

# CANCERTOOL

Exploration, visualization and representation interface to interrogate cancer datasets.

Verónica Torrano, PhD  
[vtorrano@cicbiogune.es](mailto:vtorrano@cicbiogune.es)

CIBERONC Session, 7- November 2018.

# Mechanisms of tumor progression

**Group coordinator: Arkaitz Carracedo CIC bioGUNE**

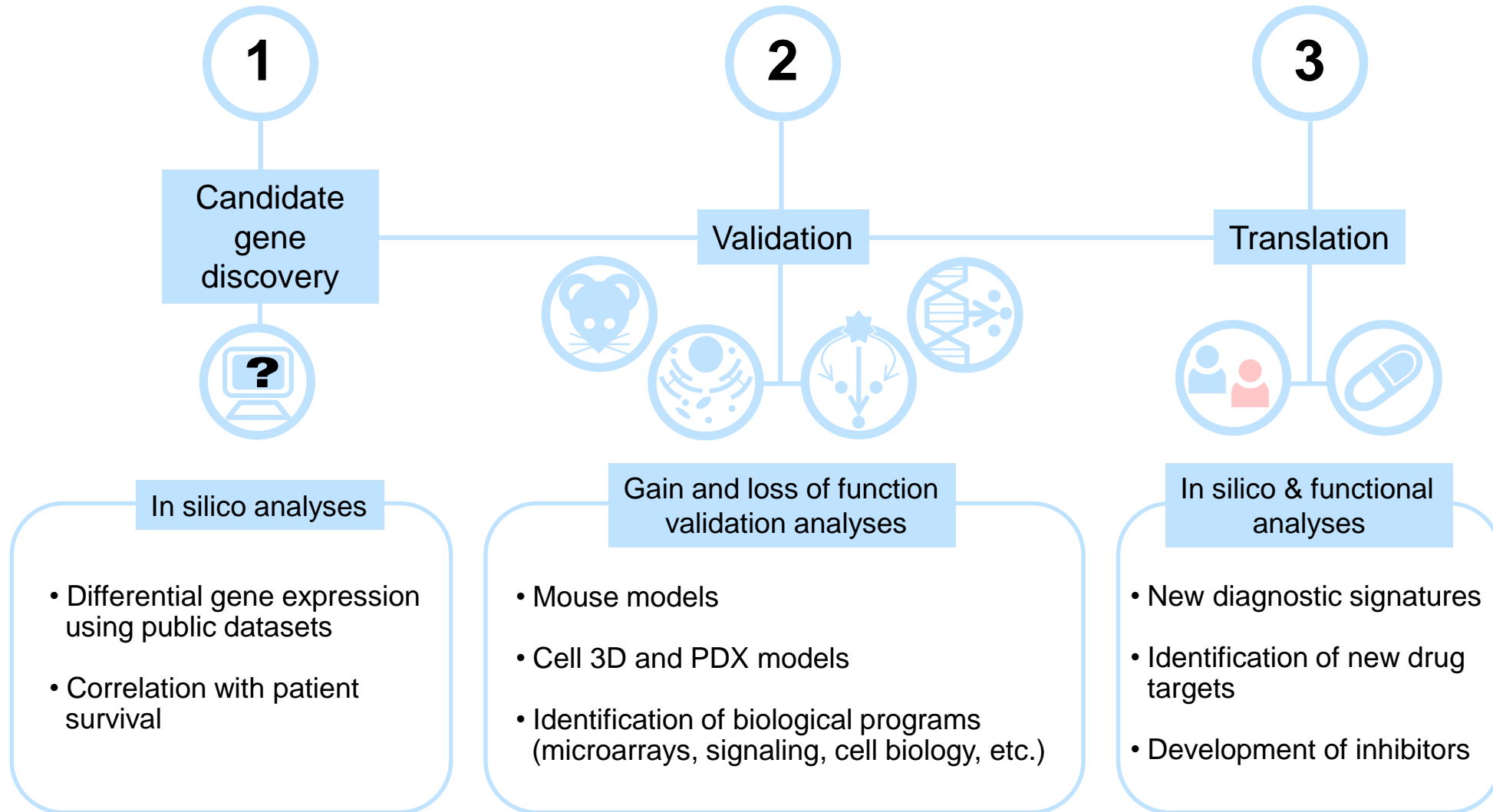
**Roger Gomis      IRB**

**Mariona Graupera IDIBELL**

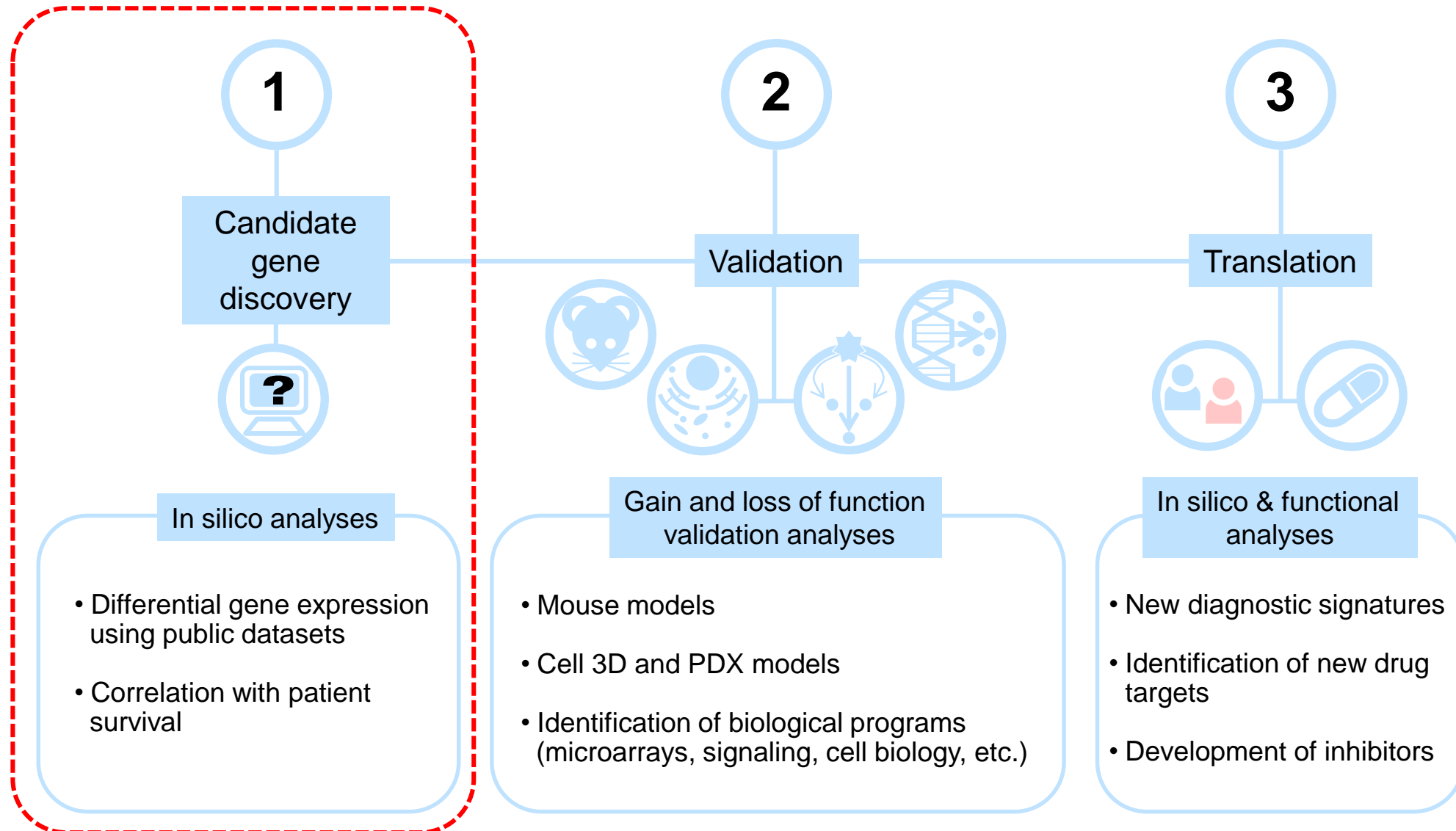
**Miguel Unda      Basurto**

**Veronica Torrano    CIC bioGUNE      —————>      University of the Basque Country**

# PIPELINE FOR THE IDENTIFICATION AND VALIDATION OF NEW TARGETS

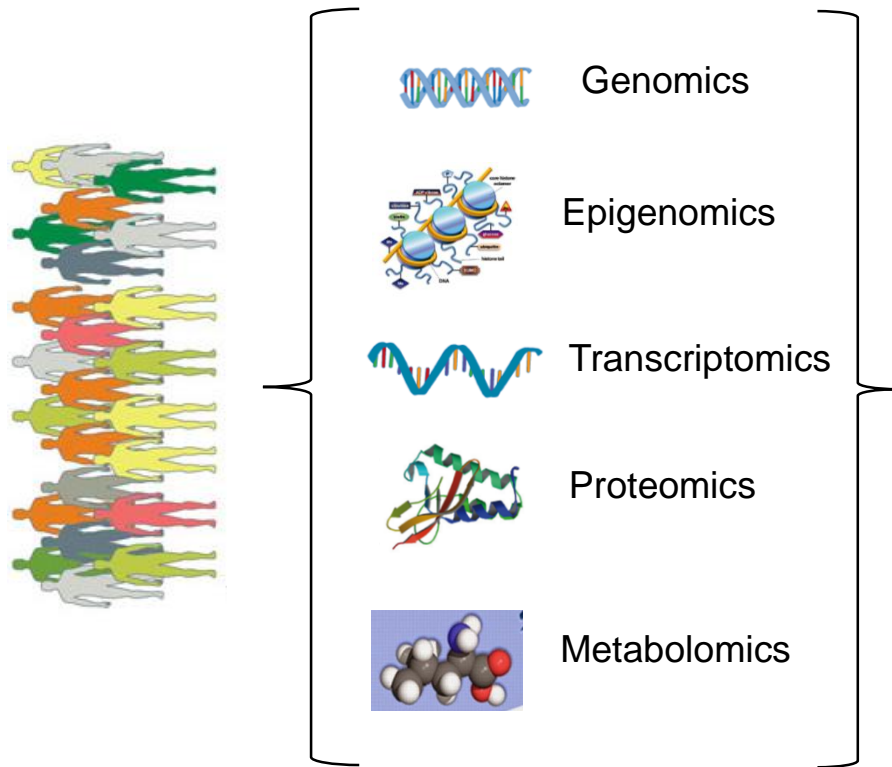


# PIPELINE FOR THE IDENTIFICATION AND VALIDATION OF NEW TARGETS

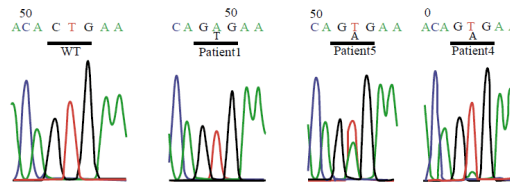
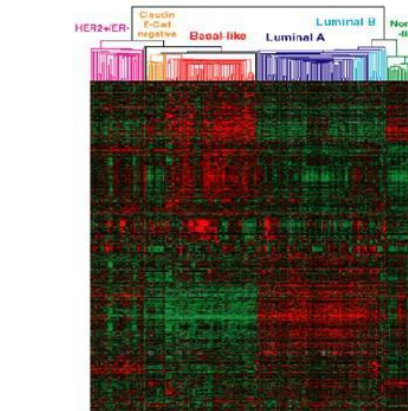


