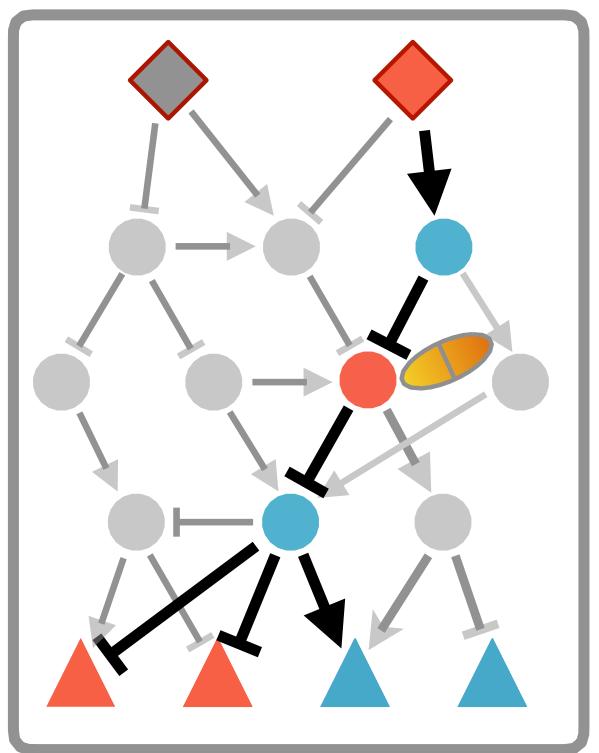
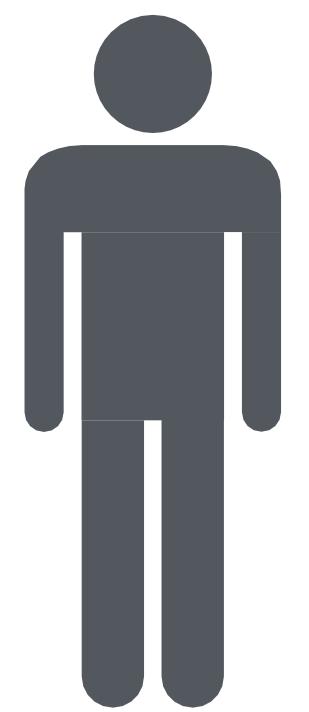
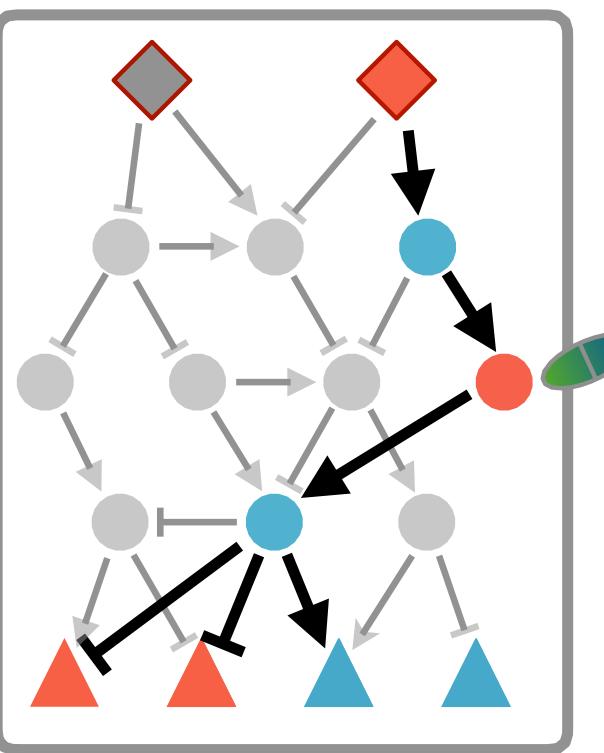
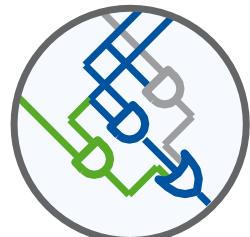


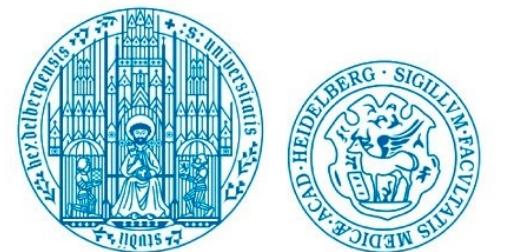
# Footprint methods for functional analysis of omics data



