

Searching for Modulators of Cancer Therapeutic Resistance

Miquel Angel Pujana

ProCURE

Catalan Institute of Oncology
IDIBELL, L'Hospitalet del Llobregat
Barcelona

Competing interests:

- **Research grants from Roche and Astellas Pharma**



Biomedical campus, translational cancer research

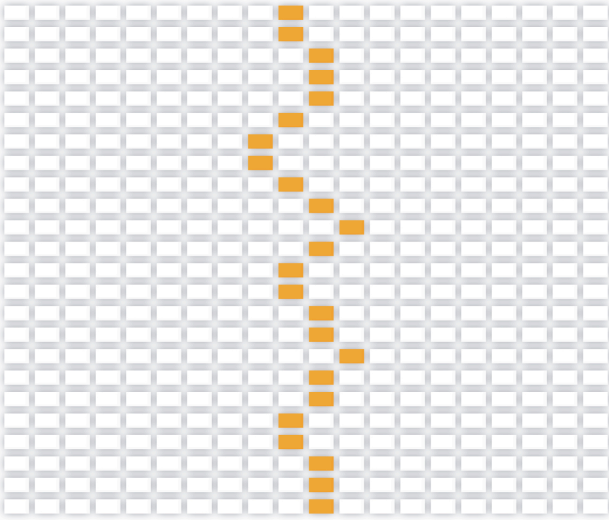


Catalan Institute of Oncology, IDIBELL

Program Against Cancer Therapeutic Resistance “ProCURE”

Generalitat de Catalunya
Departament de Salut

ICO
Institut Català d'Oncologia



Program Against
Cancer Therapeutic Resistance

ProCURE Programa
Contra la Resistència
Terapèutica del Càncer

Programa
Contra la Resistència
Terapèutica del Càncer



ProCURE:

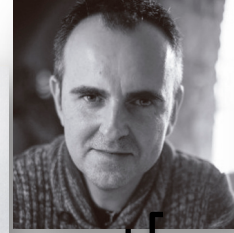
10 groups against “resistance”

R Alemany

E Martínez

DG Molleví

F Viñals



O Casanovas

JA Menéndez

A Villanueva

MA Pujana

Renal
Neuroendocrine

Colorectal

Ovarian
Testicular

Prostate

Pancreatic
Melanoma

Breast
Endometrial

Lung
Cervix



M Graupera



A Aytes

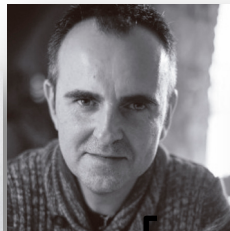
Themes by ProCURE

R Alemany

E Martínez

DG Molleví

F Viñals



O Casanovas

JA Menéndez

A Villanueva

MA Pujana

Angiogenesis

**Molecular
signaling
Kinases**

**Immunotherapies
Oncolytic virus**

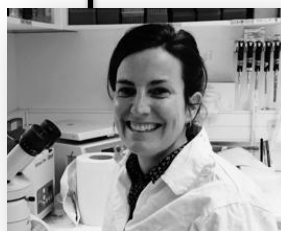
**Biomarkers
Stroma**

Genomics

PDXs

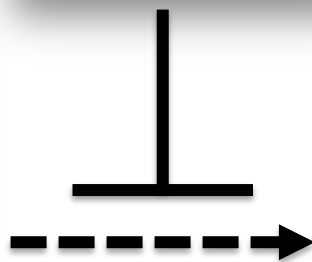
**Transcriptomics
Metabolomics
Systems biology**

M Graupera

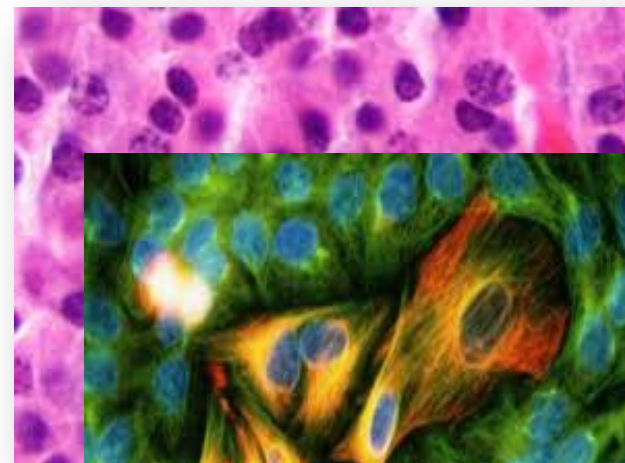
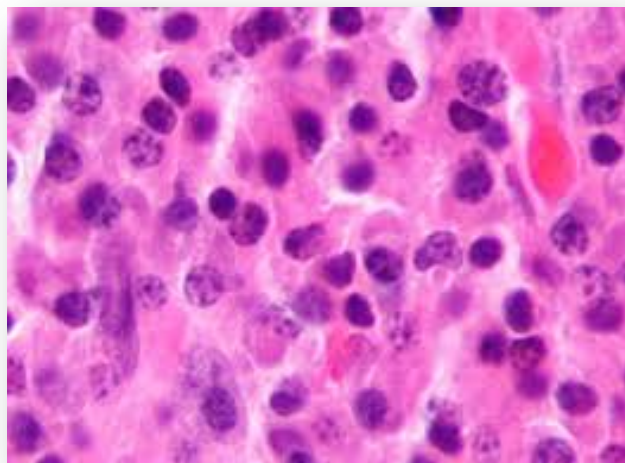


