Adrián Vallejo

PhD student

16th ASEICA
INTERNATIONAL CONGRESS
Valencia, 6th - 7th - 8th November 2018

The role of FOSL1 in KRAS-driven cholangiocarcinoma (CCA)

Dr. Vicent's group

Center for Applied Medical Research –CIMA-
University of Navarra

aseica
Asociación Española de Investigación sobre el Cáncer

THE PROBLEM: KRAS ONCOGENE

Member of RAS family of small GTPases (RAS mutations in 1/3 of human tumors)

LUNG (KRAS 25%)

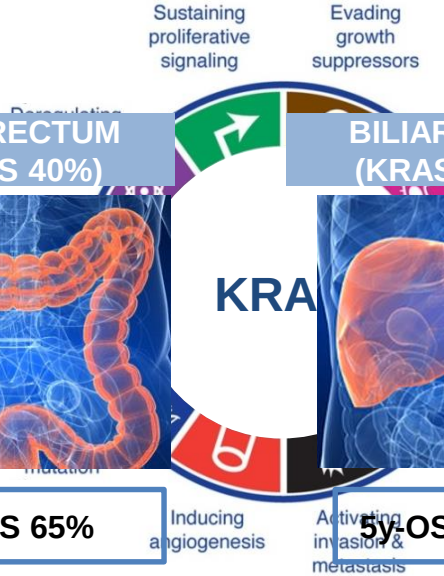
5y-OS 15%

GEF

GAP

PANCREAS (KRAS 90%)

5y-OS 7%



COLORECTUM (KRAS 40%)

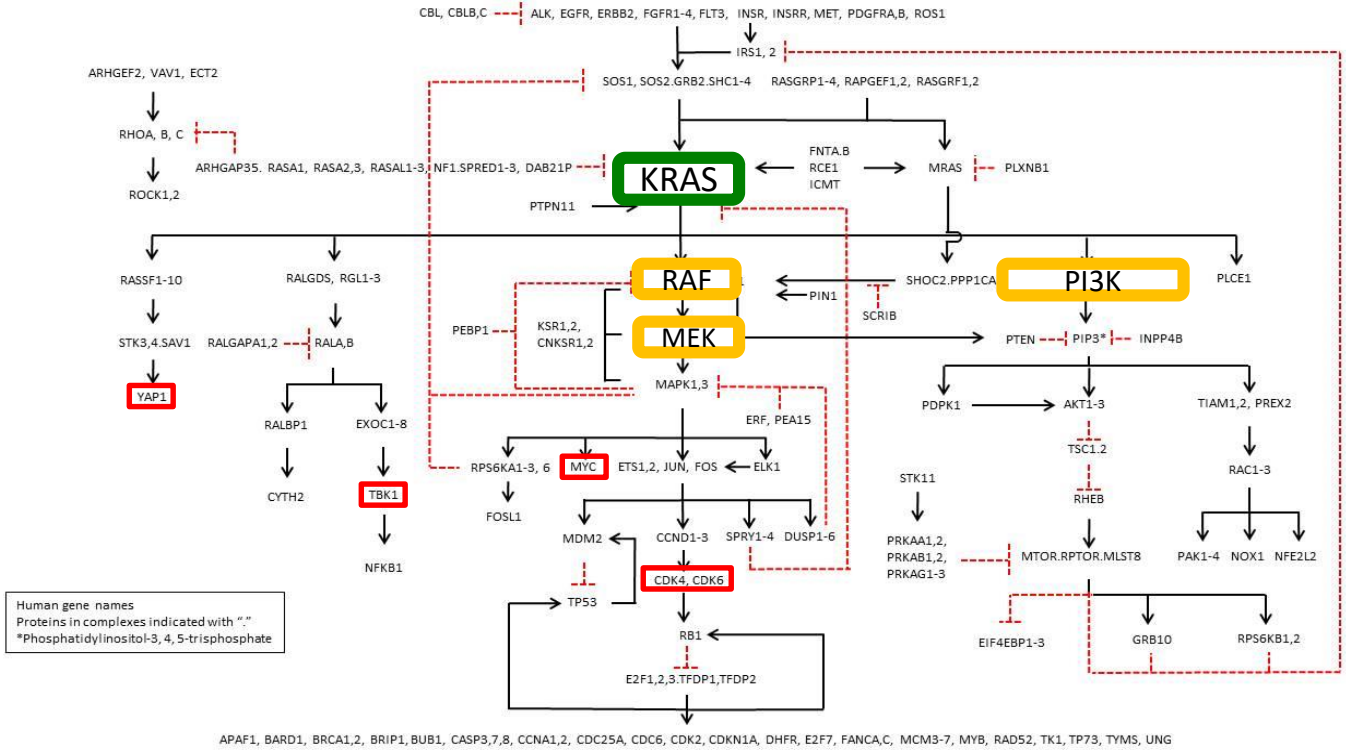
5y-OS 65%

BILIARY TRACT (KRAS 20-40%)