Rosa Hernansaiz Ballesteros



Institute for Computational Biomedicine  
[www.saezlab.org](http://www.saezlab.org) [@sysbiomed](https://twitter.com/@sysbiomed)



HEIDELBERG  
UNIVERSITY  
HOSPITAL



# Who am I?

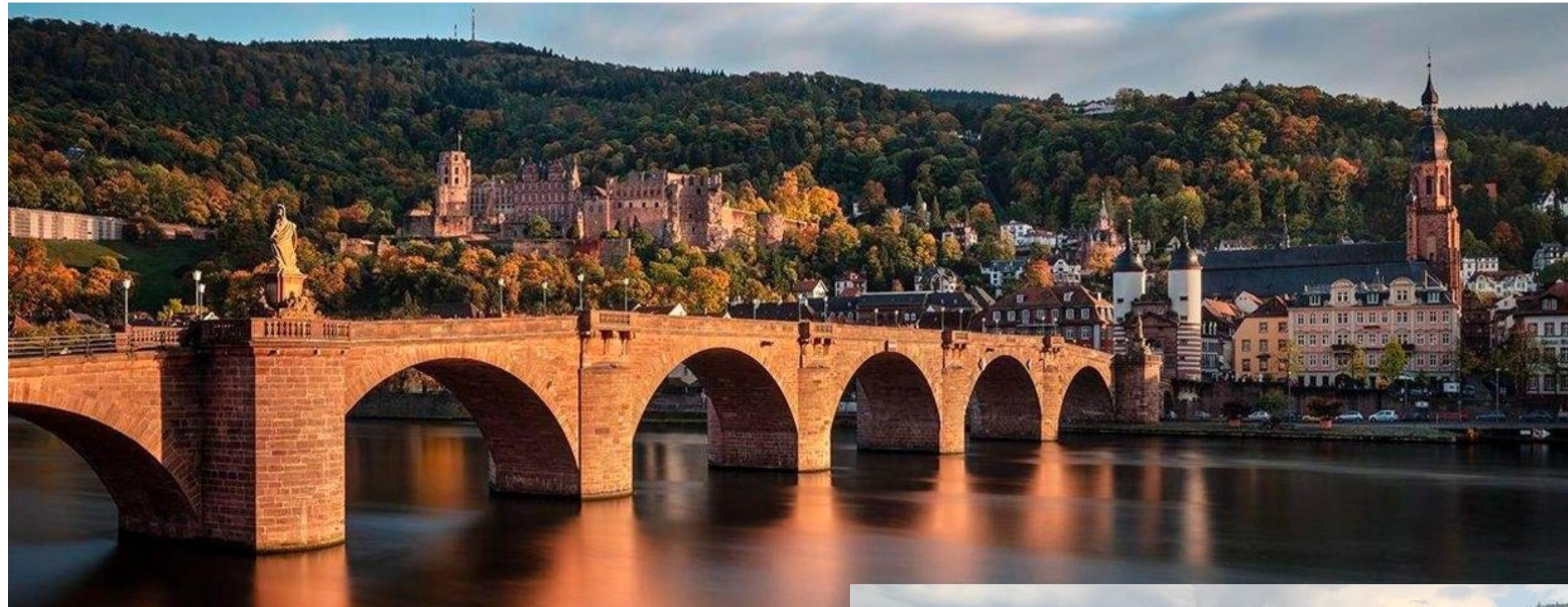


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HOSPITAL





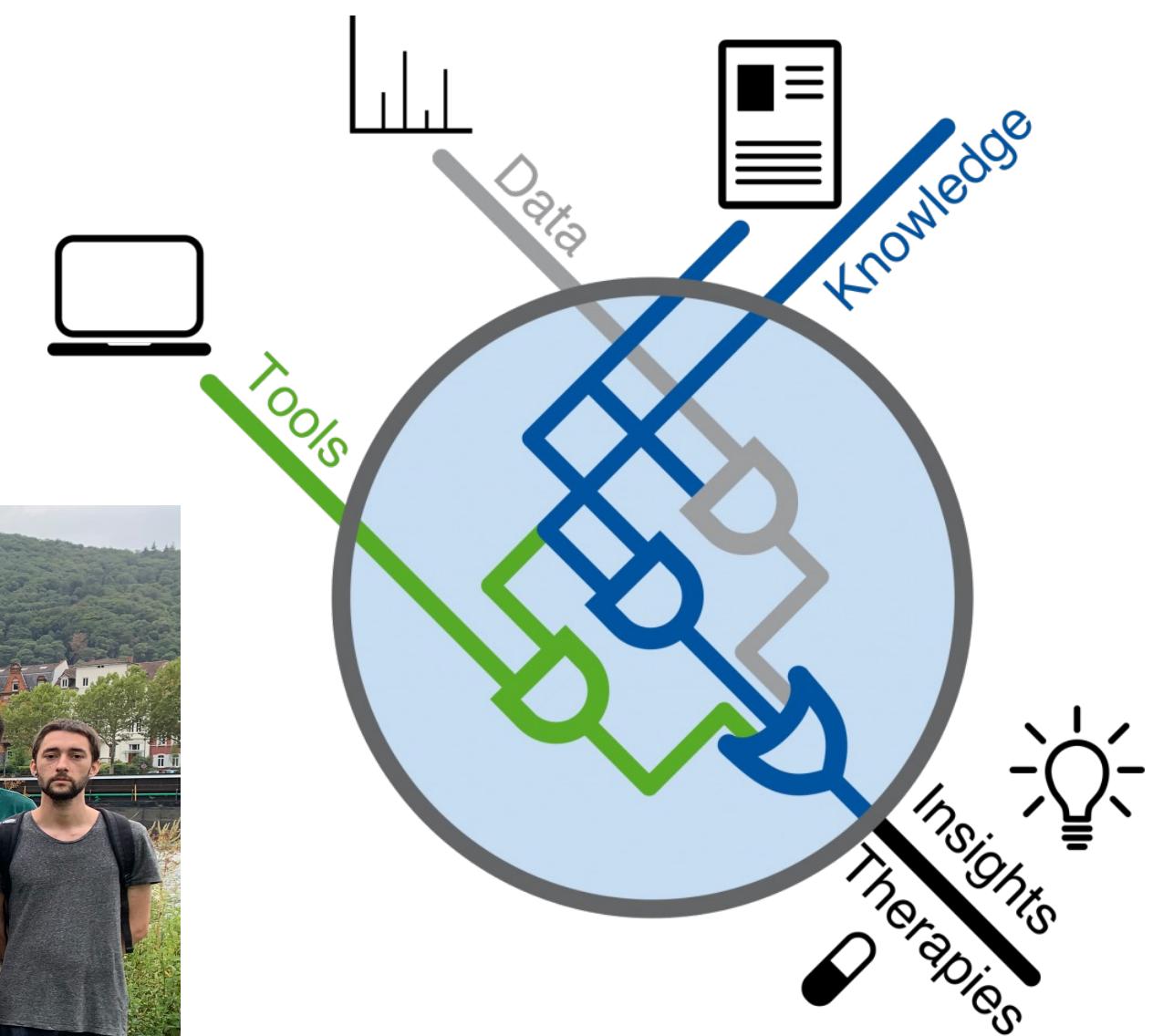
# Who are we?