# The “OMICS”: Useful tool for precision medicine

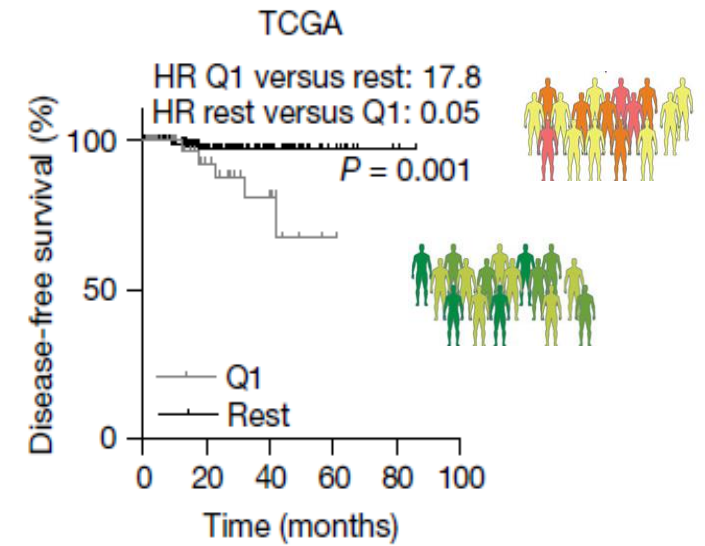
## OME layers



## Molecular characterisation

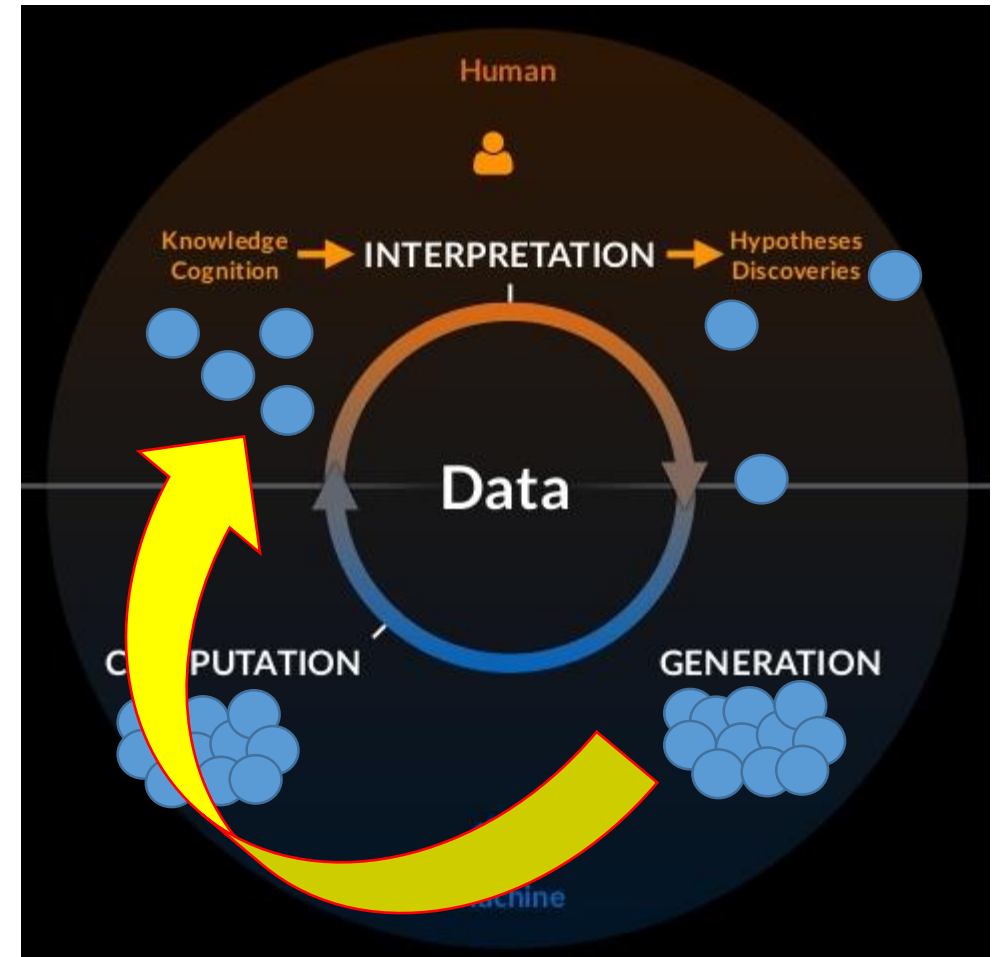
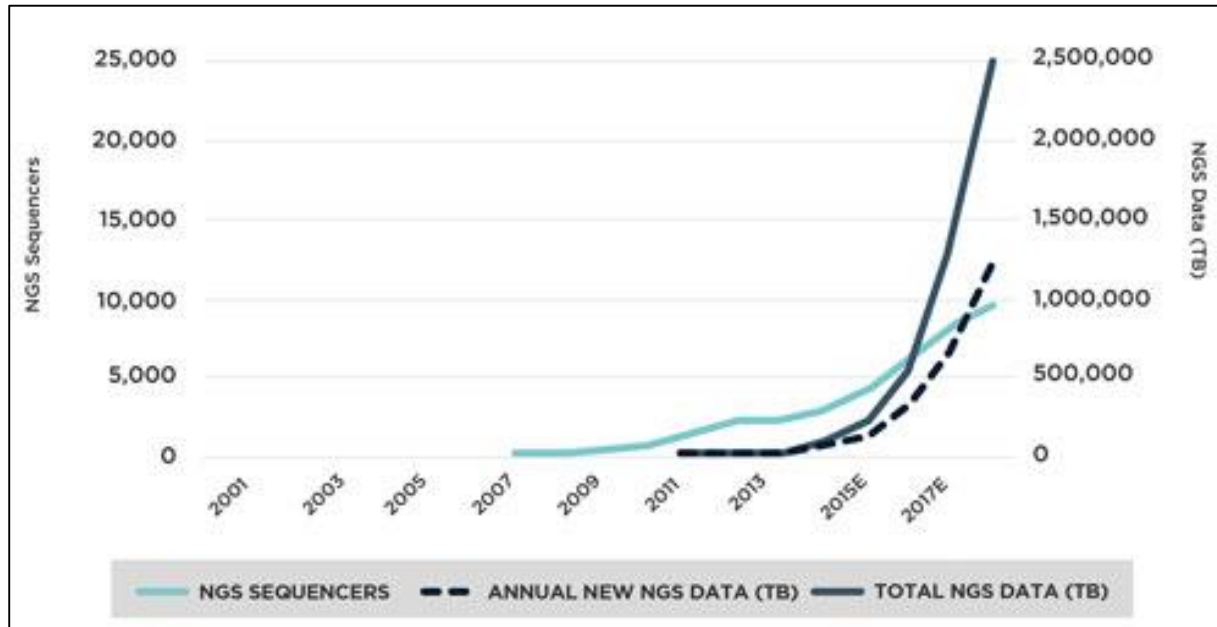


## Molecular stratification



Treatment decision

# Are we able to exploit all the generated data?



# Limitations...

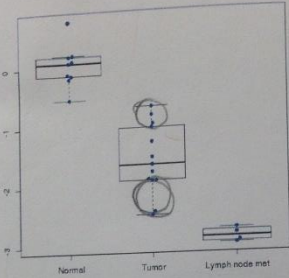




21.2.14

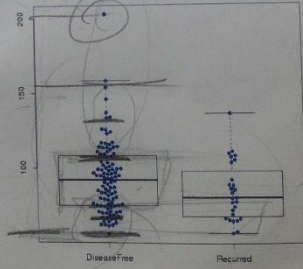
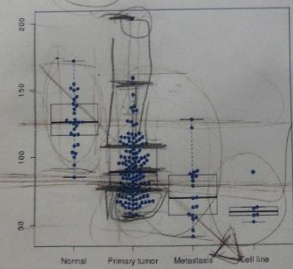
Lapointe  
p-value: 0.1356

SOMOS  
BIOINFORMATICOS



Taylor: Grupos globales  
p-value: 3.19e-15

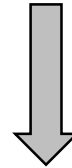
Taylor: Primary Tumors  
p-value: 0.04733



2014

Ana Rosa

Ana Rosa Cortazar's desk (2014-2016)





# Our contribution

To develop a free and easy-to-use interface that:

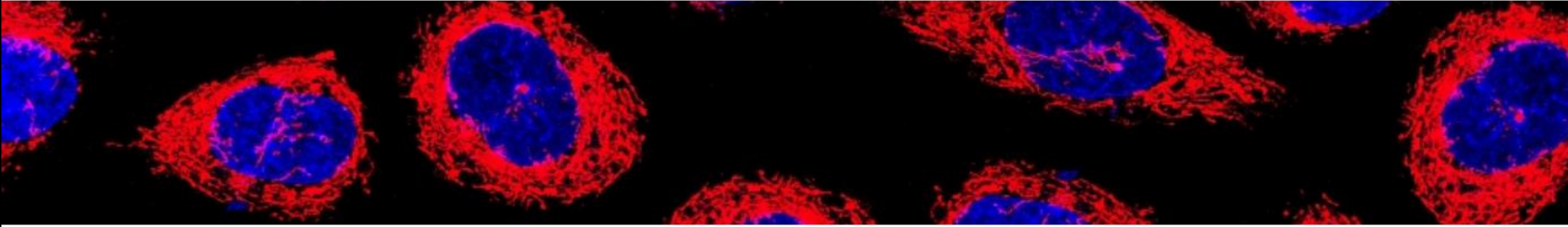
- Provide information of **patients** with cancer
- Take advantage of **existing public gene expression data**
- Provide **useful tools** for scientists:
  - Analyses
  - Visualization
  - Representation



# Exploiting publicly available datasets for the identification of new drivers of tumor progression

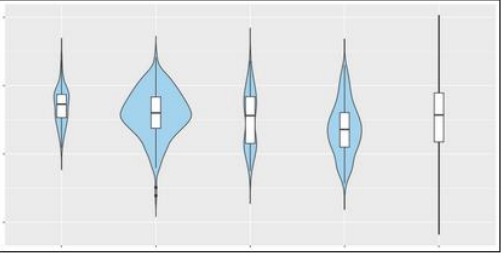
## CANCERTOOL

[HOMEPAGE](#) [DATASETS](#) [HELP](#) [ABOUT US](#) [CONTACT US](#)



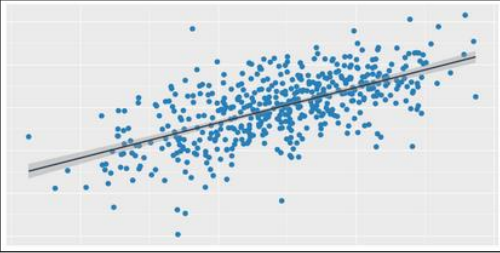
### BASIC ANALYSES

To perform gene expression comparative analyses between different groups of patient.



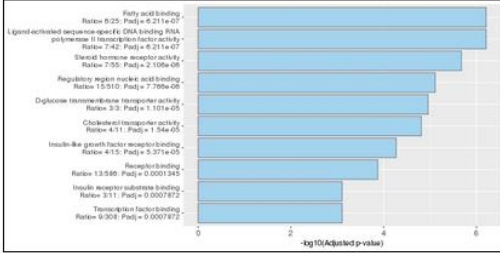
### CORRELATIONS

To study gene expression correlations among selected groups of genes.