5y-OS 0%-30%

Hanahan and Weinberg, 2011

POTENTIAL THERAPEUTIC STRATEGIES : TARGETING DISTAL EFFECTORS



aseica
Asociación Española de Investigación sobre el Cáncer

OUR GROUP´S APPROACH FOR THE IDENTIFICATION OF CRITICAL DISTAL EFFECTORS: 3 MAIN PREMISES

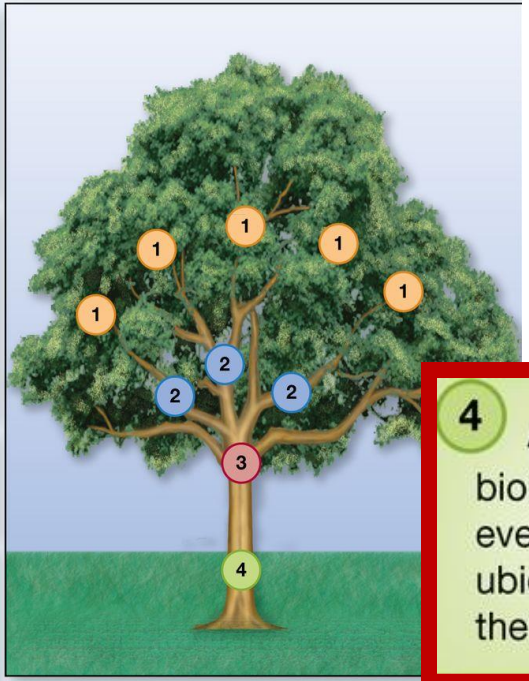
PREMISE 1: TRANSCRIPTOMICS OF CANCER EVOLUTION

1 **Tracking heterogeneity and bottlenecks:** Development of noninvasive techniques to monitor and track the subclonal dynamics of tumor architecture through treatment may enhance understanding of resistance mechanisms as branches are "pruned" at the expense of outgrowth of other branches harboring heterogeneous resistance mutations (e.g., T790M gatekeeper mutation; ref. 33).

2 **Tumor sampling bias:** Biopsies in 1 region of a heterogeneous primary or metastatic tumor will identify trunk events but may also identify as many or more heterogeneous events not shared by all regions of the tumor or by all tumor subclones. Comparison of paired primary/metastatic samples may enhance the identification of trunk events for therapeutic targeting. Regional genetic ITH may have an impact on *ex vivo* assays of cell phenotypic function.

3 **Drivers of heterogeneity:** Identification of the driver events for genomic instability that may occur at the nexus of the trunk and branch may provide new approaches to limit tumor diversity and adaptation.

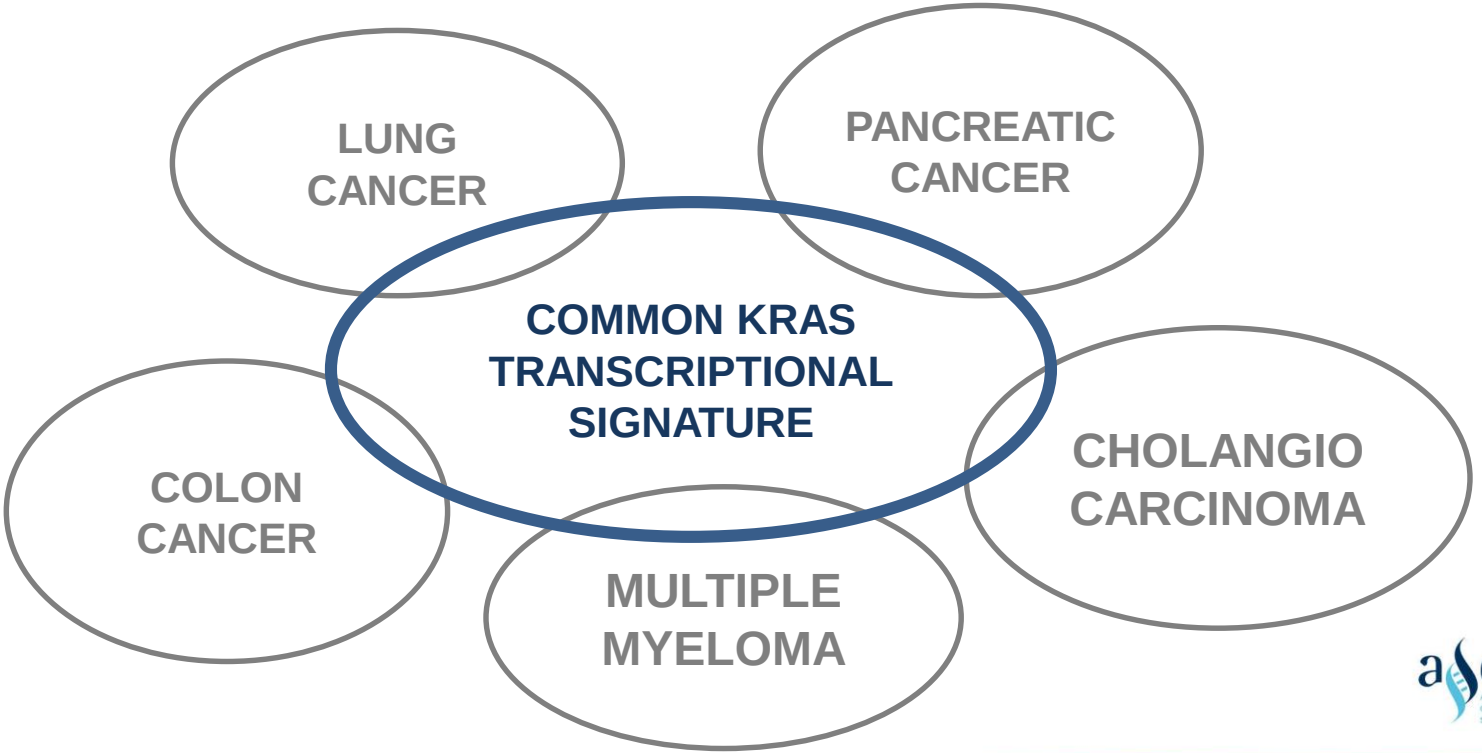
4 **Actionable mutations:** Early drivers of disease biology lead to ubiquitous somatic events present in every tumor subclone and tumor region. Such ubiquitous tumor mutations may present more robust therapeutic targets and optimal synthetic lethal targets.