Heidelberg, Germany

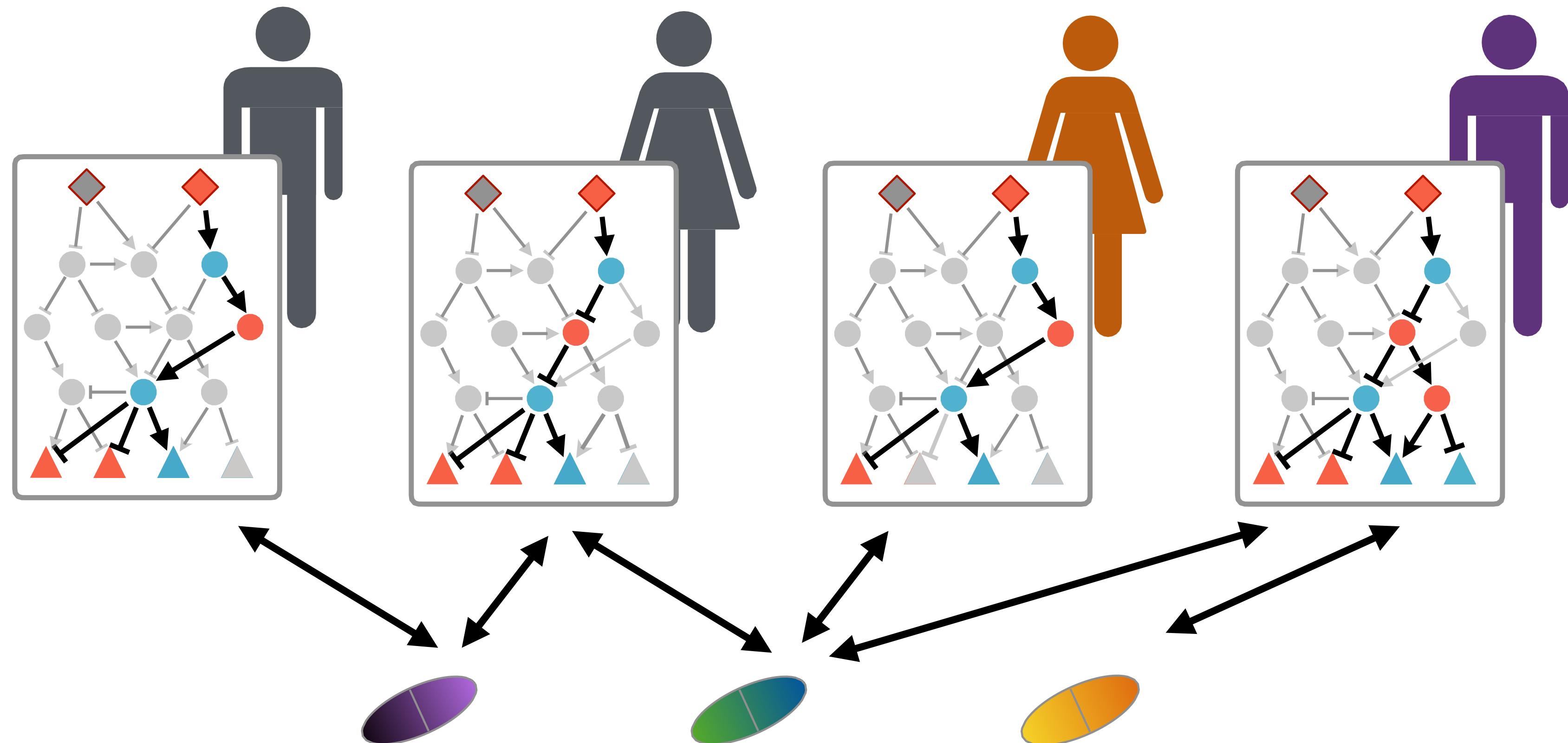


Saez-Rodriguez group





# Personalise networks to find right drug to the right patient





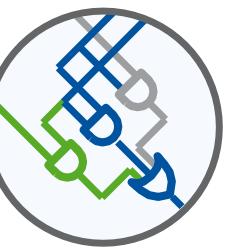
# Session content

- This is a condensed version of our **transcriptutorial**

<https://github.com/saezlab/transcriptutorial>

- We will cover the basic of:
  - Differential expression analysis