A Aytes

Therapy

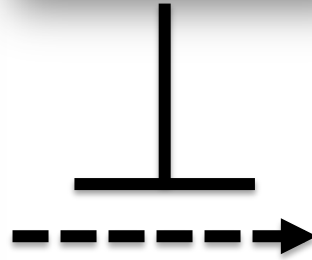


Resistance



SPL

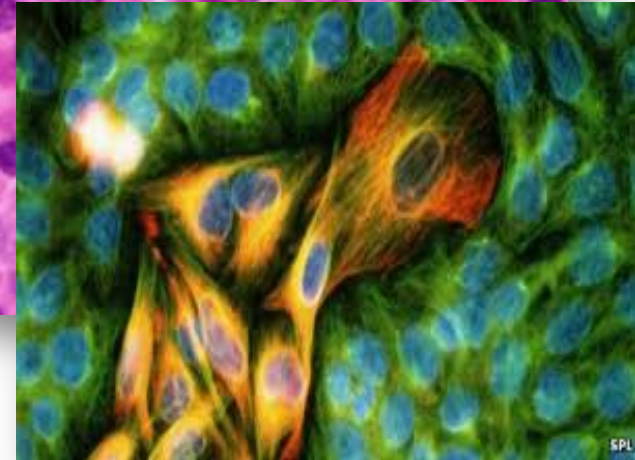
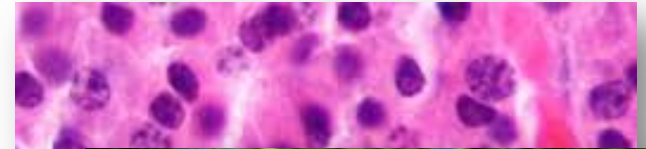
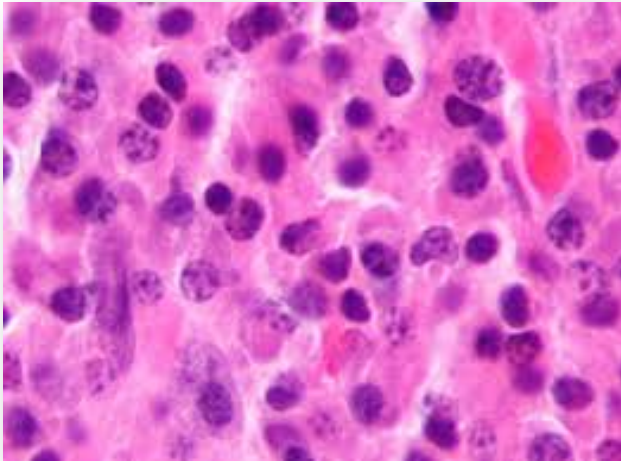
Therapy



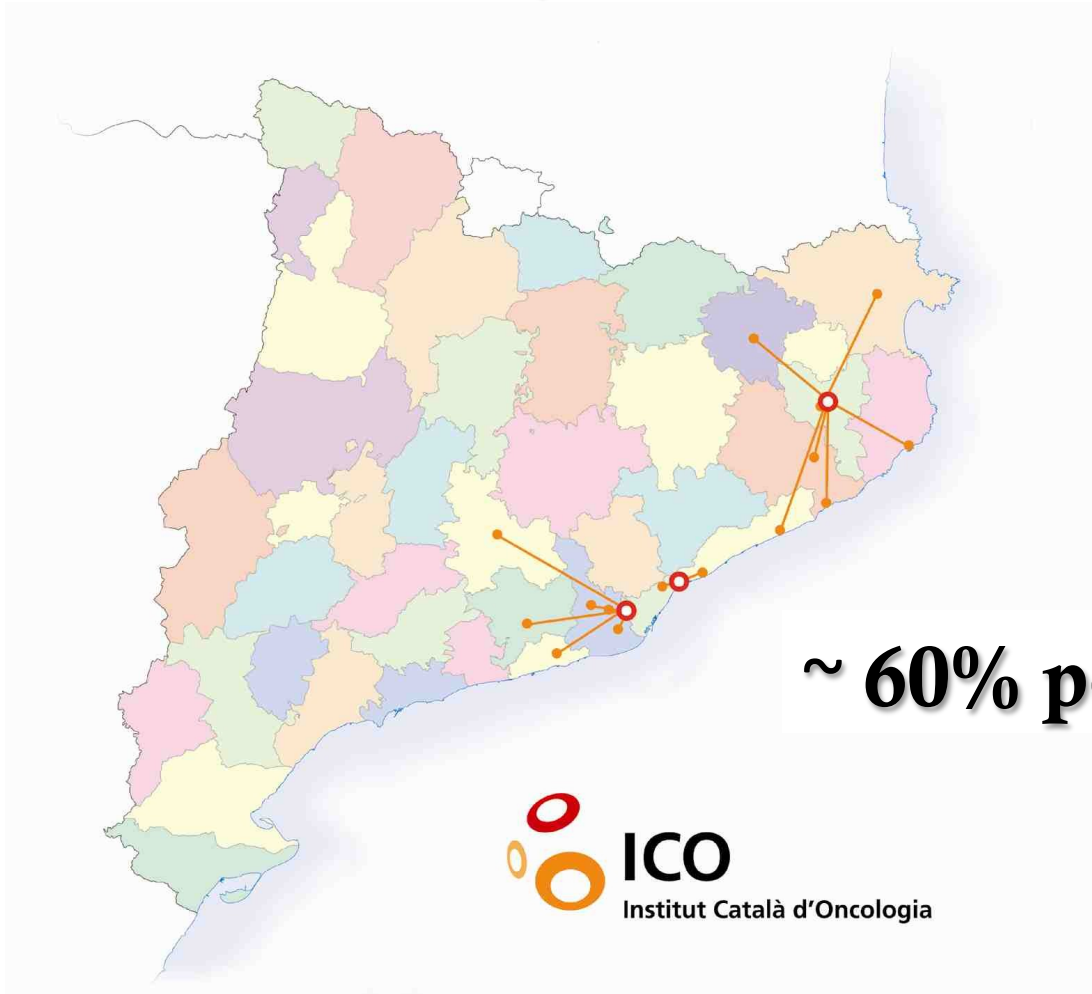
Resistance



Mechanisms
Biomarkers
Targets



Catalonia: ~34,000 incident cases/year



~ 60% population



~ 1,700 breast cancer cases

Breast cancer in Catalonia 2017

4.563 incident cases
979 deaths



An example of the impact of resistance

Year 2016, breast cancer at ICO:

- **> 300 “resistant”**
(primary progression or metastatic)
- **40% pharmaceutical budget (3.5 M EUR)**

Outline

- **What is a “modulator”?**
- **Examples to identify modulators**
- **A landscape of modulators**

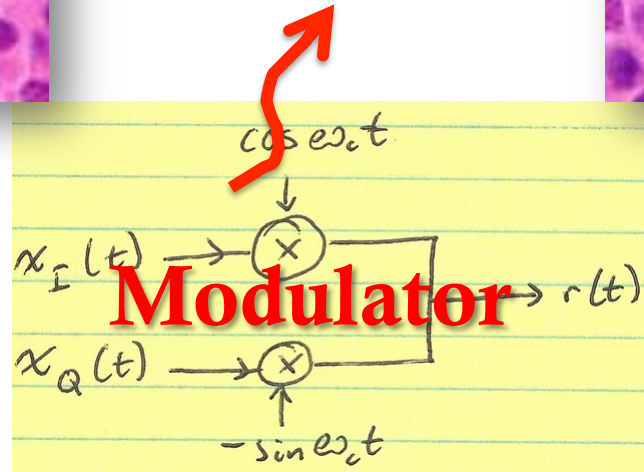
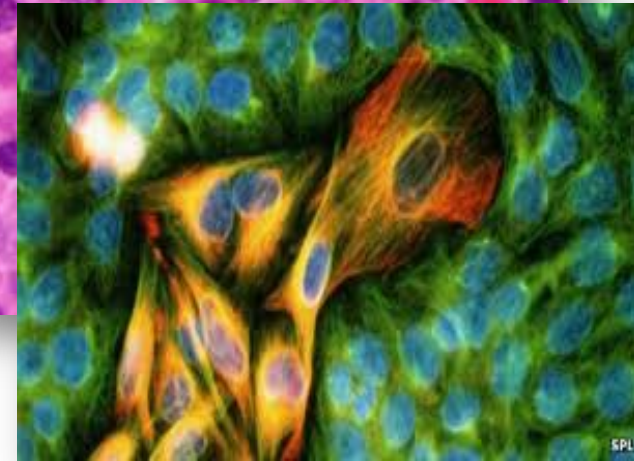
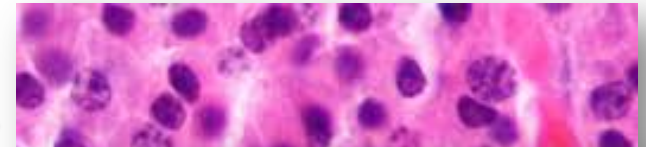
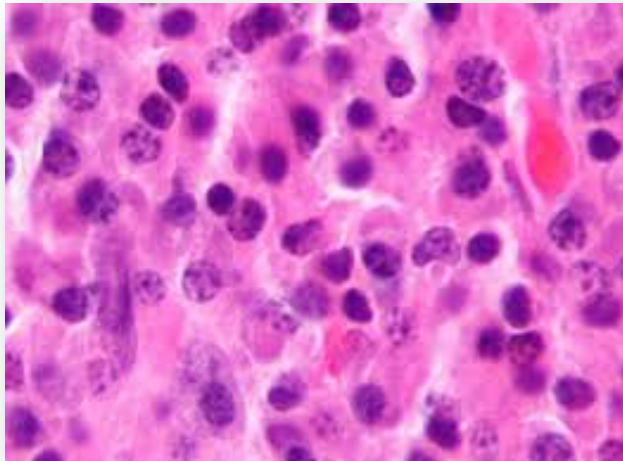
Therapy