4 **Actionable genes**: Early drivers of disease biology lead to ubiquitous **expression changes** in every tumor subclone and tumor region. Such ubiquitous **gene expression** present more robust therapeutic targets and optimal synthetic lethal targets.

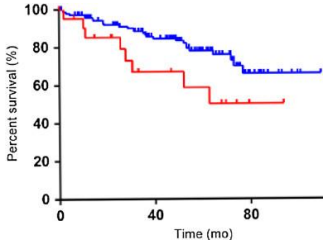
Burrell, R. A. & Swanton, C. The evolution of the unstable cancer genome. Curr. Opin. Genet. Dev. (2014)

PREMISE 2: COMMON GENES ACROSS TUMORS

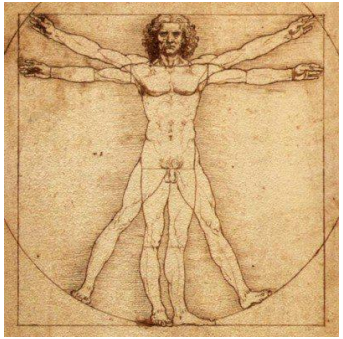


PREMISE 3: CONSERVED MOLECULAR MECHANISMS CROSS-SPECIES

Bioinformatics tools



Patient clinical data



Robust KRAS dependent candidates:
Genes and ncRNAs

Vicent et al, JCI, 2010
Vicent et al, Cancer Res, 2012
Vallejo et al, Nat Comms, 2017

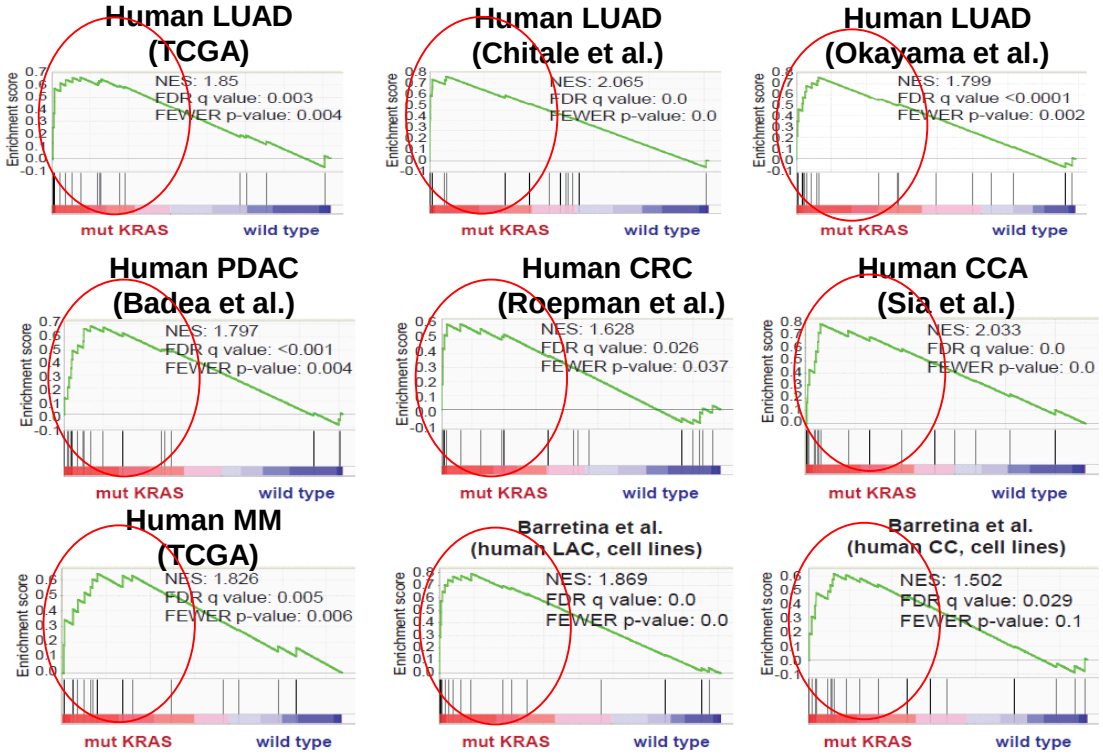
aseica Asociación Española de Investigación sobre el Cáncer