### ENRICHMENT

To identify functions and processes that are over-represented in a selected set of genes.



| Biological Process   | Rank  | Padj      |
|--|-------|-----------|
| Fatty acid binding   | 620   | 6.211e-07 |
| Ligand-dependent sequence-specific DNA binding RNA polymerase II transcription factor activity | 742   | 6.211e-07 |
| Steroid hormone receptor activity  | 750   | 2.108e-06 |
| Regulatory region nucleic acid binding   | 1530  | 7.708e-06 |
| Diglyceride transmembrane transporter activity   | 33    | 1.101e-05 |
| Cholesterol transporter activity   | 411   | 1.58e-05  |
| Insulin-like growth factor receptor binding  | 415   | 9.371e-05 |
| Receptor binding   | 13589 | 0.0001345 |
| Insulin receptor substrate binding   | 311   | 0.0007872 |
| Transcription factor binding   | 9309  | 0.0007872 |

CIBERONC Collab  
XR Bustelo  
RR Gomis  
S Vincent  
V Quesada

CIBEREHD Collab  
AM Aransay

Cortazar et al., Cancer Res 2018

Valcarcel & Macchia et al., Cell Death Dis 2018

# Exploiting publicly available datasets for the identification of new drivers of tumor progression



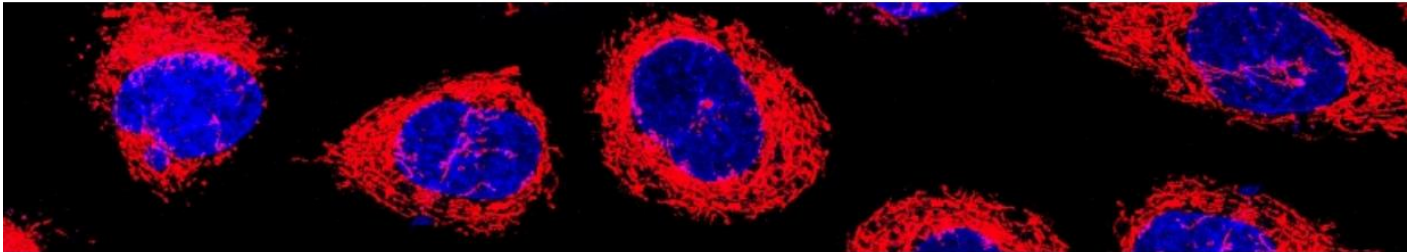
# Exploiting publicly available datasets for the identification of new drivers of tumor progression

## CANCERTOOL

HOME PAGE

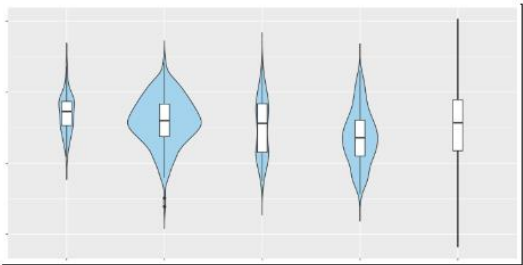
DATASETS

HELP



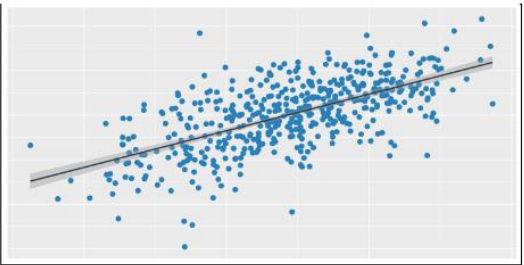
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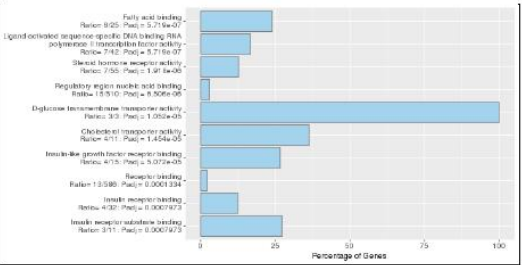
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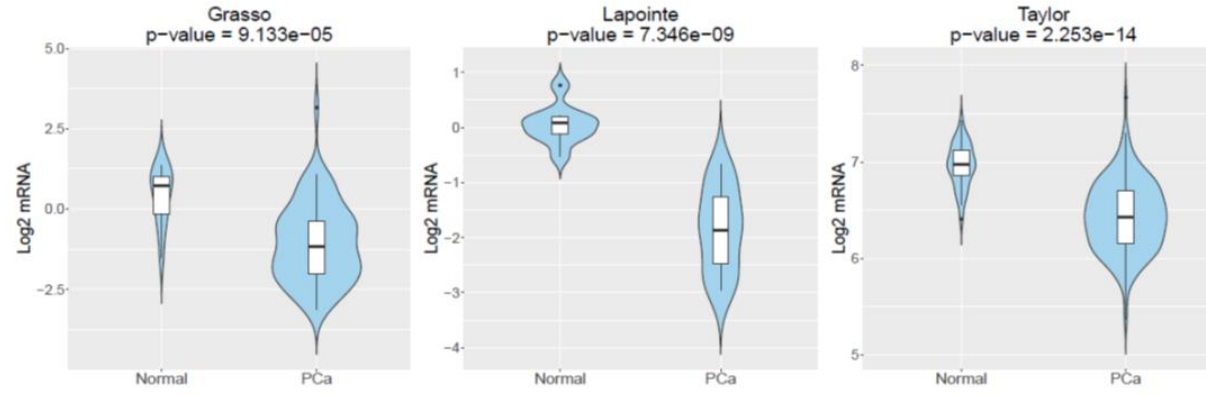
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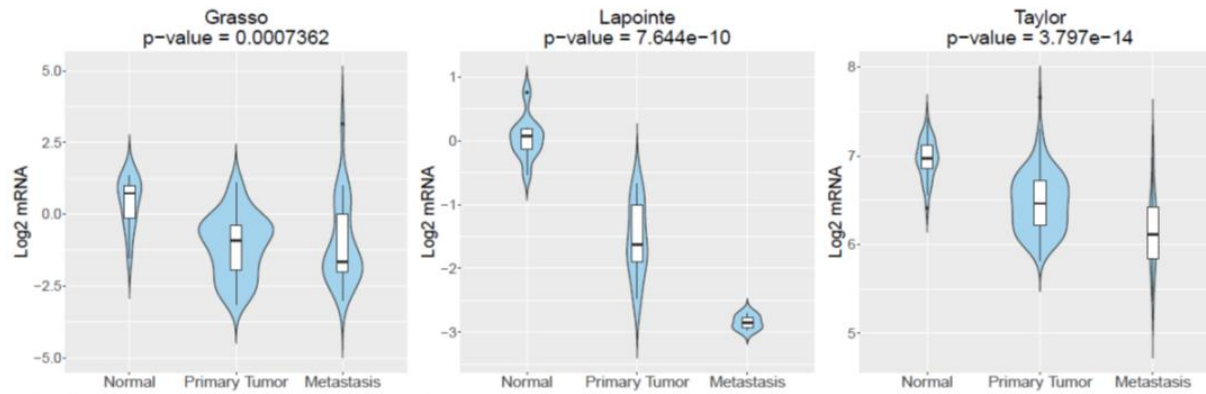


# PPARGC1A

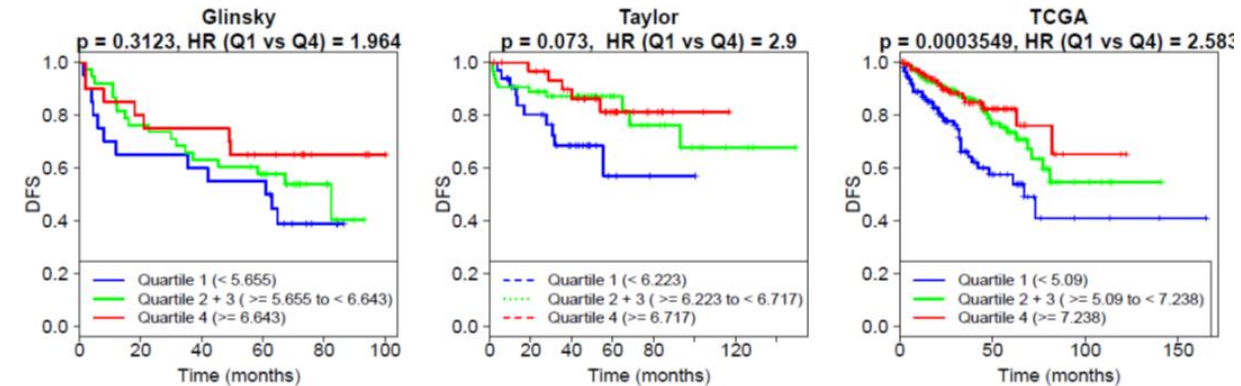
## A. Status in prostate cancer



## B. Status by Progression



## D. Disease-Free Survival



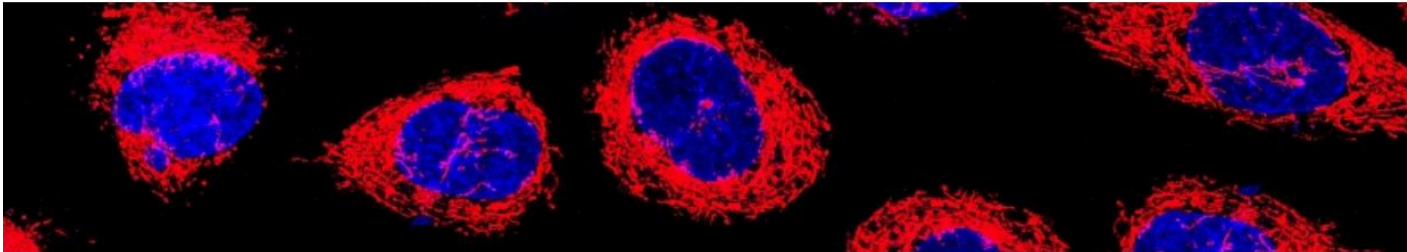
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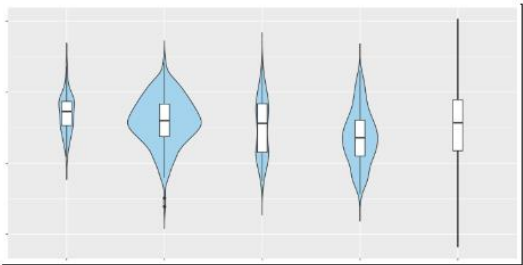
DATASETS

HELP



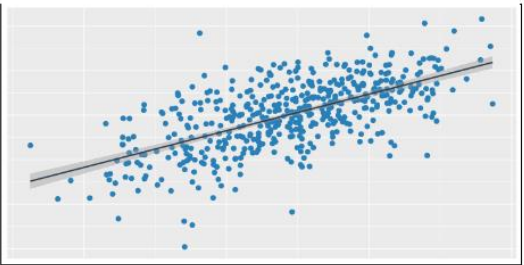
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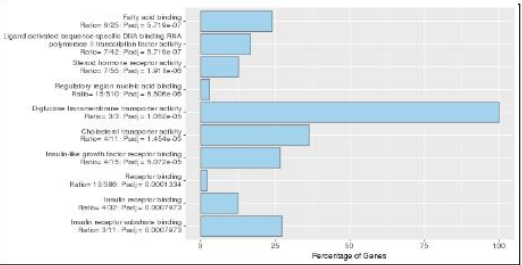
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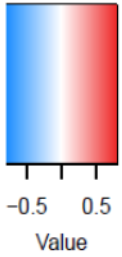


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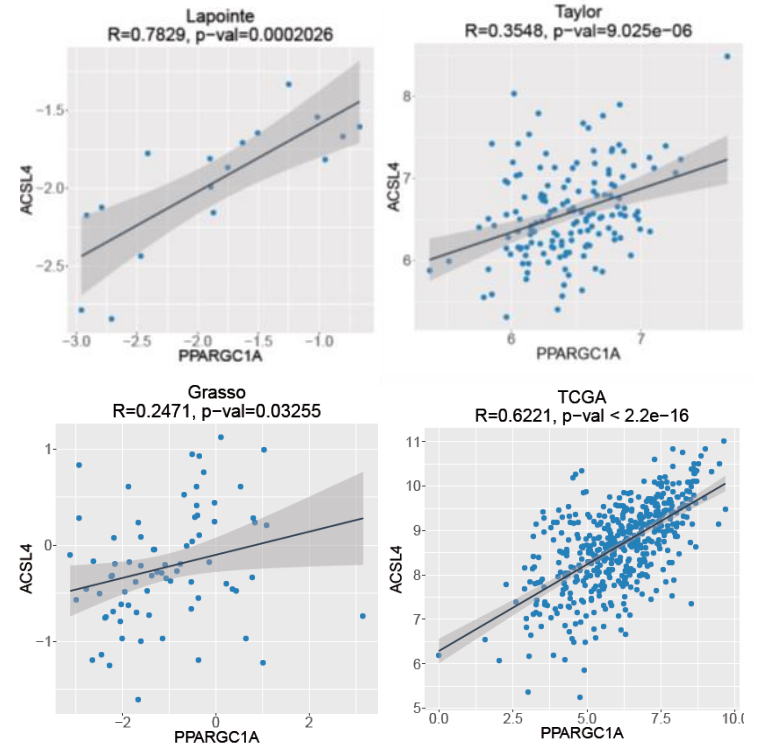