Cancer target



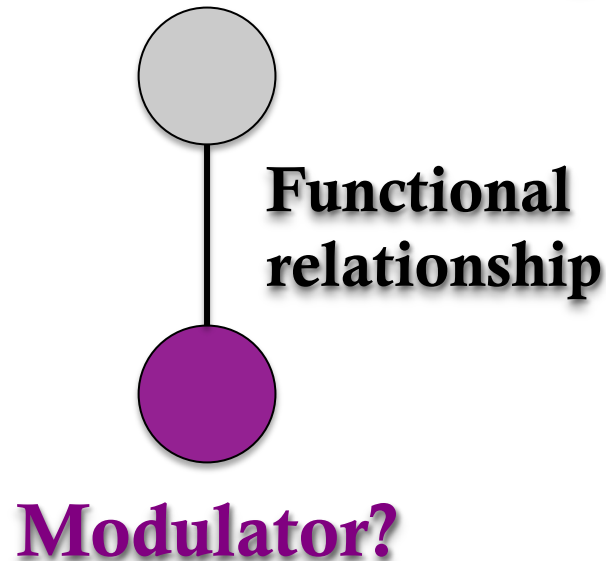
Cancer driver



Identifying cancer modulators

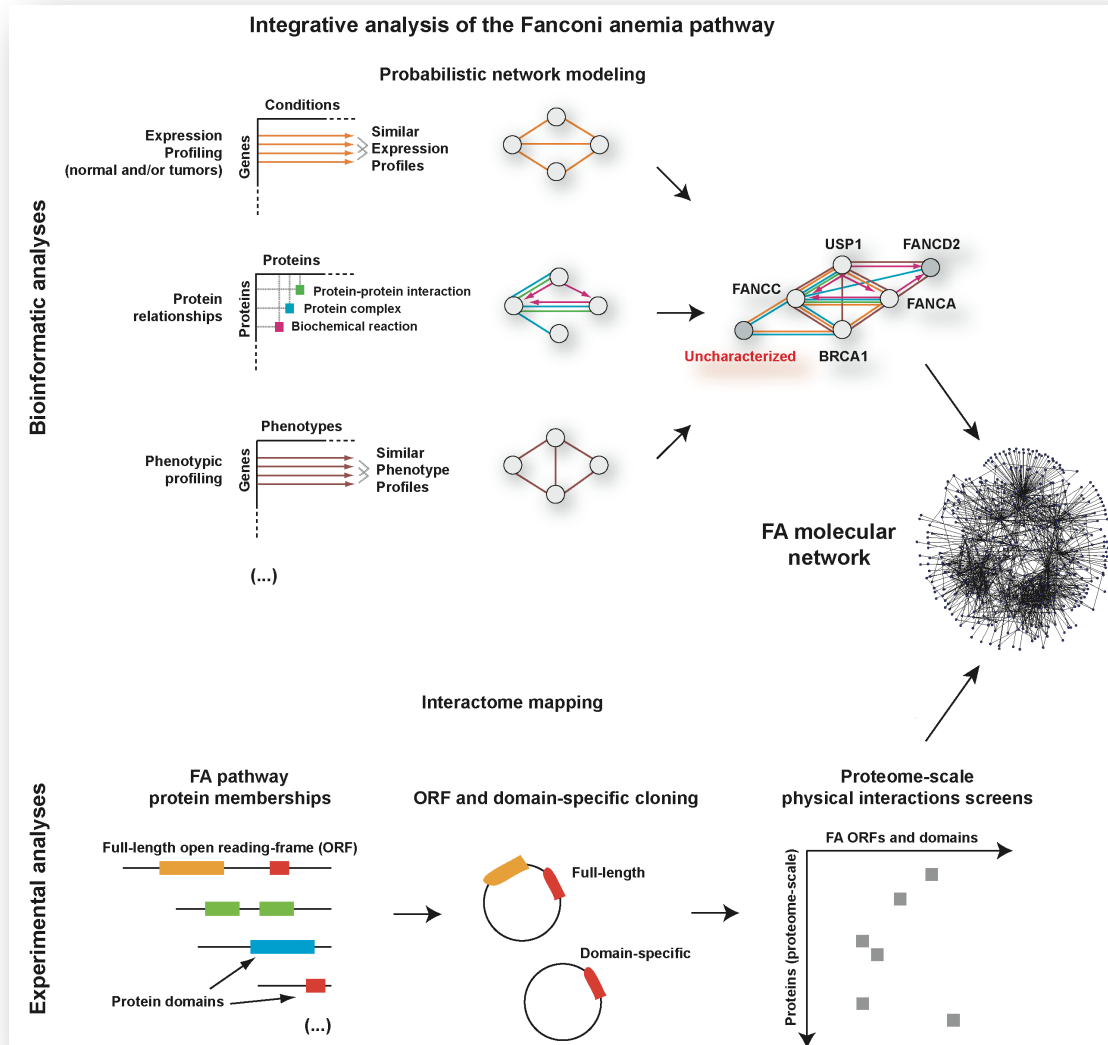
Candidate approaches

Cancer driver and/or target



Identifying cancer modulators

Integrative approach



Identifying cancer modulators

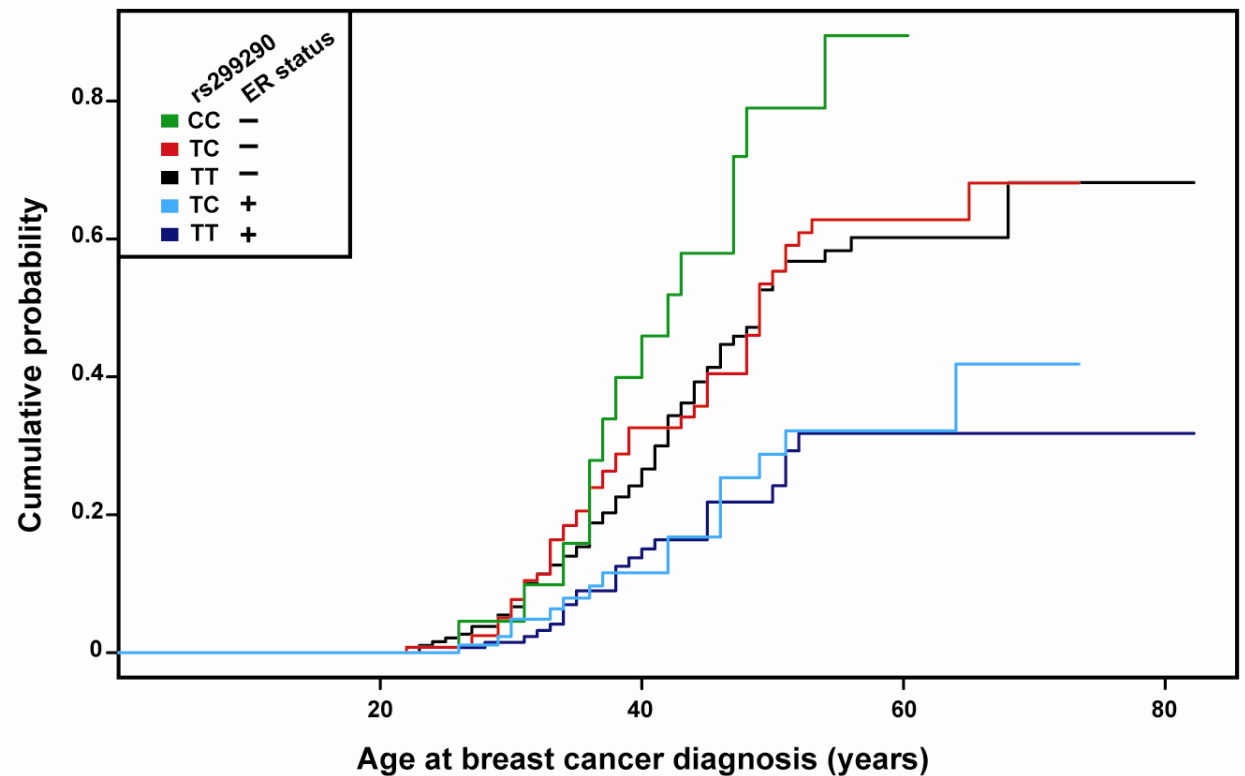
Integrative approach

OPEN ACCESS Freely available online

PLoS BIOLOGY

Interplay between BRCA1 and RHAMM Regulates Epithelial Apicobasal Polarization and May Influence Risk of Breast Cancer