CAN WE IDENTIFY POTENTIAL KRAS VULNERABILITIES USING GENE-EXPRESSION ANALYSES?

ARE THESE CANDIDATES FUNCTIONALLY RELEVANT ACROSS TUMORS?

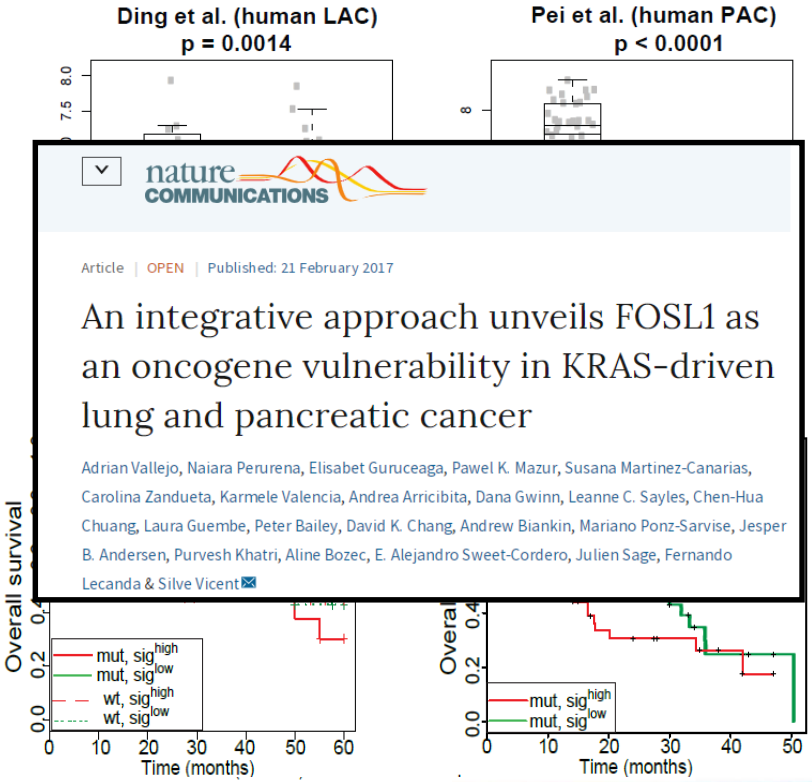
ACROSS SIGNATURE CANDIDATES

AREG
DUSP4
DUSP6
FOSL1/ FRA1
LAMB3
LAMC2
PHLDA1
SPRY4



Vallejo, Perurena, Guruceaga et al, Nat Comms, 2017

THE CROSS-TUMORS SIGNATURE PREDICTS KRAS STATUS AND SURVIVAL

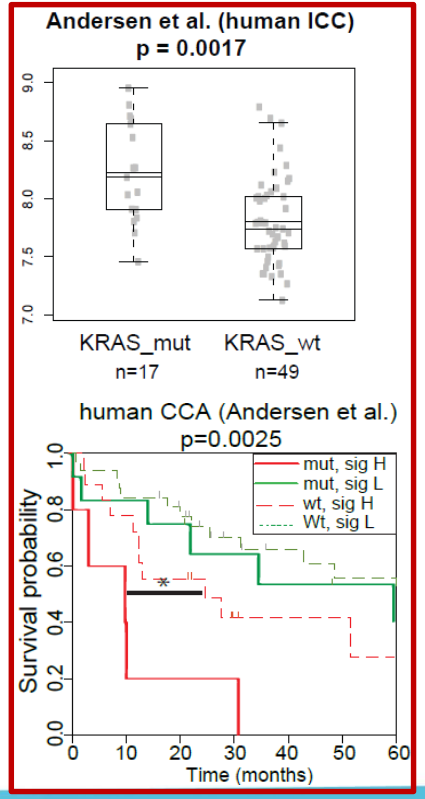


nature COMMUNICATIONS

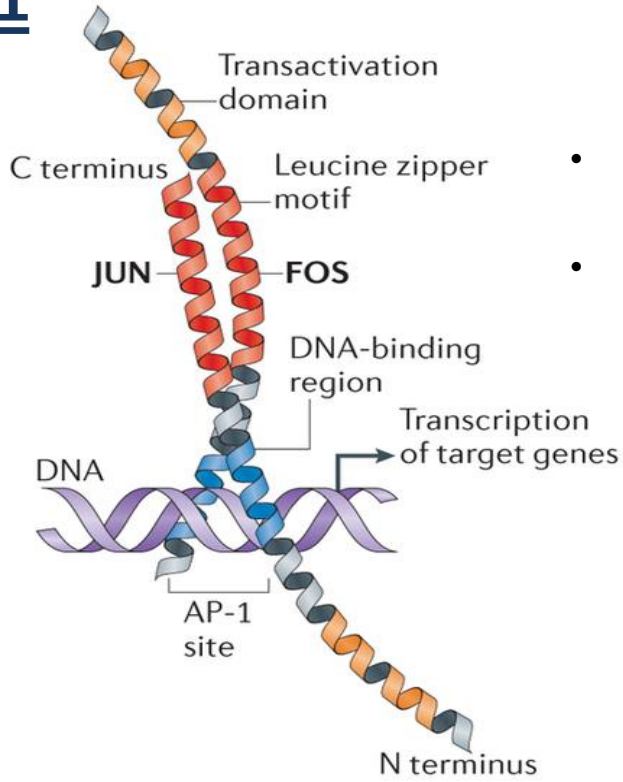
Article | OPEN | Published: 21 February 2017

An integrative approach unveils FOSL1 as an oncogene vulnerability in KRAS-driven lung and pancreatic cancer