Color Key



### All tumors

|                    | Glinsky                          | Grasso                          | Lapointe                         | Taylor                           | TCGA                            | Tomlins                | Varambally                       |       |
|--------------------|----------------------------------|---------------------------------|----------------------------------|----------------------------------|---------------------------------|------------------------|----------------------------------|-------|
| Direct correlation | R = 0.408<br>p = 0.000187<br>(*) | R = 0.114<br>p = 0.331          | R = 0.54<br>p = 0.0251<br>(*)    | R = 0.496<br>p = 1.29e-10<br>(*) | R = 0.716<br>p < 2.2e-16<br>(*) | R = 0.044<br>p = 0.778 | R = 0.122<br>p = 0.691           | GSTM4 |
| Direct correlation | R = 0.329<br>p = 0.00305<br>(*)  | R = 0.381<br>p = 0.00074<br>(*) | NA                               | R = 0.297<br>p = 0.000232<br>(*) | R = 0.45<br>p < 2.2e-16<br>(*)  | NA                     | R = -0.762<br>p = 0.00248<br>(*) | ANG   |
| Direct correlation | R = 0.067<br>p = 0.554           | R = 0.247<br>p = 0.0326<br>(*)  | R = 0.783<br>p = 0.000203<br>(*) | R = 0.355<br>p = 9.02e-06<br>(*) | R = 0.622<br>p < 2.2e-16<br>(*) | NA                     | R = 0.343<br>p = 0.251           | ACSL4 |



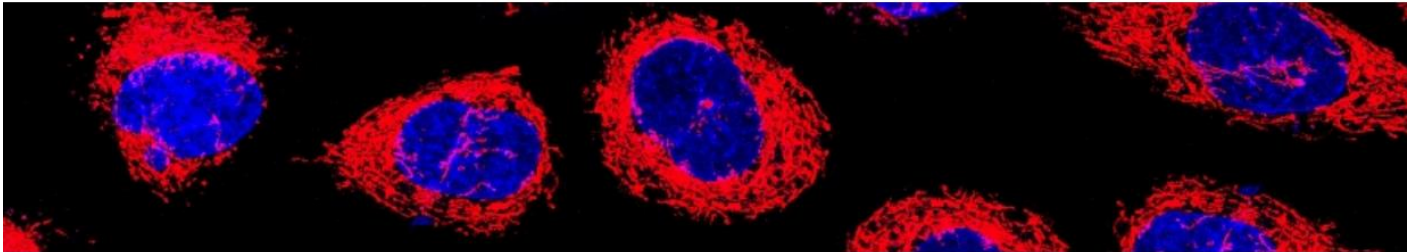
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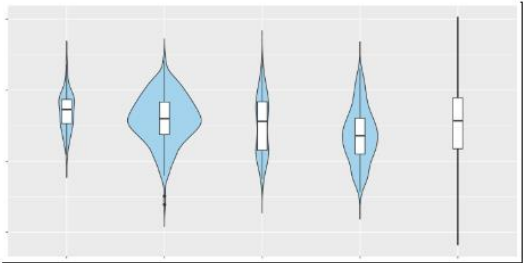
DATASETS

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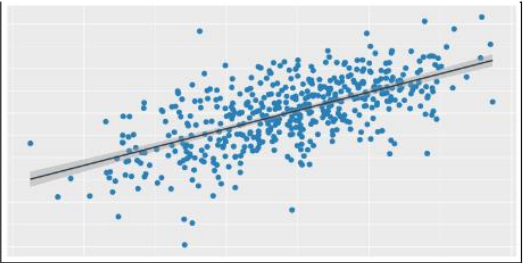
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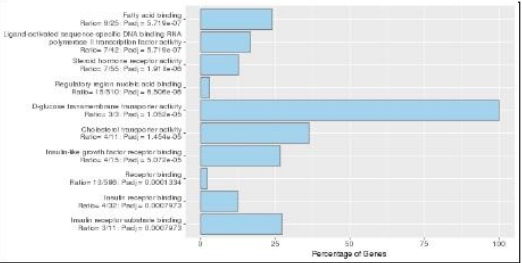
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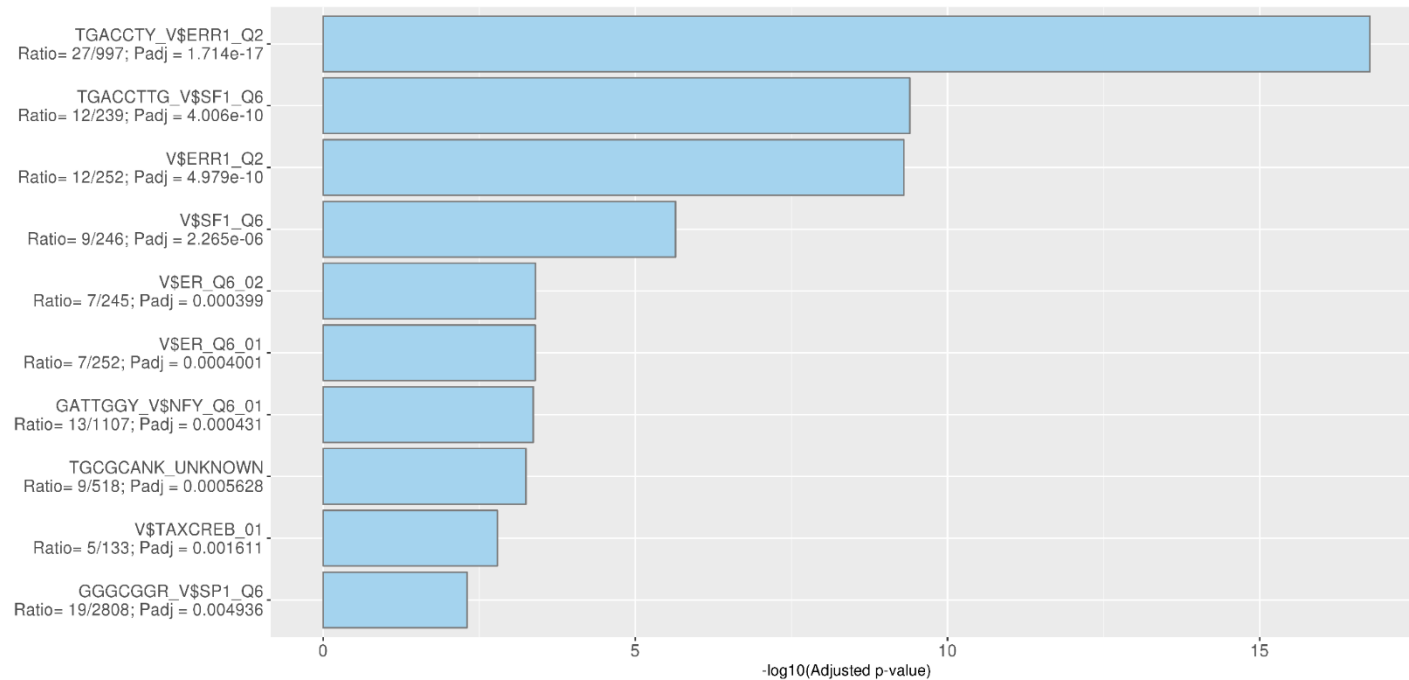
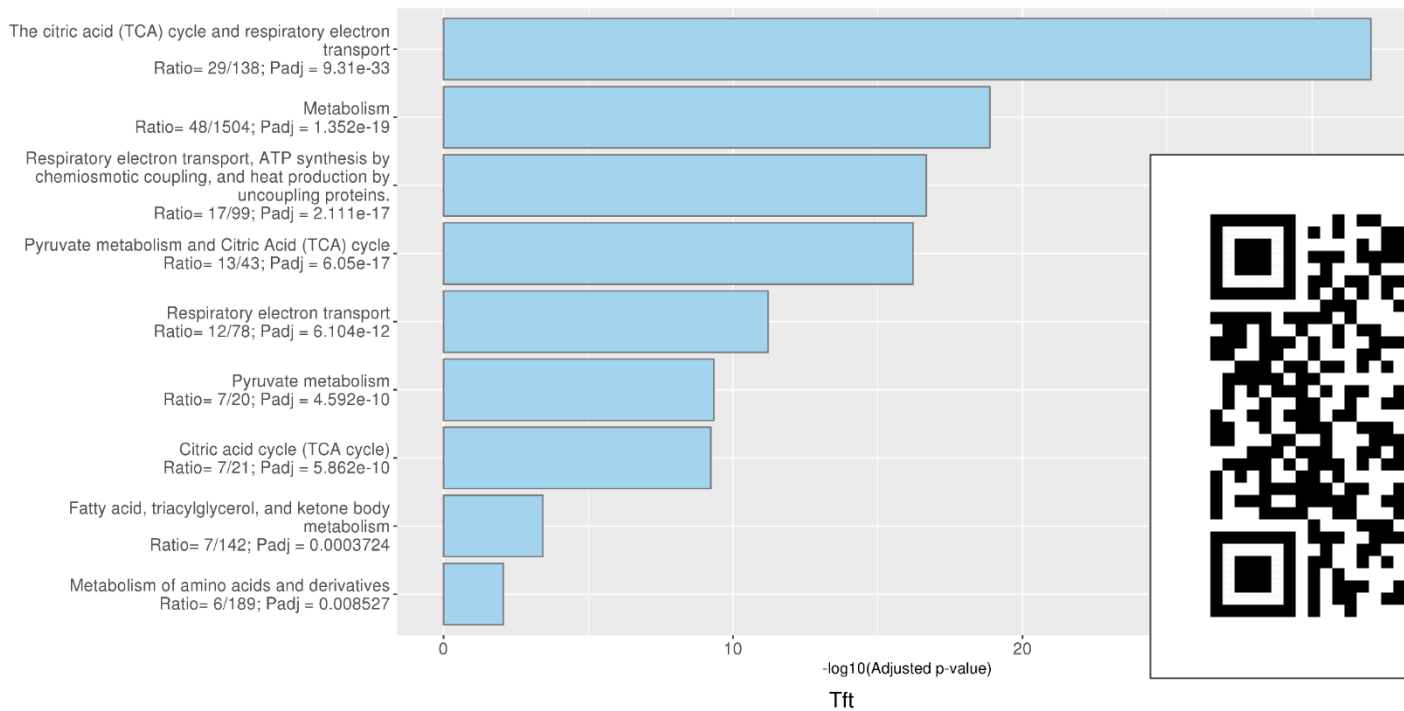
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Pathway




**Resource Report**

**Convergence and Technologies: Resource Report**

**Cancer Research**

## CANCERTOOL: A Visualization and Representation Interface to Exploit Cancer Datasets



Ana R. Cortazar<sup>1,2</sup>, Veronica Torrano<sup>1,2</sup>, Natalia Martín-Martín<sup>1,2</sup>, Alfredo Caro-Maldonado<sup>1</sup>, Laura Camacho<sup>1,3</sup>, Ivana Hermanova<sup>1</sup>, Elizabeth Guruceaga<sup>2,4</sup>, Luis F. Lorenzo-Martín<sup>2,5,6</sup>, Ruben Caloto<sup>2,5,6</sup>, Roger R. Gomis<sup>2,7,8</sup>, Iñigo Apaolaza<sup>9</sup>, Victor Quesada<sup>2,10</sup>, Jan Trka<sup>11,12</sup>, Antonio Gomez-Muñoz<sup>3</sup>, Silvestre Vincent<sup>2,13,14,15</sup>, Xose R. Bustelo<sup>2,5,6</sup>, Francisco J. Planes<sup>9</sup>, Ana M. Aransay<sup>1,16</sup>, and Arkaitz Carracedo<sup>1,2,3,17</sup>

