Universidad de Navarra

Facultad de Ciencias

MÁSTER EN INVESTIGACIÓN BIOMÉDICA

Research Project Proposal

Academic year 2025-2026

Project Nº 20	

Title: *Characterization of drug persister cells in response to second generation KRAS inhibitors in cholangiocarcinoma using single cell technologies*

Department/ Laboratory Oncogenes and Effector Targets (OnTarget) Group, Lab 2.01
Program in Solid Tumors (Cancer Division), CIMA

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Summary

The advent of targeted therapies to oncogenic drivers of human cancer has revolutionized patient treatment in the last decade. However, anticancer responses are compromised by drug persister populations which resist treatment and eventually lead to cancer relapse. Persister cancer populations are characterized by the development of non-genomic changes that enable cancer cells with a highly plastic phenotype that sustains treatment resistance. Thus, the identification and functional characterization of persister cancer populations is key for the implementation of therapeutic strategies to maximize the effect of targeted therapies.

KRAS oncogene is mutated in one fifth of human cancers including those of the lung, pancreas and colorectum, the three main causes of death by cancer in the US, but also equally fatal cancers such as those of the biliary tract, esophagus, endometrium, stomach, ovary, or cervix. Cholangiocarcinoma is a cancer of the biliary tract where KRAS is among the most frequently mutated oncogenes, reaching about one quarter of patients. Unpublished data from our lab using second generation KRAS inhibitors (KRASi) has shown that CCA is sensitive to pharmacological KRAS inhibition but anticancer responses are not curative due to the presence of drug persister cancer cells across multiple in vivo models.

The goal of this study is to understand the molecular mechanisms associated with the persister phenotype if the overall goal is to nominate targets to inhibit in combination with KRASi. We plan to achive this goal by combining single cell and spatial transcriptomics to provide a deep characterization of the persister cancer populations in response to KRASi in CCA models in vivo. This will be coupled to functional analysis using CRISPR/Cas9-based inhibition of biologically relevant targets as well as drug repurposing approaches using gene signatures representative of the drug persister state.

yes	X
no	

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