Adrian Vallejo, Naiara Perurena, Elisabet Guruceaga, Pawel K. Mazur, Susana Martinez-Canarias, Carolina Zandueta, Karmele Valencia, Andrea Arricibita, Dana Gwinn, Leanne C. Sayles, Chen-Hua Chuang, Laura Guembe, Peter Bailey, David K. Chang, Andrew Biankin, Mariano Ponz-Sarvise, Jesper B. Andersen, Purvesh Khatri, Aline Bozec, E. Alejandro Sweet-Cordero, Julien Sage, Fernando Lecanda & Silve Vicent

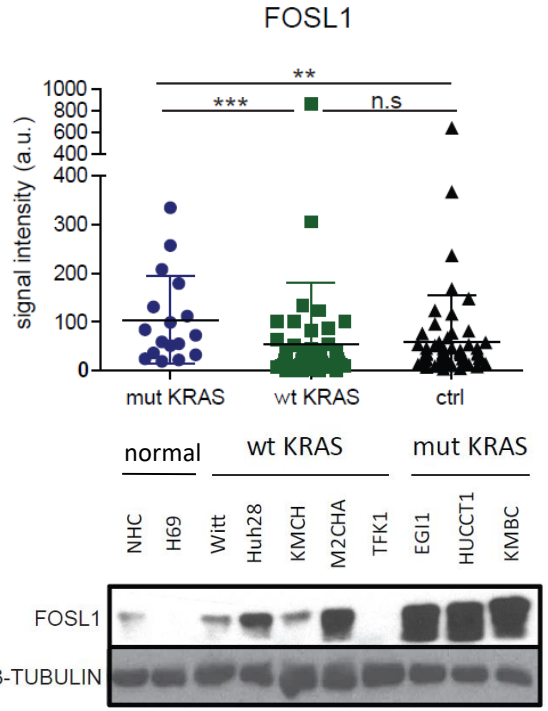


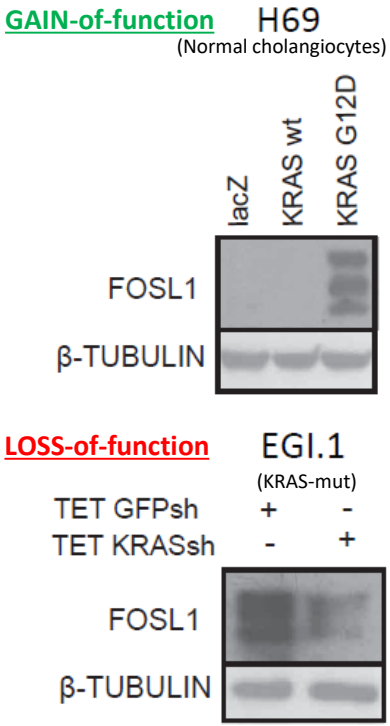
FOSL1

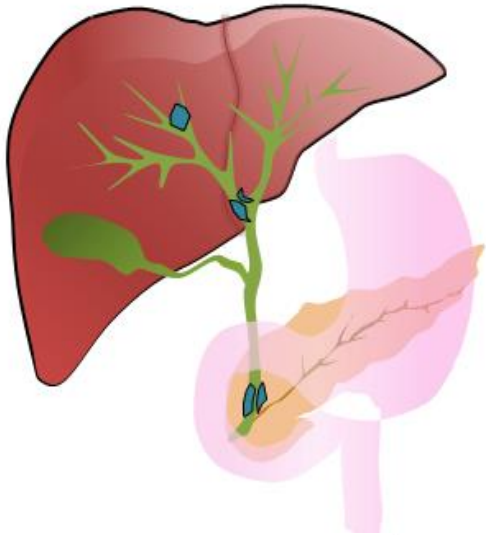


- Classic basic-region leucine-zipper TF
- Member of the FOS family (cfos, fosb, fosl1/fra1 and fosl2/fra2)
  FOS + JUN→ **AP-1 complex**