**Proof of Concept**

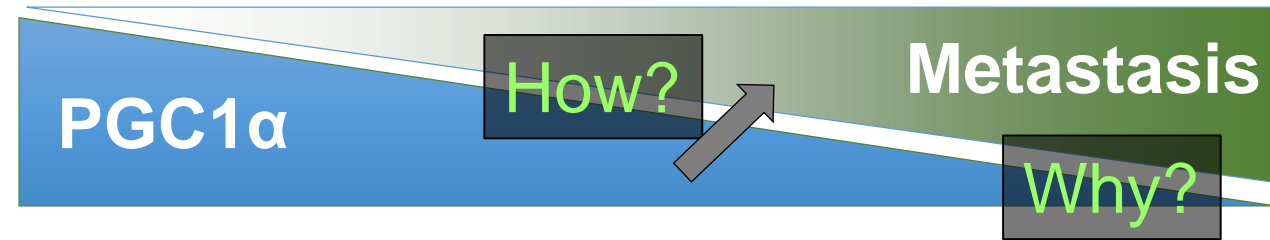
Valcarcel-Jimenez et al. *Cell Death and Disease* (2018)9:1041  
DOI 10.1038/s41419-018-1096-6

Cell Death & Disease

**ARTICLE** **Open Access**

## Integrative analysis of transcriptomics and clinical data uncovers the tumor-suppressive activity of MITF in prostate cancer

Lorea Valcarcel-Jimenez<sup>1</sup>, Alice Macchia<sup>1</sup>, Natalia Martín-Martín<sup>1,2</sup>, Ana Rosa Cortazar<sup>1,2</sup>, Ariane Schaub-Clerigué<sup>1</sup>, Mikel Pujana-Vaquero<sup>1</sup>, Sonia Fernández-Ruiz<sup>1</sup>, Isabel Lacasa-Viscasillas<sup>3</sup>, Aida Santos-Martín<sup>3</sup>, Ana Loizaga-Iriarte<sup>3</sup>, Miguel Unda-Urzaiz<sup>3</sup>, Ivana Hermanova<sup>1</sup>, Ianire Astobiza<sup>1</sup>, Mariona Graupera<sup>4</sup>, Julia Starkova<sup>5</sup>, James Sutherland<sup>6</sup>, Rosa Barrio<sup>7</sup>, Ana M. Aransay<sup>8</sup>, Arkaitz Carracedo<sup>1,2,6</sup> and Verónica Torrano<sup>1,2</sup>



*Torrano\* and Valcarcel\* et al. Nat Cell Bio 2016*

*Valcarcel\* and Torrano\* et al. Cell Cycle 2016*

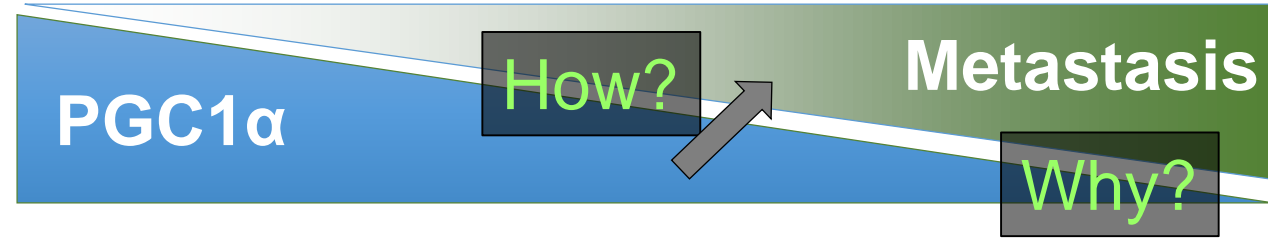
*Valcarcel\*, Gaude\*, Torrano\* et al. Trends Endo Metabolism. 2017*

*Torrano. Cell Metabolism 2017*

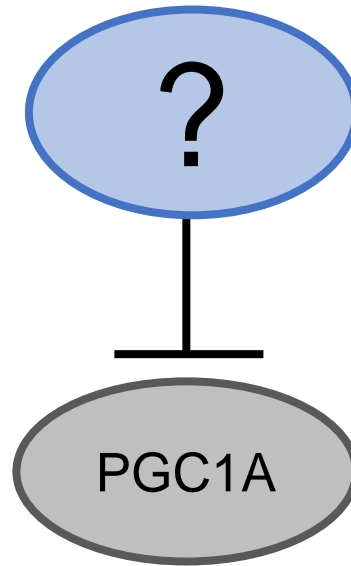
*Martin-Martin, Carracedo, Torrano. Frontiers 2018*



Poster#4



Why?



Lorea Valcarcel,  
PhD



Alice Macchia

Poster#35

*Torrano\* and Valcarcel\* et al. Nat Cell Bio 2016*

*Valcarcel\* and Torrano\* et al. Cell Cycle 2016*

*Valcarcel\*, Gaude\*, Torrano\* et al. Trends Endo Metabolism. 2017*

*Torrano. Cell Metabolism 2017*

*Martin-Martin, Carracedo, Torrano. Frontiers 2018*

# Screening of PGC1 $\alpha$ transcriptional regulators



1

Discovery



In silico analyses

- Differential gene expression using public datasets
- Correlation with patient survival

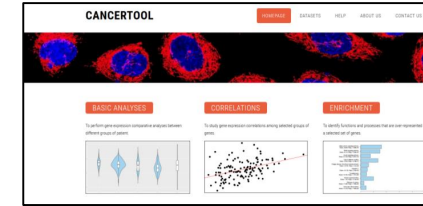
16 PPARGC1A  
transcriptional  
regulators  
  
PubMed

16

Correlation  
 $R > 0.2$   
p.value  $< 0.05$   
4 out of 7

+

N vs PT  
Expression



Selection criteria:

- 1- Consistent correlation with PGC1A expression in different prostate cancer cohorts
- 2- Consistently altered in different prostate cancer cohorts

# Screening of PGC1 $\alpha$ transcriptional regulators



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Discovery



In silico analyses

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16 PPARGC1A transcriptional regulators

16

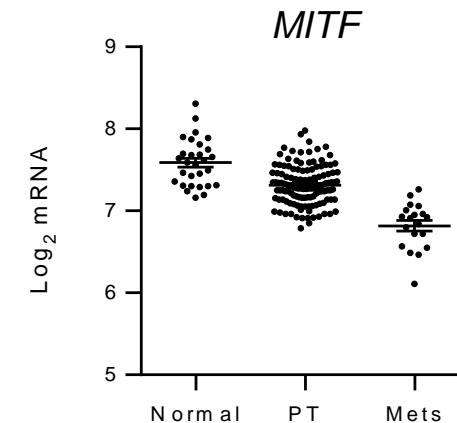
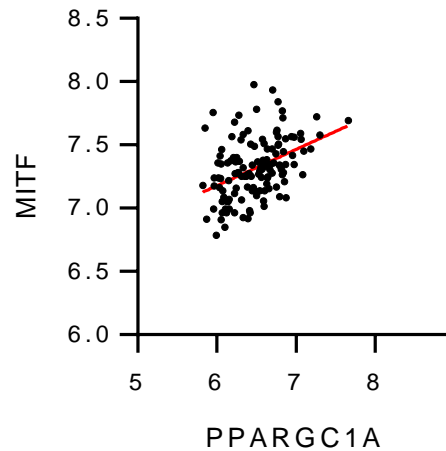
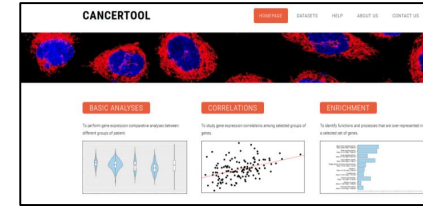
Correlation  
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4 out of 7

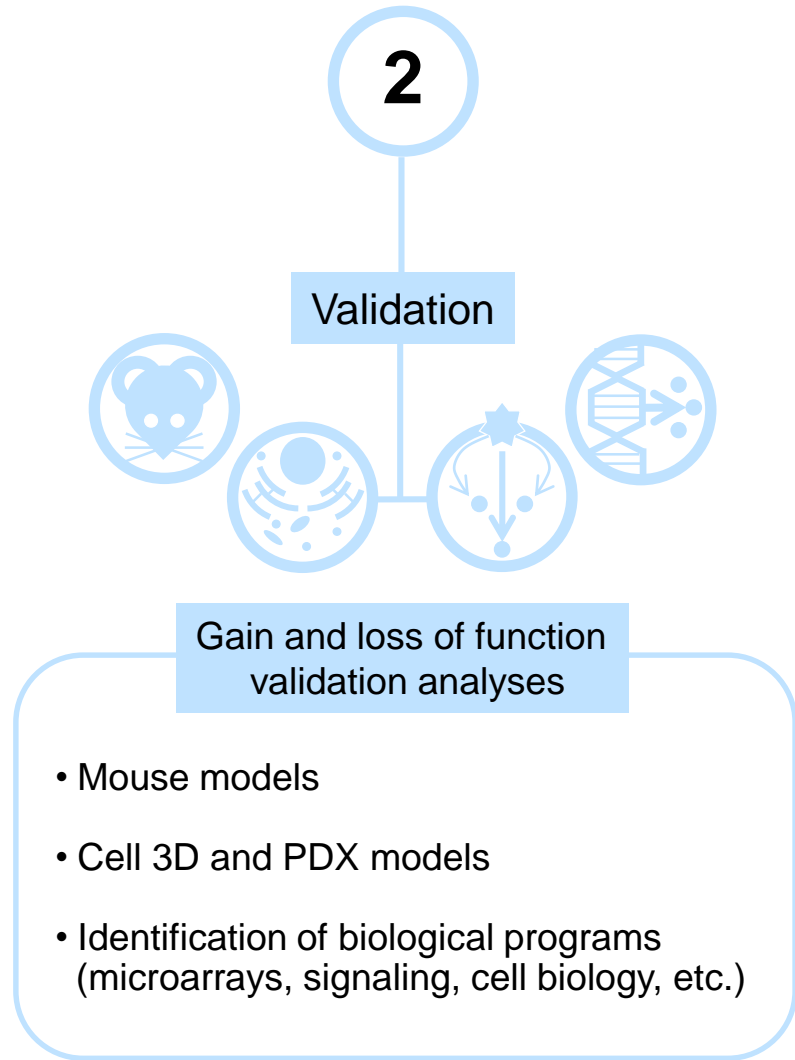
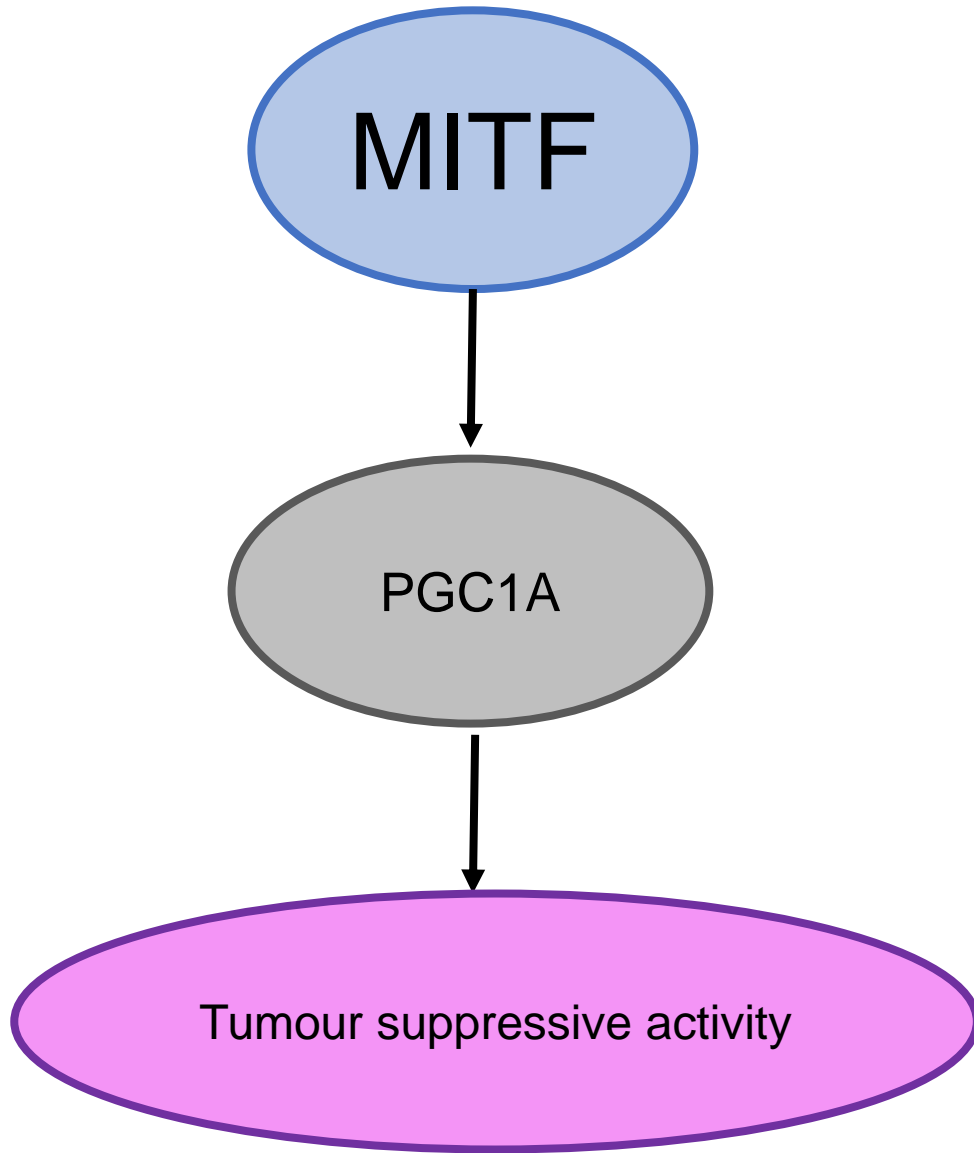
+

