidate genes as potential therapeutic targets in combination with immunotherapy and other targeted therapies in mutant KRAS tumors in human and mouse in vivo models.*

**References**

- 1. Stephen et al., Dragging Ras back in the ring. Cancer Cell. 2014 Mar17; 25 (3):272-81*
- 2. Roman et al., KRAS oncogene in non-small cell lung cancer: clinical perspectives on the treatment of an old target. Mol Cancer. 2018 Feb 19;17(1):33*
- 3. 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*
- 4. Ajona et al., A Combined PD-1/C5a Blockade Synergistically Protects against Lung Cancer Growth and Metastasis. Cancer Discovery Cancer 2017 Jul 7(7):694-703.*
- 5. Roman et al., Inhibitor of differentiation-1 (Id1) sustains mutant KRAS-driven lung adenocarcinoma progression, maintenance and metastasis via regulation of a FOSL1 network. Cancer Research (under review).*
- 6. Boj SF et al, Organoid models of human and mouse ductal pancreatic cancer. Cell. 2015, Jan 15; 160 (1-2): 324-38*

yes	X
no	

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