Universidad de Navarra
Facultad de Ciencias

MÁSTER EN INVESTIGACIÓN BIOMÉDICA
Research Project Proposal
Academic year 2026-2027

Project Nº 56

Title: *Dissecting tumor cell plasticity as a resistance mechanism to KRAS inhibitors*

Department/ Laboratory
Oncogenes and Effector Targets (OnTarget Lab)
CIMA

Director 1 *Silvestre Vicent*
Contact: *silvevicent@unav.es*
Codirector: *Konstantina Morali*
Contact: *kmorali@unav.es*

Summary

Activating mutations in KRAS define a prevalent subset of advanced cholangiocarcinoma (CCA) with poor prognosis, characterized by residual response to first-line chemo-immunotherapy. The development of clinically efficacious and tolerable, broad-spectrum inhibitors that target the active (GTP-bound) state of both mutant and wild-type RAS isoforms has brought renewed optimism for therapeutically disrupting RAS-mutant tumors. Such panRASi provide an unprecedented opportunity for the treatment of CCA. Our recently published preclinical work testing the activity of panRASi in mutant KRAS CCA shows strong anticancer responses across multiple CCA models (Entrialgo-Cadierno, and Morali et al, Cancer Cell, 2026). However, long-lasting anticancer responses are compromised by the emergence of resistance, highlighting a critical challenge to panRASi treatment. Notably, even though many tumors feature overt responses on treatment, recurrence follows in a large fraction of cases with unknown resistance mechanisms. Thus, understanding how resistance arises and evolves under panRASi treatment is of paramount importance and will enable the identification of cancer vulnerabilities to implement novel combinatorial treatments for CCA.

This project will address this biological and clinical gap through the integration of unique, well-defined in vivo CCA models of tumor resistance to panRASi with state-of-the-art single cell technologies, functional genomics, drug repurposing approaches, and a clinically-guided roadmap for the evaluation of selected intervention strategies with panRASi.

yes	X
no	

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