N vs PT  
Expression

1

MITF

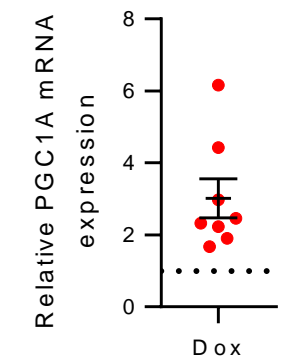
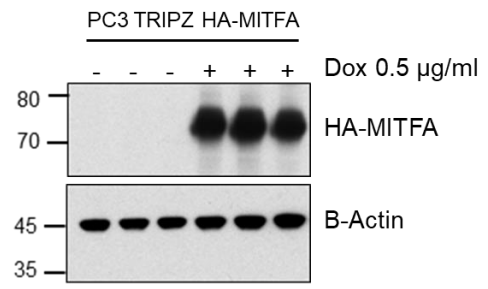
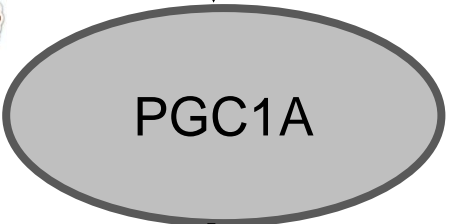
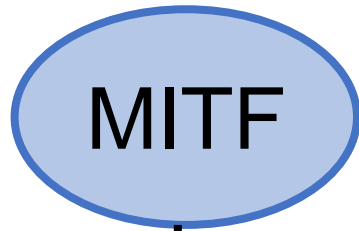




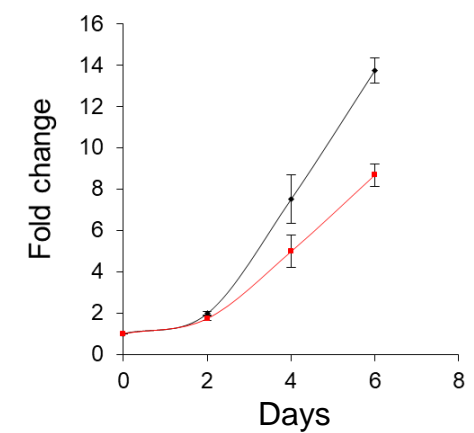




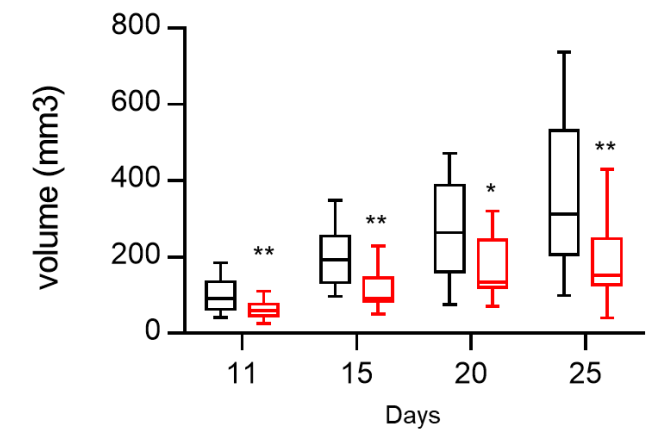
# MITF reduces cell proliferation and tumor growth



2D growth (n=5)



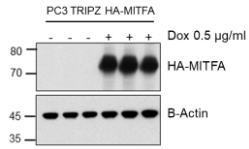
Tumor growth



● No dox  
● Dox



# ....but **DO NOT** depend on PGC1 $\alpha$

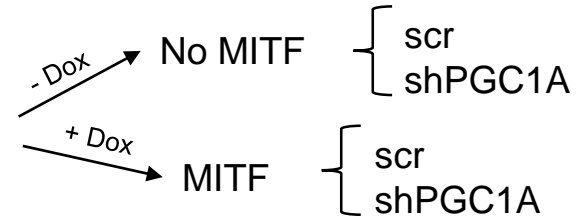


PC3 TRIPZ-HA\_MITFA

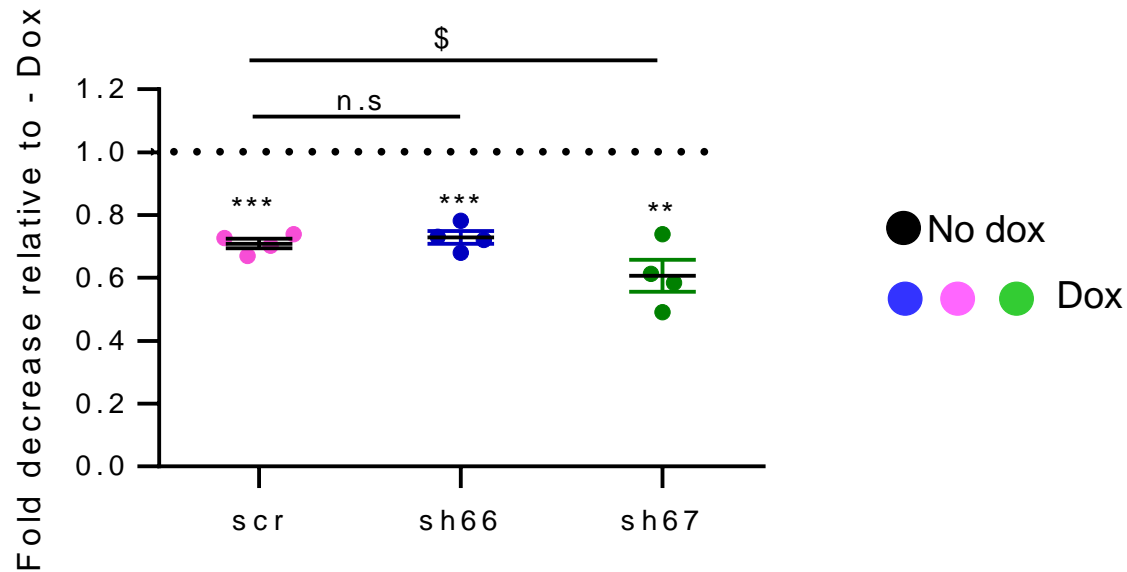


pLKO-shPGC1a or scr

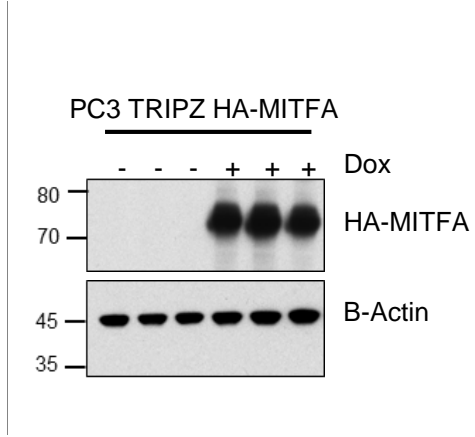
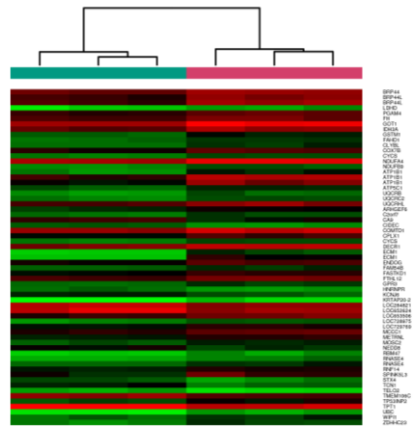
PC3 TRIPZ-  
HA\_MITFA shPGC1A



## 2D Growth



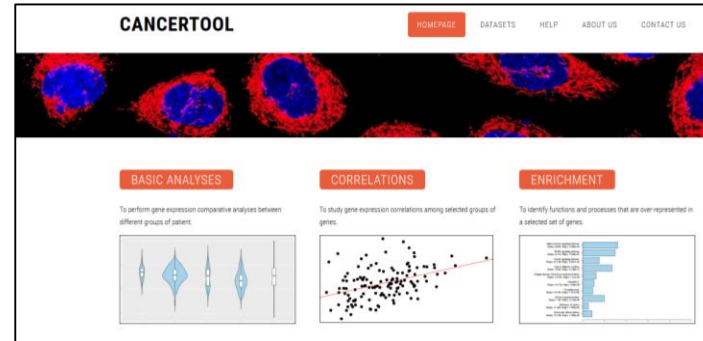
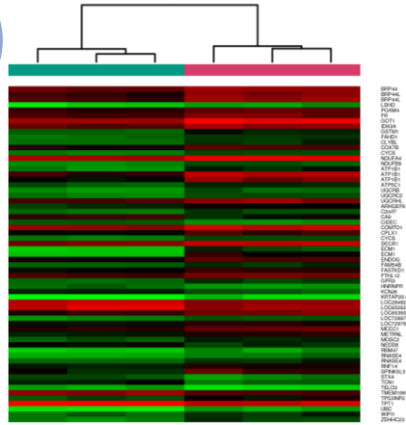
# Candidate gene screening