Christopher A. Maxwell^{1,2,3*}, Javier Benítez^{2,3}, Laia Gómez-Baldó¹



Identifying cancer modulators

Protein-protein interaction screens

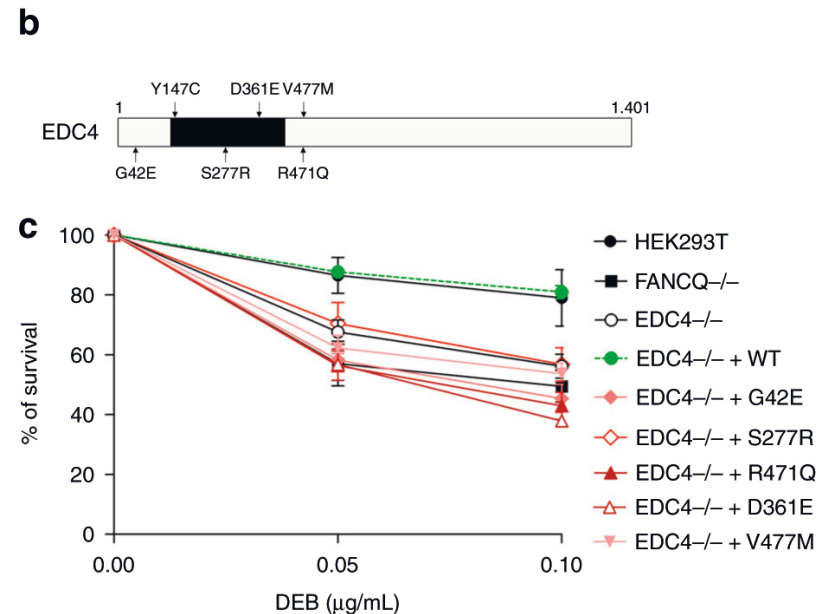
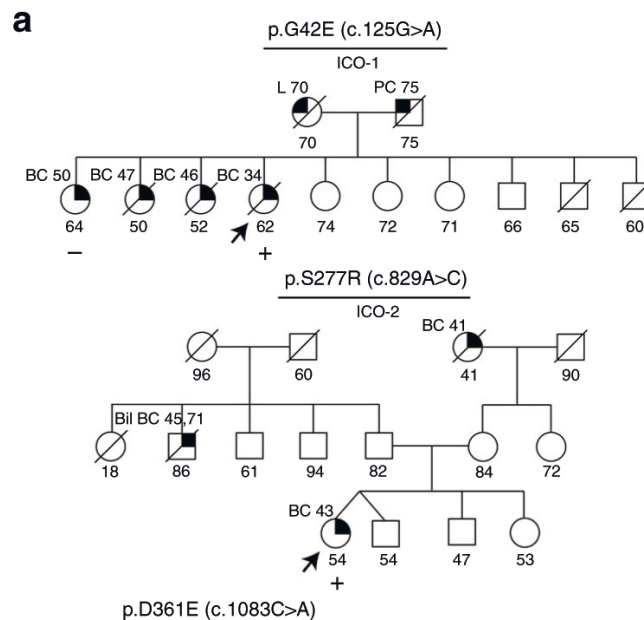


ARTICLE

DOI: 10.1038/n41467-018-03433-3 OPEN

Decapping protein EDC4 regulates DNA repair and phenocopies BRCA1

Gonzalo Hernández^{1,2}, María José Ramírez^{1,2}, Jordi Minguil Miriam Aza-Carmona^{1,2}, Massimo Bogliolo^{1,2}, Roser Pujol^{1,2}, Nadia García⁴, Adrià López⁵, Sara Gutiérrez-Enríquez⁷, Oriol Alex Teulé³, Joan Brunet^{3,6}, Paolo Radice¹⁰, Paolo Peterl Xose S Puente¹³, Conxi Lázaro³, Miquel Àngel Pujana^{4,14} &



In collaboration with J. Surrallés (UAB, St Pau)

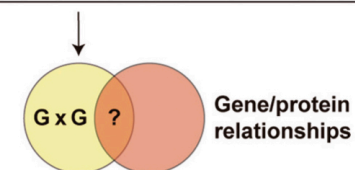
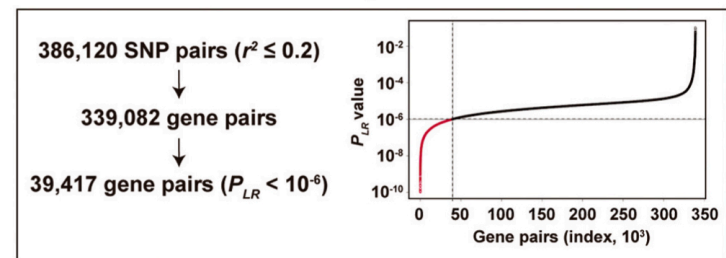
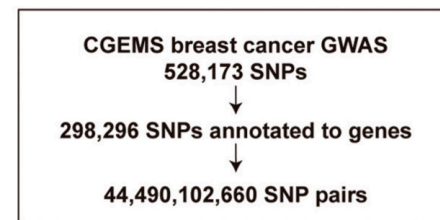
Identifying cancer modulators

Genetic interactions

Carcinogenesis vol.35 no.3 pp.578–585, 2014
 doi:10.1093/carcin/bgt403
 Advance Access publication December 2, 2013

