Universidad de Navarra

Máster en Investigación Biomédica
Facultad de Ciencias

Research Project Proposal
Academic year 2016-2017

Project Nº 8 ASIGNADO
Title: Functional elucidation of the role of KRAS oncogene effectors in epithelial cancers
Department/ Laboratory Oncogenes and Metastasis lab, Program in Solid Tumors and Biomarkers, Center for Applied Medical Research(CIMA)
Director: Dr. Silvestre Vicent Cambra **Contact:** silvevicent@unav.es, 948194700 (ext. 1003)
Summary KRAS represents the dominant oncogene driving human tumorogenesis in 30% of human tumors. Mutations in KRAS are found in epithelial cancer types including lung and pancreatic adenocarcinomas as well as cholangiocarcinomas. Given the uniqueness 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 a preliminary study where we undertook an integrative cross-tumors analysis to identify genes specifically regulated by mutant KRAS. This strategy identified a KRAS-dependent signature representative of mouse and human cancers harbouring KRAS mutations, including lung adenocarcinoma (LAC) and cholangiocarcinoma. Follow-up functional experiments showed that LAMC2 is necessary for cell viability of KRAS-driven lung LAC and a marker of poor survival in patients with this tumor. Thus, the goal of this proposal is to test the molecular mechanisms regulated by LAMC2 and the potential as a therapeutic target in LAC and other KRAS-driven epithelial tumors. A series of aims are planned to achieve this goal: a) To elucidate the cellular mechanisms (apoptosis, cell cycle, senescence, DNA damage, ...) involved in LAMC2 loss in human LAC. b) To dissect the molecular mechanisms involved in LAMC2 loss in human LAC c) To characterize the effect of targeting LAMC2 in established tumors via RNAi and blocking antibodies using “humanized” xenograft LAC models. d) To explore the role of LAMC2 in other KRAS-driven epithelial tumors such as cholangiocarcinoma
References Malvezzi, M., Bertuccio, P., Levi, F., La Vecchia, C., and Negri, E. 2013. European cancer mortality predictions for the year 2013. Ann Oncol 24:792-800.

Stephen AG, Esposito D, Bagni RK, McCormick F. Dragging ras back in the ring. Cancer Cell. 2014 Mar 17;25(3):272-81

POSSIBILITY OF PhD

We anticipate that the findings derived from this project will open the possibility for the project to be continued as a Ph. D. student (doctoral thesis).

YES*

* (PhD grant required)