6 differentially expressed genes

6

# Candidate gene screening

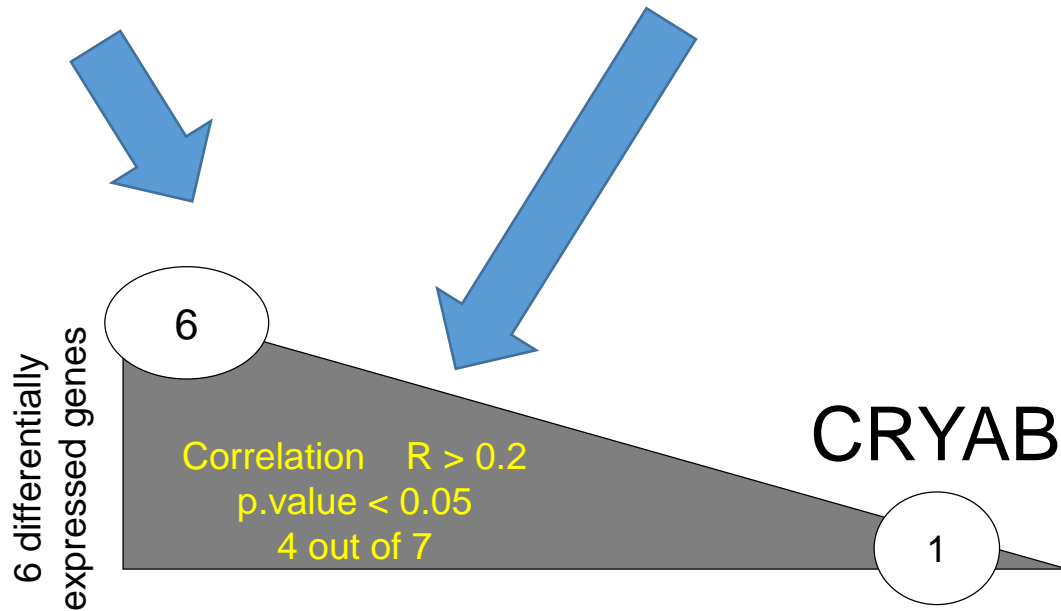
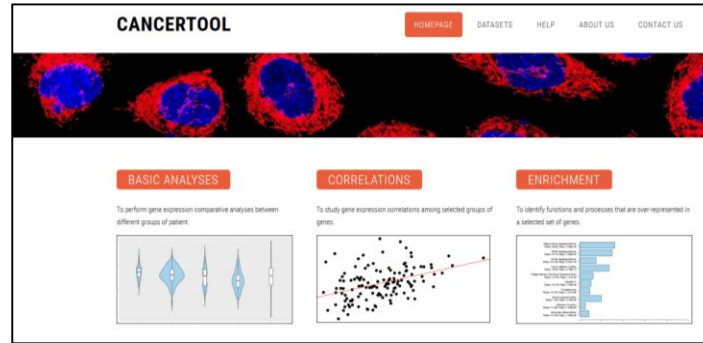
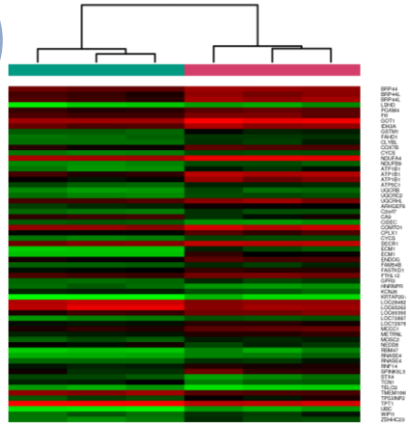


6 differentially  
expressed genes

6

Correlation  $R > 0.2$   
p.value  $< 0.05$   
4 out of 7

# Candidate gene screening



Direct correlation

|         | Glinsky                   | Grasso                    | Lapointe                | Taylor                   | TCGA                       | Tomlins                  | Varambally              |  |
|---------|---------------------------|---------------------------|-------------------------|--------------------------|----------------------------|--------------------------|-------------------------|--|
| CRYAB   | R = 0.395<br>p = 0.000346 | R = 0.495<br>p = 0.000478 | R = 0.544<br>p = 0.0581 | R = 0.596<br>p < 2.2e-16 | R = 0.57<br>p < 2.2e-16    | R = -0.032<br>p = 0.89   | R = -0.107<br>p = 0.84  |  |
| UPP1    | R = 0.204<br>p = 0.0731   | R = 0.303<br>p = 0.0391   | R = 0.462<br>p = 0.115  | R = -0.009<br>p = 0.92   | R = 0.195<br>p = 1.29e-05  | R = -0.477<br>p = 0.0351 | R = 0.071<br>p = 0.906  |  |
| KRT75   | R = 0.104<br>p = 0.365    | R = 0.35<br>p = 0.359     | R = 0.335<br>p = 0.263  | R = 0.12<br>p = 0.171    | R = -0.034<br>p = 0.527    | NA                       | R = -0.214<br>p = 0.662 |  |
| GDF15   | R = -0.153<br>p = 0.181   | R = -0.229<br>p = 0.121   | R = -0.071<br>p = 0.821 | R = -0.182<br>p = 0.0375 | R = -0.234<br>p = 1.52e-07 | NA                       | R = -0.393<br>p = 0.396 |  |
| UBC     | R = 0.232<br>p = 0.0409   | R = 0.592<br>p = 1.73e-05 | NA                      | R = -0.115<br>p = 0.191  | R = -0.023<br>p = 0.603    | NA                       | R = -0.679<br>p = 0.11  |  |
| TM4SF19 | NA                        | R = 0.191<br>p = 0.263    | NA                      | R = -0.097<br>p = 0.272  | R = 0.11<br>p = 0.0177     | NA                       | NA                      |  |

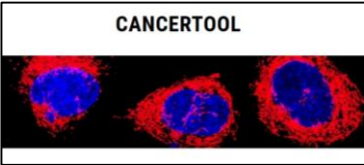
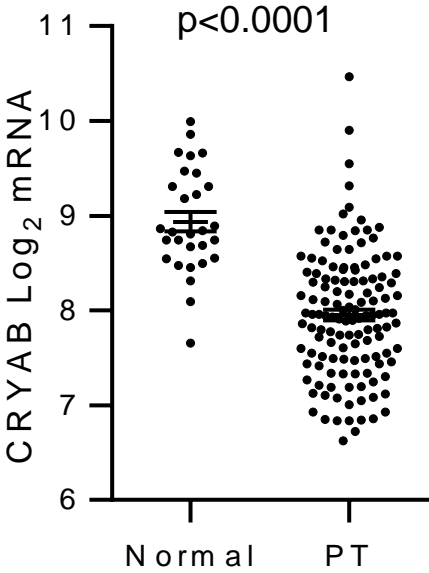
Color Key  
Value: -0.6 0 0.6

# CRYAB is deregulated in PCa

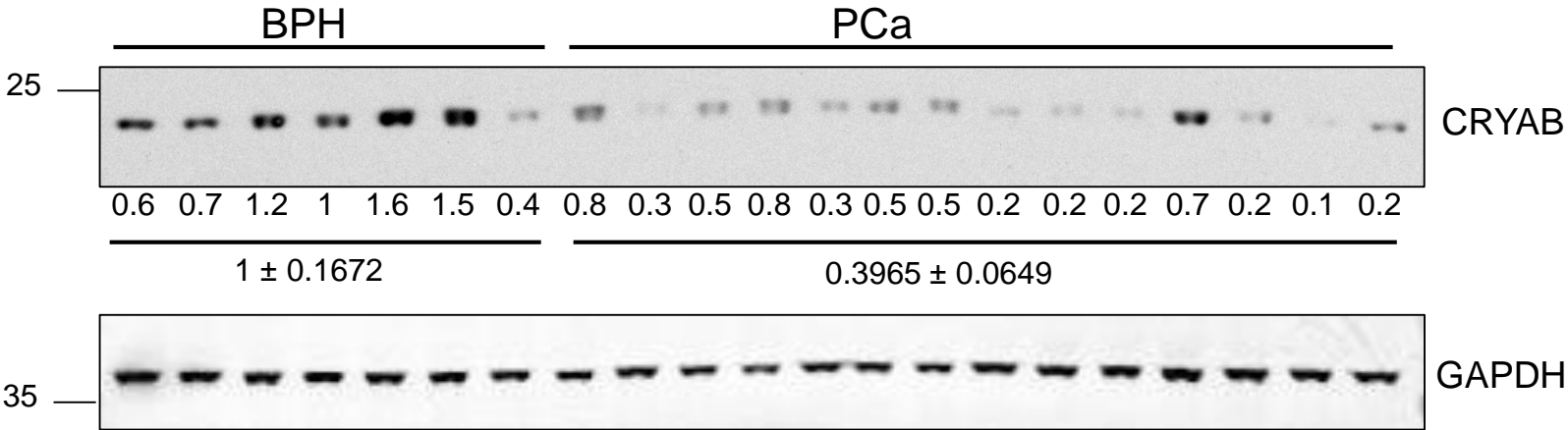


*Taylor et al.*

*Basurto Cohort*

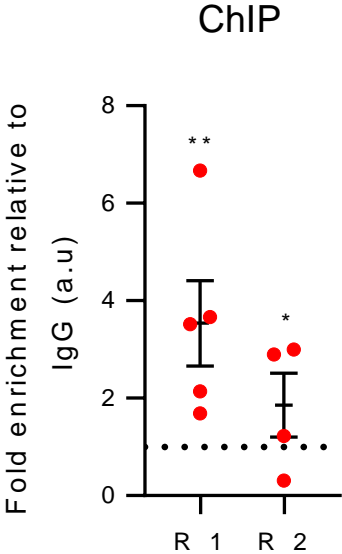
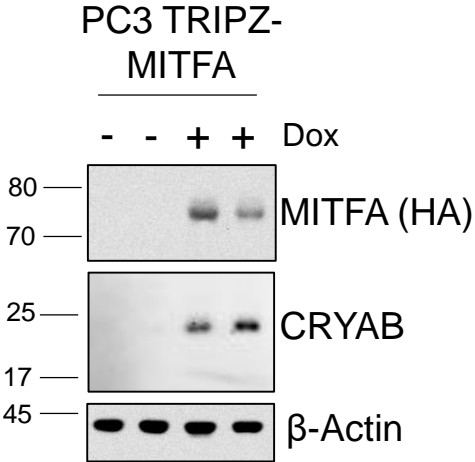