Integrating gene expression and epidemiological data for the discovery of genetic interactions associated with cancer risk

Núria Bonifaci¹, Eva Colas², Jordi Serra-Musach^{1,3},
 Nazanin Karbalai^{4,5}, Joan Brunet³, Antonio Gómez⁶,
 Manel Esteller⁶⁻⁸, Enrique Fernández-Taboada¹,
 Antoni Berenguer⁹, Jaume Reventós^{2,10}, Bertram Müller-
 Myhsok^{4,5,11}, Laufey Amundadottir¹², Eric J. Duell¹³ and
 Miquel Àngel Pujana^{1,*}



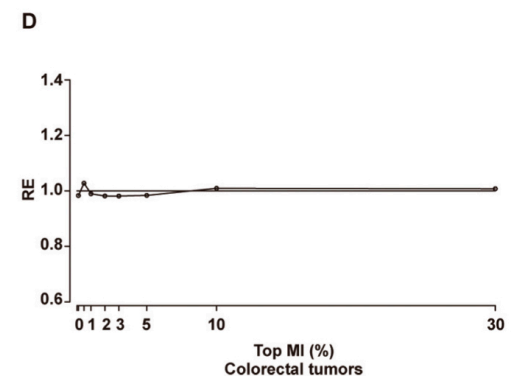
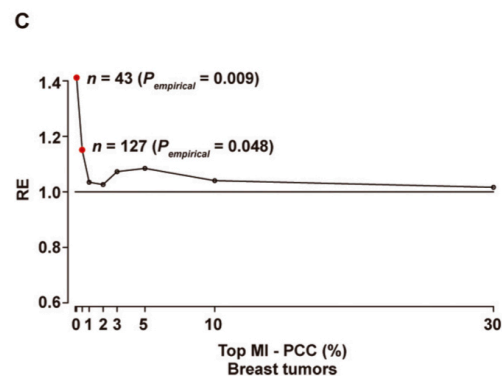
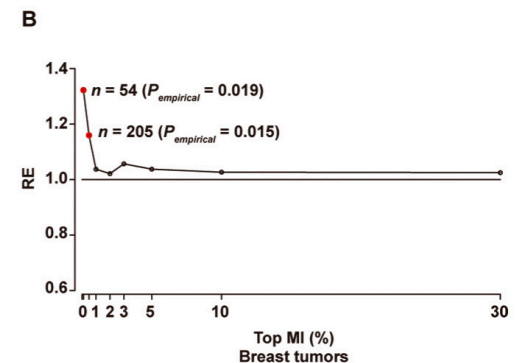
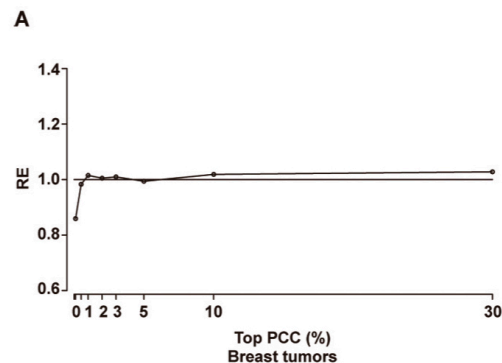
Identifying cancer modulators

Genetic interactions

Carcinogenesis vol.35 no.3 pp.578–585, 2014
doi:10.1093/carcin/bgt403
Advance Access publication December 2, 2013

Integrating gene expression and epidemiological data for the discovery of genetic interactions associated with cancer risk

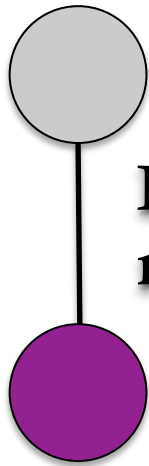
Núria Bonifaci¹, Eva Colas², Jordi Serra-Musach^{1,3},
Nazanin Karbalai^{4,5}, Joan Brunet³, Antonio Gómez⁶,
Manel Esteller^{6–8}, Enrique Fernández-Taboada¹,
Antoni Berenguer⁹, Jaume Reventós^{2,10}, Bertram Müller-
Myhsok^{4,5,11}, Laufey Amundadottir¹², Eric J. Duell¹³ and
Miquel Àngel Pujana^{1,*}



Identifying cancer modulators

Transcriptional regulators

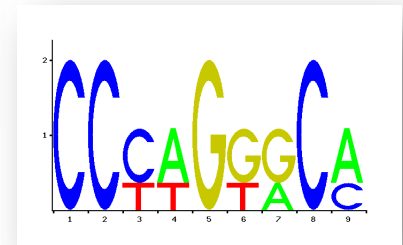
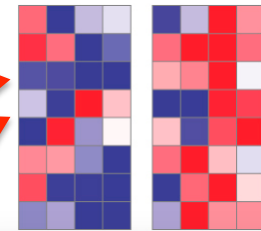
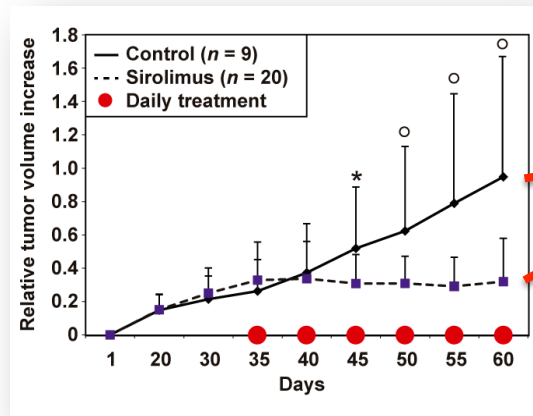
Cancer driver and/or target



Functional relationship

Modulator?

Master regulators?