CHARACTERIZATION OF FOSL1 IN HUMAN CCA: UP-REGULATION IN MUTANT KRAS PATIENTS AND TUMOR CELL LINES





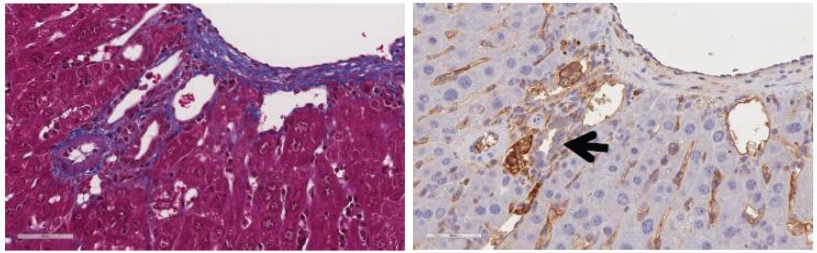


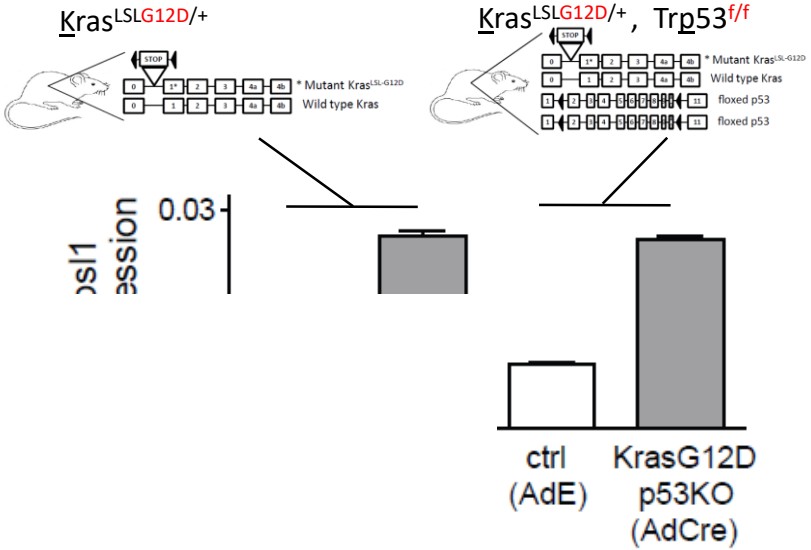
aseica
Asociación Española de Investigación sobre el Cáncer

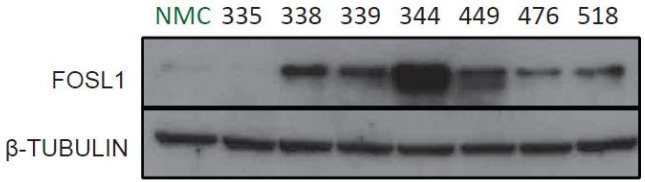
GEMMs

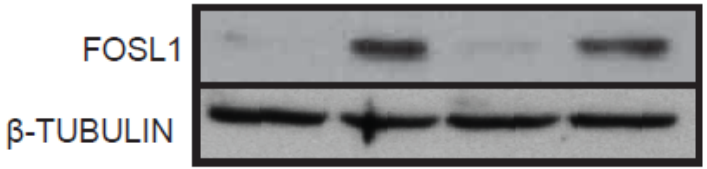
FOSL1 EXPRESSION IN A CCA GEMM DRIVEN BY MUTANT KRAS AND P53 LOSS

Normal tissue



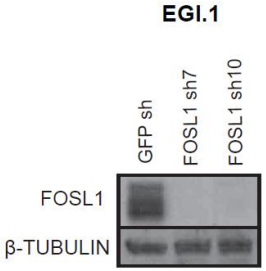


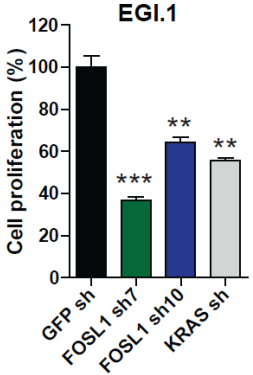


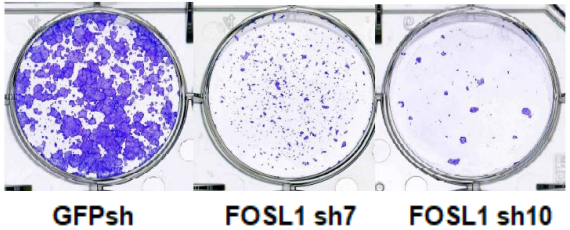


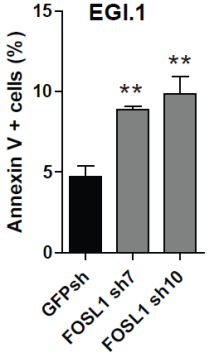
FOSL1 DEPLETION IMPAIRS CELL PROLIFERATION, CLONOGENIC POTENTIAL AND APOPTOSIS OF CCA WITH MUTANT KRAS