  - Use of footprint methods through R
  - Running footprint methods using FUNKI: <https://saezlab.shinyapps.io/funki/>

# **Data and framework of research**





# Framework of research

I'm working on drug repurposing  
and I need help!

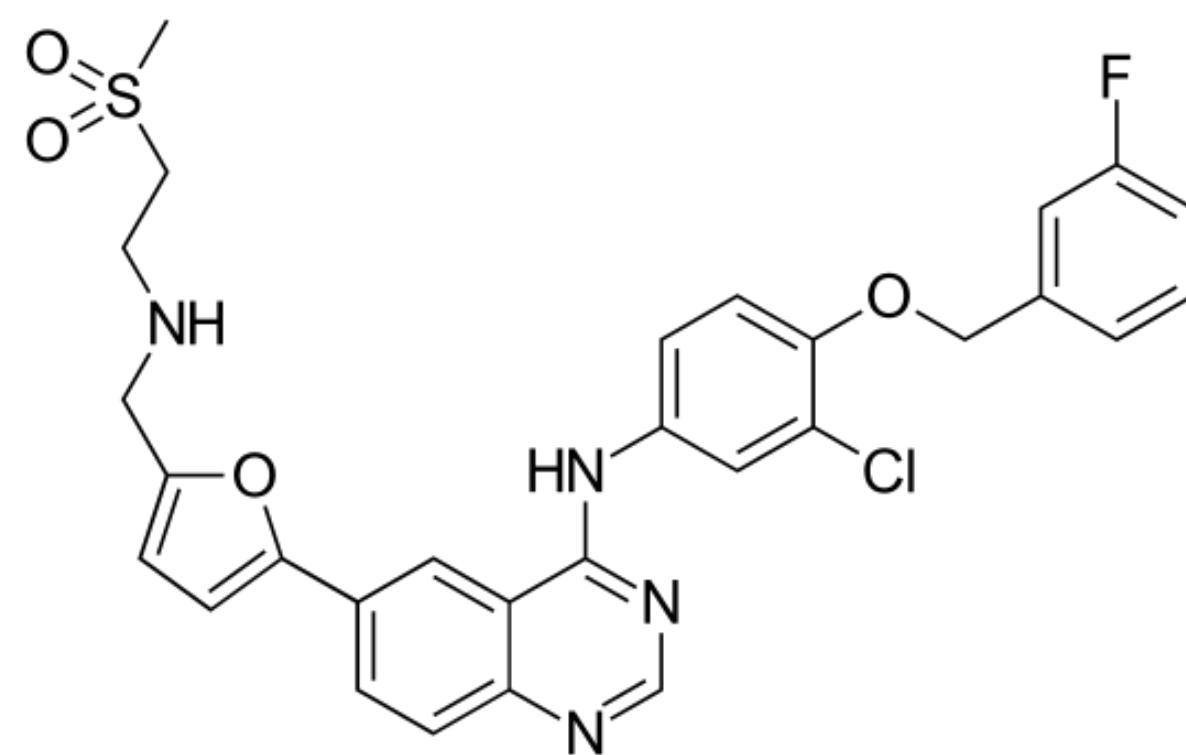
Is there any effect on the response  
of lung cancer cell lines when  
treated with lapatinib?