Identifying cancer modulators Transcriptional regulators

OPEN

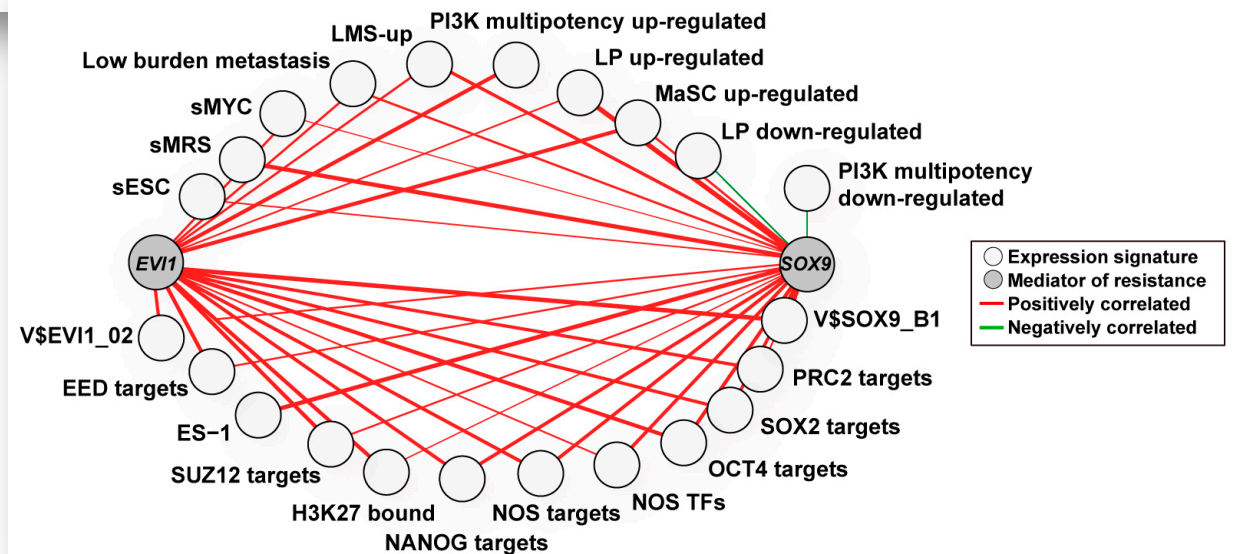
Oncogene (2017) 36, 2737–2749
www.nature.com/onc

ORIGINAL ARTICLE

Stem cell-like transcriptional reprogramming mediates metastatic resistance to mTOR inhibition

F Mateo^{1,49}, EJ Arenas^{2,49}, H Aguilar^{1,49}, J Serra-Musach¹, G Ruiz de Garibay¹, J Boni¹, M Maicas³, S Du⁴, F Iorio^{5,6}, C Herranz-Ors¹, A Islam⁷, X Prado¹, A Llorente¹, A Petit⁸, A Vidal⁸, I Català⁸, T Soler⁸, G Venturas⁸, A Rojo-Sebastian⁹, H Serra¹⁰, D Cuadras¹¹, I Blanco¹², J Lozano¹³, F Canals¹⁴, AM Sieuwerts¹⁵, V de Weerd¹⁵, MP Look¹⁵, S Puertas¹⁶, N García¹, AS Perkins¹⁷, N Bonifaci¹, M Skowron¹, L Gómez-Baldó¹, V Hernández¹⁸, A Martínez-Aranda¹⁸, M Martínez-Iniesta¹⁸, X Serrat¹⁹, J Cerón¹⁹, J Brunet²⁰, MP Barretina²¹, M Gij²², C Faló²², A Velasco²³, I Morilla²², S Pernas²², MJ Plà²³, X Andreu²⁴, MA Segur²⁵, R Ballester²⁶, E Castellà²⁷, M Nellist²⁸, S Morales²⁹, J Valls³⁰, A Palomero¹, X Matias-Guiu²⁹, A Figueras¹⁰, JV Sánchez-Mut³⁰, M Sánchez-Céspedes³⁰, A Cordero³⁰, J Gómez-Miragaya³⁰, L Palomero¹, A Gómez³⁰, TF Gajewski³¹, EEW Cohen³², M Jesiot³³, L Bodnar³⁴, M Quintela-Fandino³⁵, N López-Bigas^{36,37}, R Valdés-Mas³⁸, XS Puente³⁸, F Viñals¹⁰, O Casanovas¹⁰, M Graupera¹⁰, J Hernández-Losa³⁹, S Ramón y Cajal³⁹, L García-Alonso⁵, J Saez-Rodriguez⁵, M Esteller^{30,37,40}, A Sierra⁴¹, N Martín-Martín⁴², A Matheu^{43,44}, A Carracedo^{42,44,45}, E González-Suárez⁴⁶, M Nanjundan⁴⁶, J Cortés⁴⁷, C Lázaro¹², MD Otero³, JWM Martens¹⁵, G Moreno-Bueno⁴⁸, MH Barcellos RR Gomis^{2,37} and MA Pujana¹

Co-expression network in TCGA



Outline

- What is a “modulator”
- Approaches to identify modulators
- **A landscape of modulators**