KRAS-mut

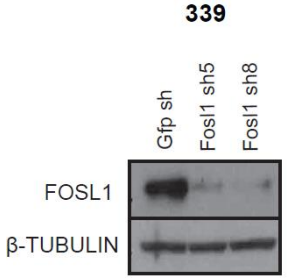


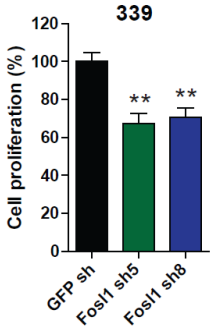


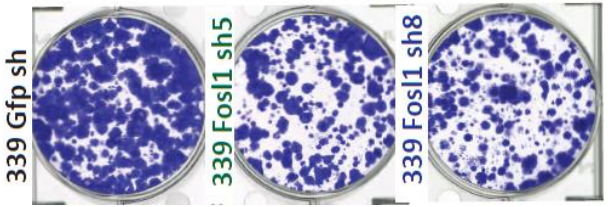




KRAS-mut



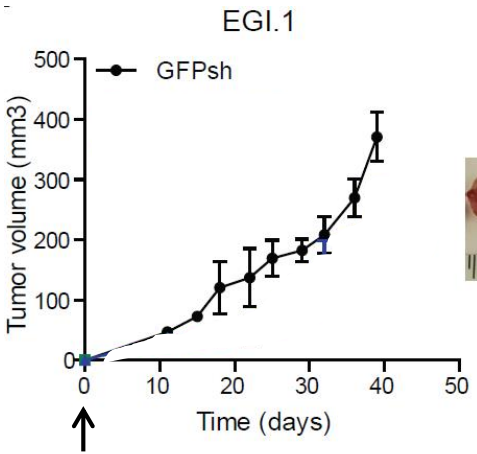


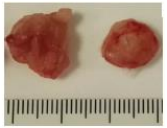


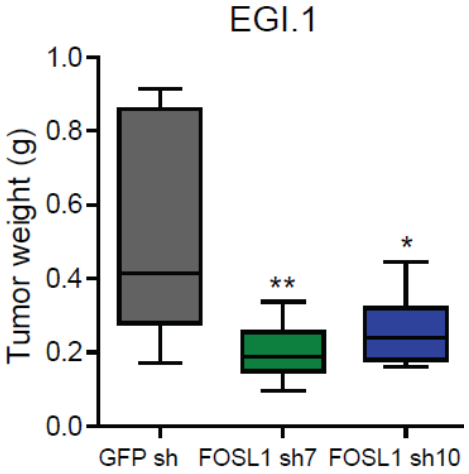
aseica
Asociación Española de Investigación sobre el Cáncer

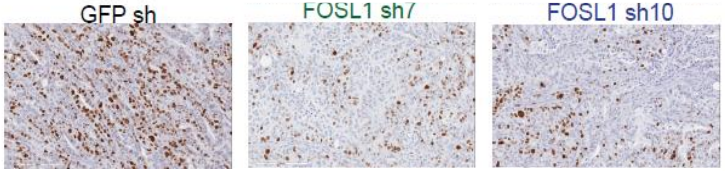
INHIBITION OF FOSL1 DELAYS TUMOR GROWTH OF HUMAN CCA

Xenografts





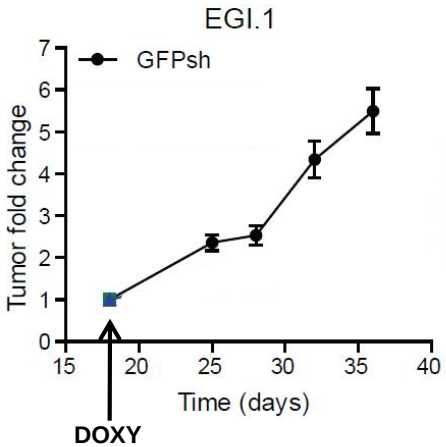


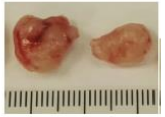


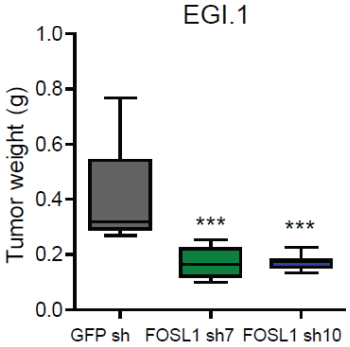
GFP sh	FOSL1 sh7	FOSL1 sh10
70±18	25±8 **	34±12 ***