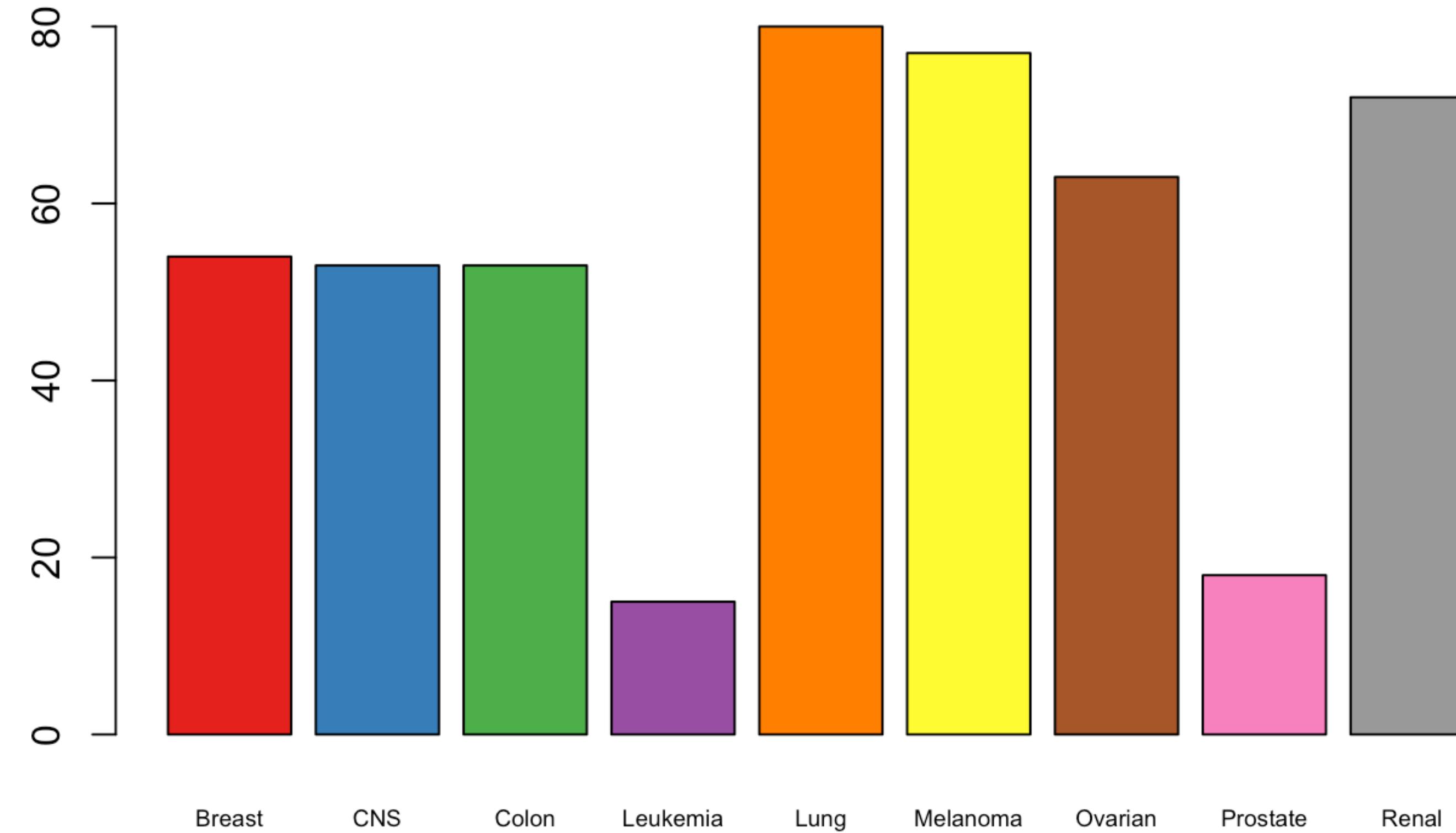
# Lapatinib in cancer

- It is a dual tyrosine kinase inhibitor which interrupts the HER2/neu and epidermal growth factor receptor (EGFR) pathways.
- Approved to treat breast cancer and other solid tumours



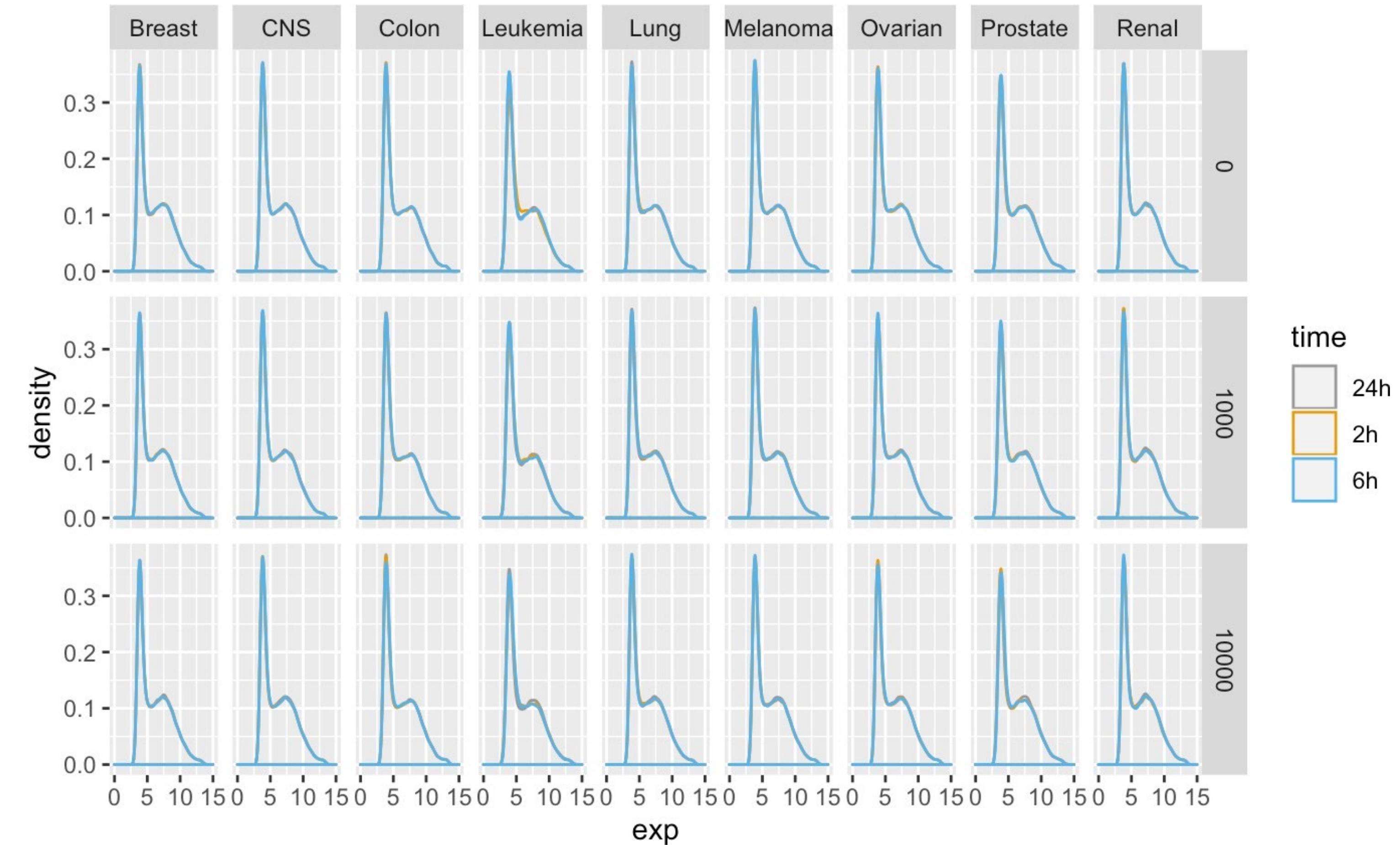


# Samples' distribution





# Expression distribution





# PCA and MDS

- Principal component analysis (PCA)

It is used for finding patterns in data of high dimensions and expressing the data in such a way as to highlight their similarities and differences.