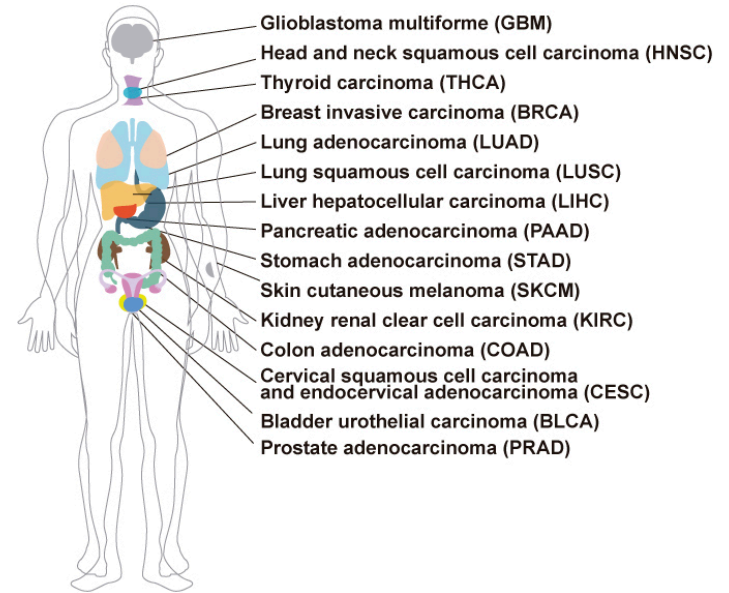
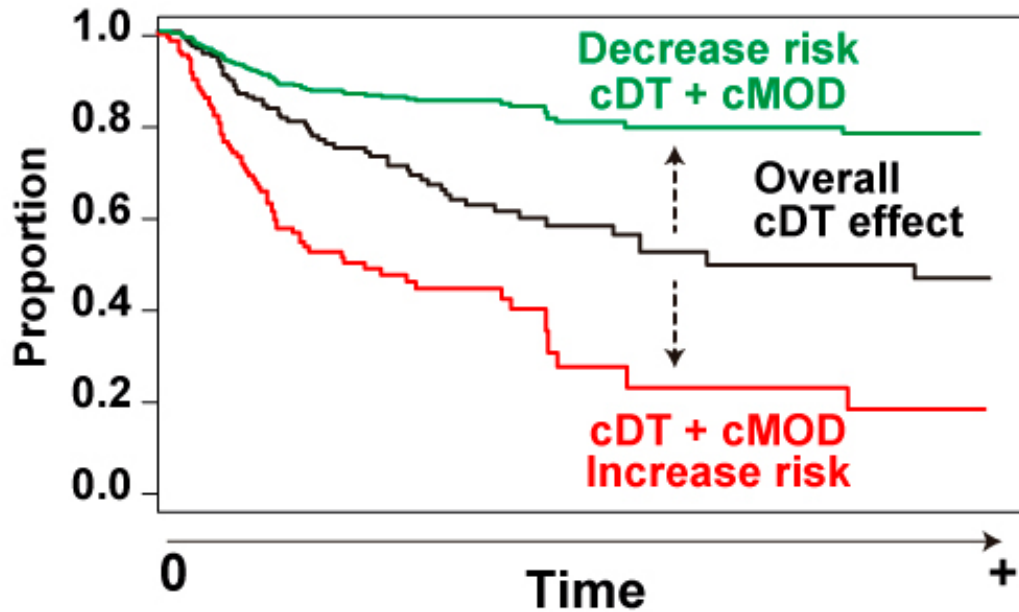
Dozens of cancer therapies



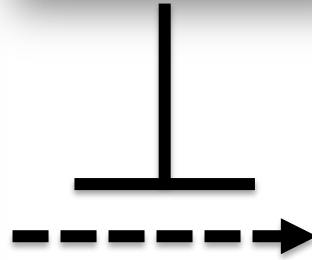
**Hundreds of cancer drivers/targets:
>700
(sources COSMIC, IntoGen, TCGA...)**

Pan-cancer study (*unpublished*)

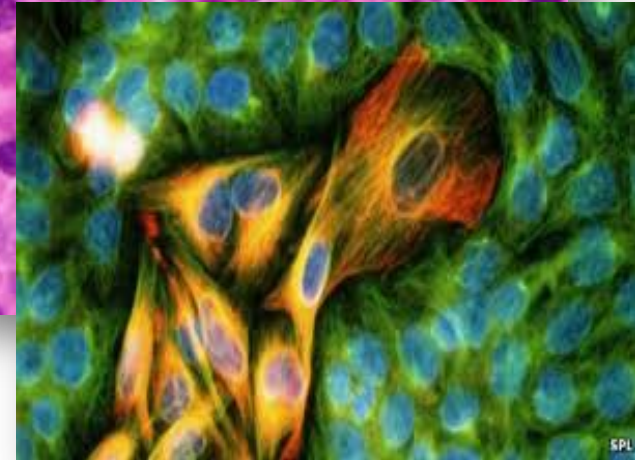
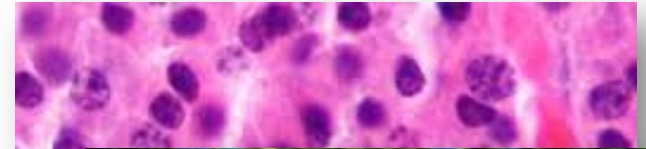
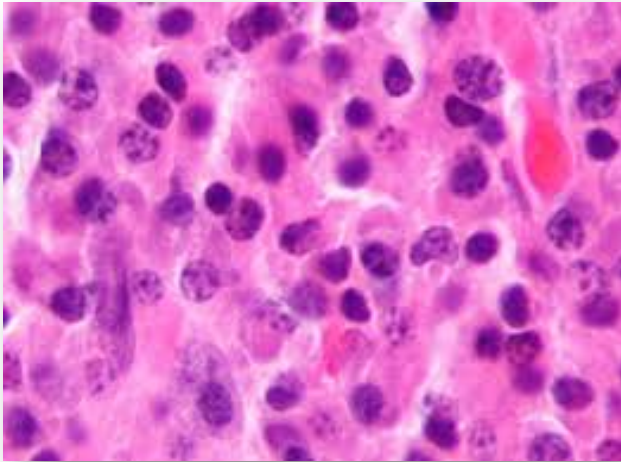
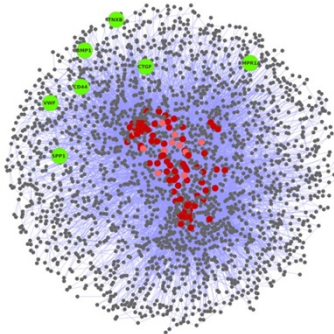
Relapse-free survival



Therapy



Resistance



Thanks to



Francesca Mateo
Luis Palomero



ProCURE
Alvaro Aytes group