Raw data

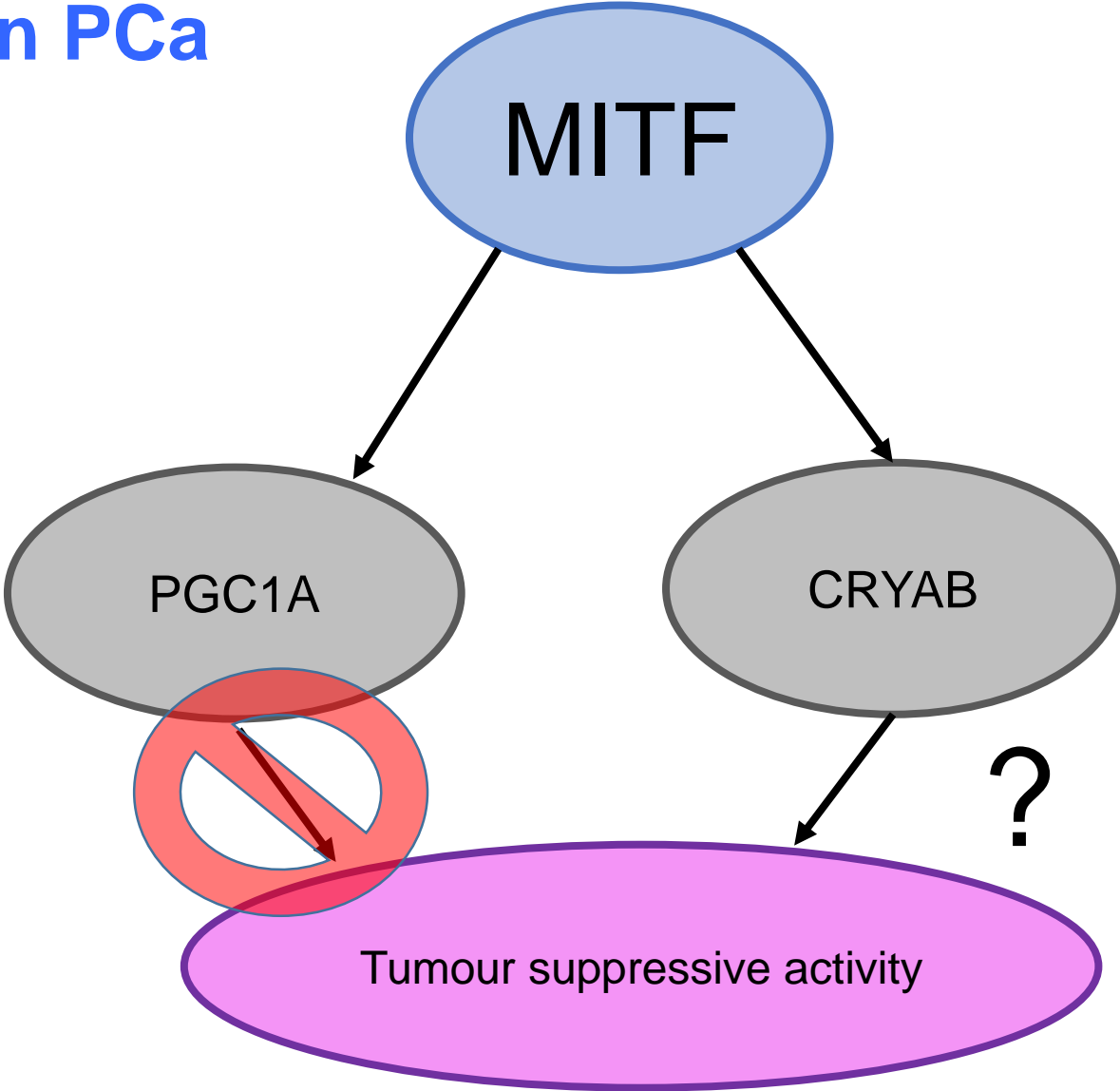
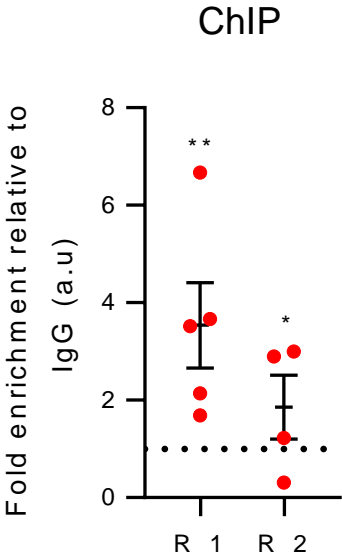
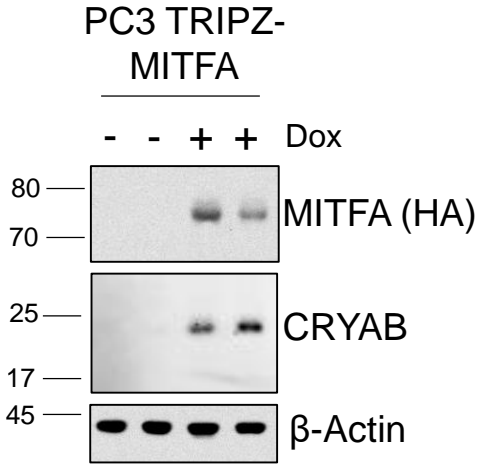


PT: primary tumors  
BPH: Bening prostatic hiperplasia  
PCa: prostate cancer

# CRYAB is a MITF target gene in PCa

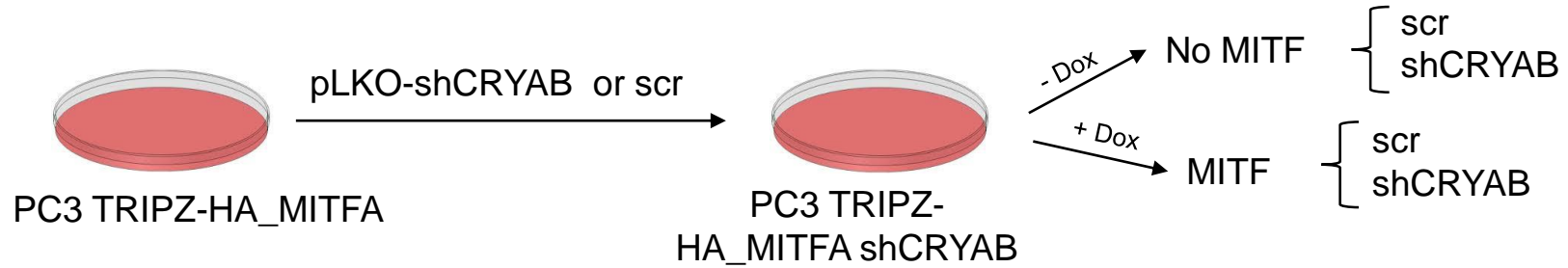


# CRYAB is a MITF target gene in PCa

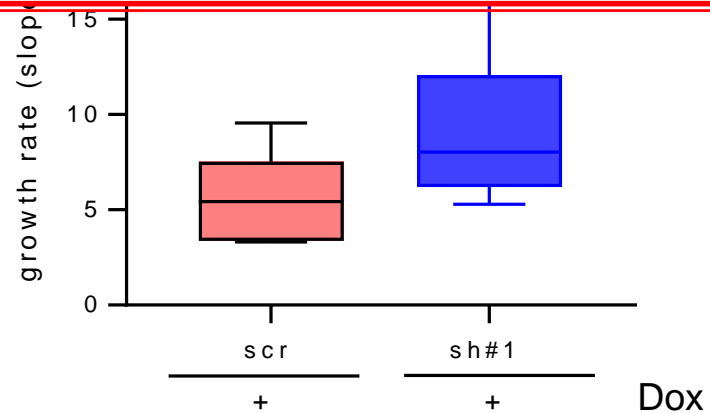
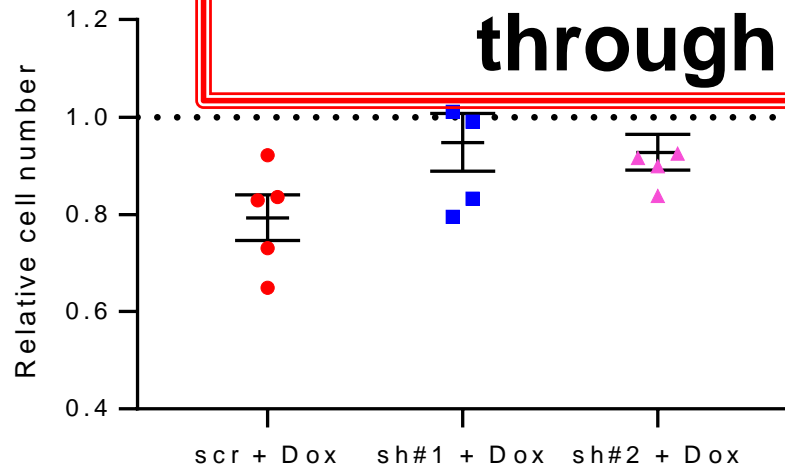




# Biological effects of MITF are dependent of CRYAB



**MITF elicits prostate tumor suppression through the control of CRYAB**

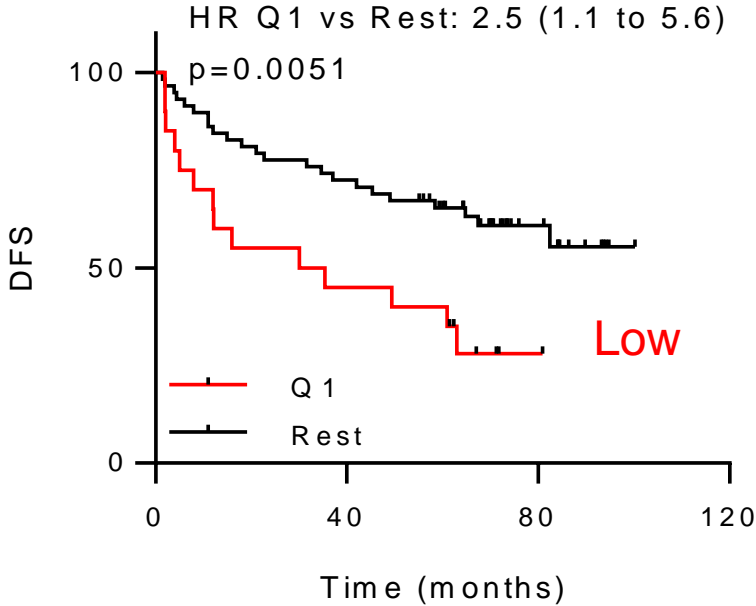
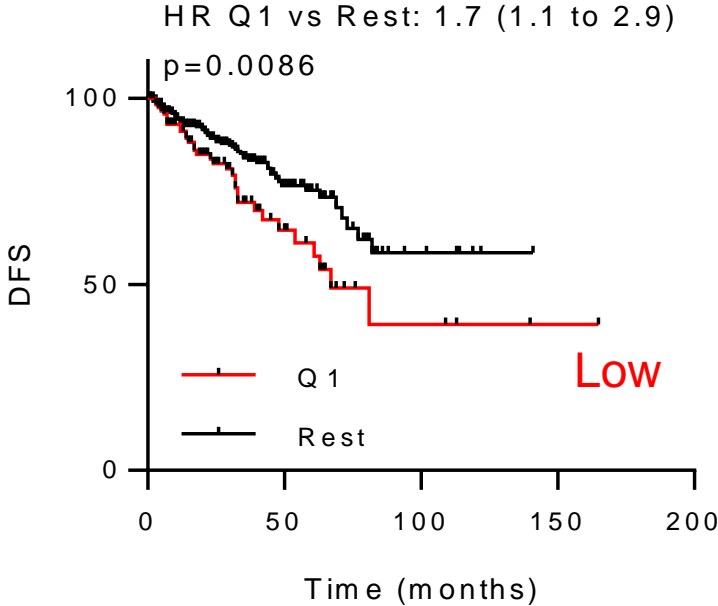
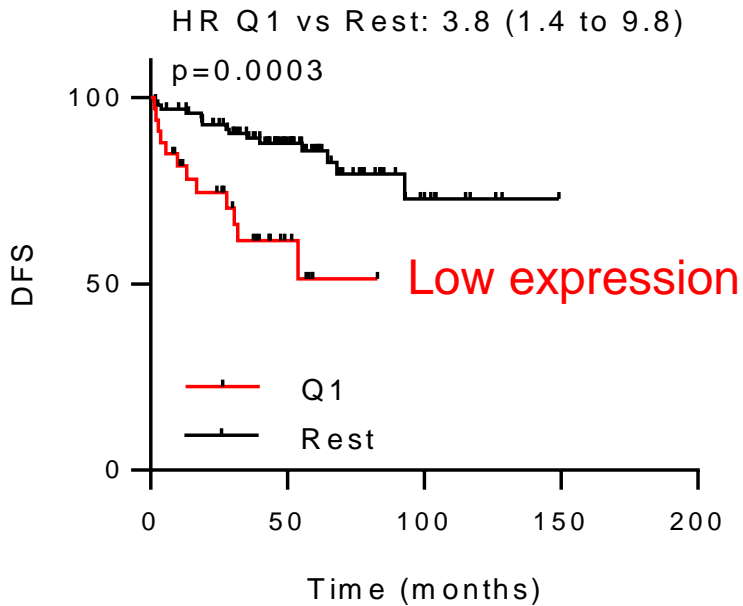


# MITF-CRYAB transcriptional axis has stratification potential

Taylor et al.

TCGA

Glinsky et al.



# TAKE HOME MESSAGE

- **Cancertool** serve as a discovery platform for cancer-related genes
- A novel **MITF-CRYAB** transcriptional axis elicits tumor suppression in PCa

# Thank you! Gracie! Milesker! Gràcies! Gracias!

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fundación vasca de innovación e investigación sanitarias

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