PCA minimizes dimensions, preserving covariance of data.

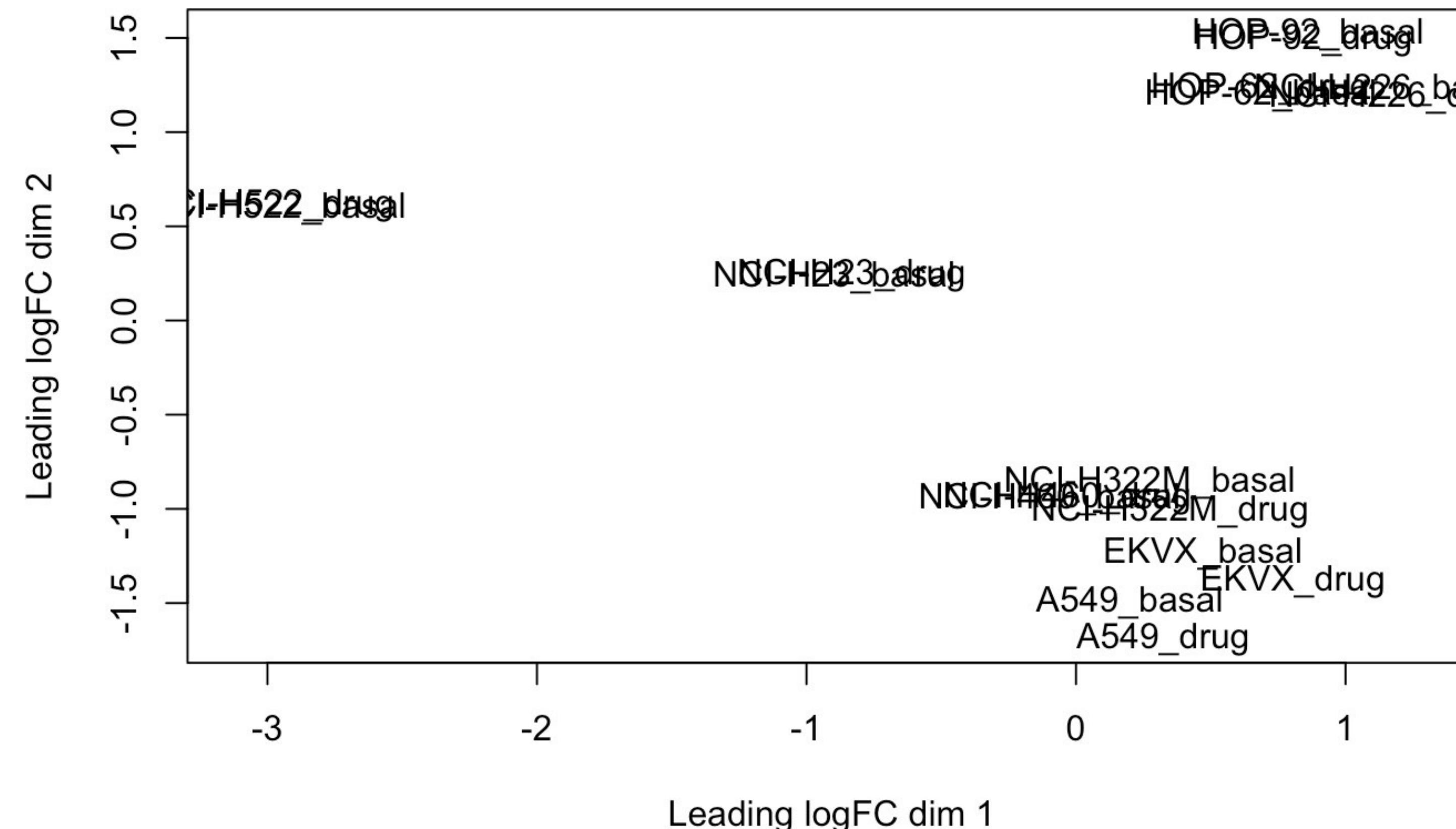
- Multidimensional scaling (MDS)

The main aim is to reconstruct a map that preserves the distances.