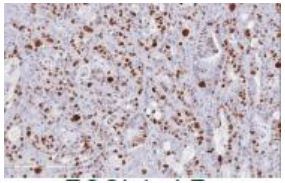
FOSL1 DEPLETION IN ESTABLISHED TUMORS REDUCES HUMAN CCA GROWTH

Xenografts

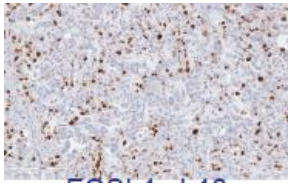






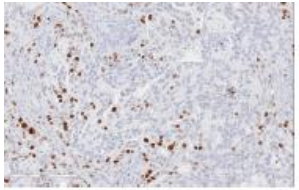


78±22



***

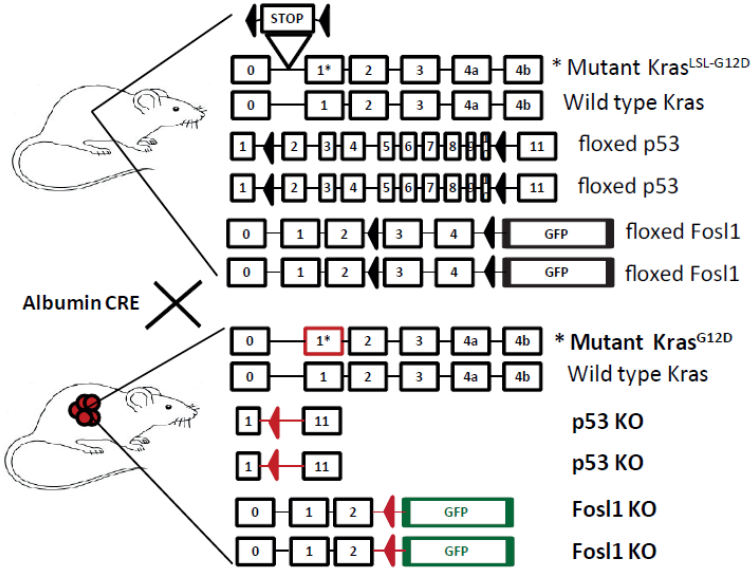
31±10



***

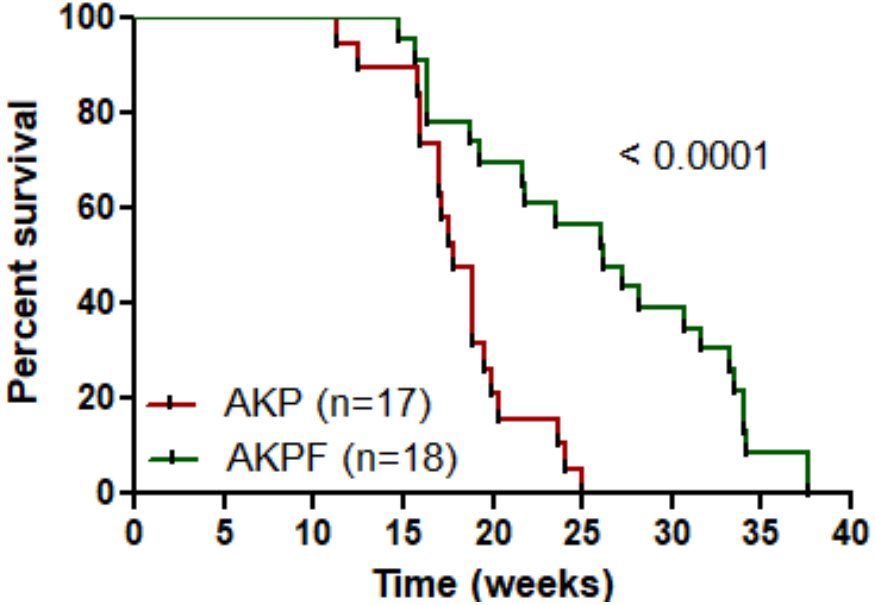
28±13

FOSL1 KNOCKOUT IN A CCA GEMM EXTENDS MICE SURVIVAL



AKP: Albumin$^{+/+}$, Kras$^{LSL G12D/+}$, Trp53$^{f/f}$

AKPF: Albumin$^{+/+}$, Kras$^{LSL G12D/+}$, Trp53$^{f/f}$, Fosl1$^{f/f}$



ACKNOWLEDGMENTS

Adrián Vallejo | Oihane Erice, PhD | Karmele Valencia, PhD | Iker Feliu | Ester Blanco | Silve Vicent, PhD

Jesus Bañales´s group (Biodonostia, Spain)

Jesper Andersen´s group (BRIC, Copenhagen, Denmark)

worldwide cancer research formerly known as AICR

GOBIERNO DE ESPAÑA · MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

FUNDACIÓN CAJANAVARRA · Obra Social Fundación "la Caixa" · SEVENTH FRAMEWORK PROGRAMME · MARIE CURIE ACTIONS · IASLC International Association for the Study of Lung Cancer · cima CENTRO DE INVESTIGACIÓN MÉDICA APLICADA UNIVERSIDAD DE NAVARRA · aseica Asociación Española de Investigación sobre el Cáncer