MDS minimizes dimensions, preserving distance between data points.



# MDS. How do you interpret it?





# DEA's results using *limma* package

Gene <chr>	logFC <dbl>	AveExpr <dbl>	t <dbl>	P.Value <dbl>	adj.P.Val <dbl>	B <dbl>
HMGCR	-1.6919453	8.768422	-8.119039	2.171521e-07	0.00267072	2.2937492
FDFT1	-1.4559380	10.256105	-7.768525	4.038590e-07	0.00267072	2.0761358
DHCR7	-1.5138652	8.775729	-6.723074	2.833044e-06	0.01248995	1.3289178
HSD17B7P2	-1.0548120	8.300365	-6.469807	4.643933e-06	0.01535516	1.1236500
NSDHL	-0.9056188	7.439253	-6.110794	9.496243e-06	0.02511946	0.8151885
MSMO1	-1.7759590	10.761254	-5.985824	1.223012e-05	0.02695926	0.7028766
IDI1	-1.4105213	10.128410	-5.846811	1.624389e-05	0.03069167	0.5748952
SQLE	-1.2301969	8.709981	-5.773760	1.887521e-05	0.03120544	0.5063453

Estimate of the log2-fold-change corresponding to the effect or contrast

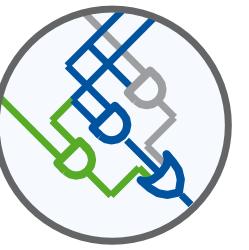
Average log2-expression for the probe over all arrays and channels

Moderated t-statistic

Raw p-value and adjusted p-value

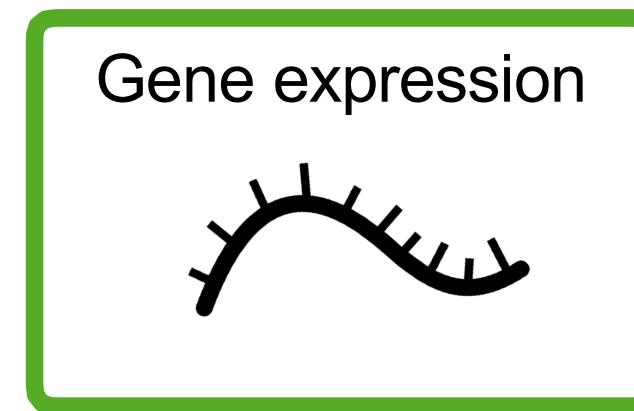
log-odds that the gene is differentially expressed

# Footprint methods

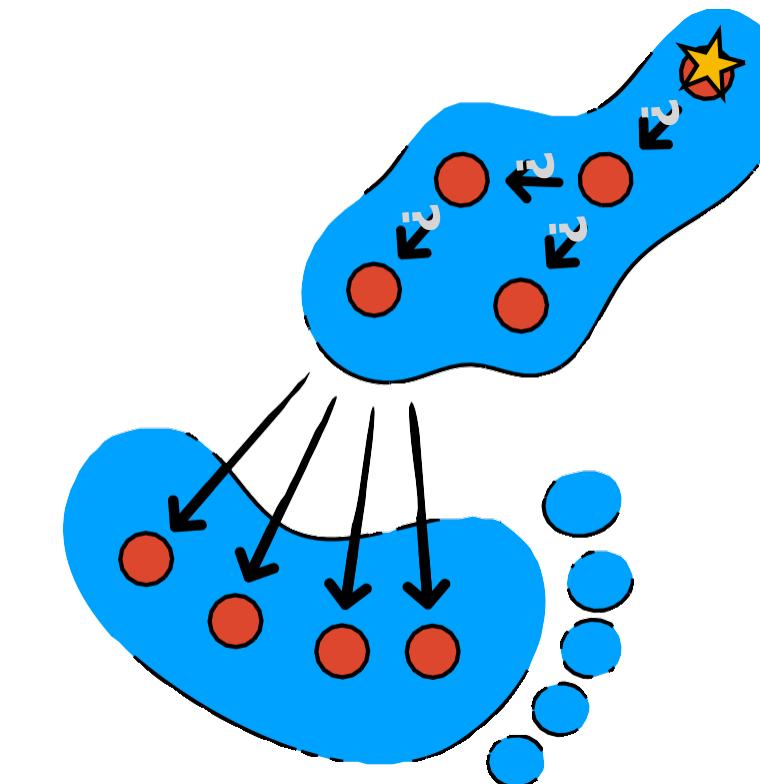




# Why use footprint methods?

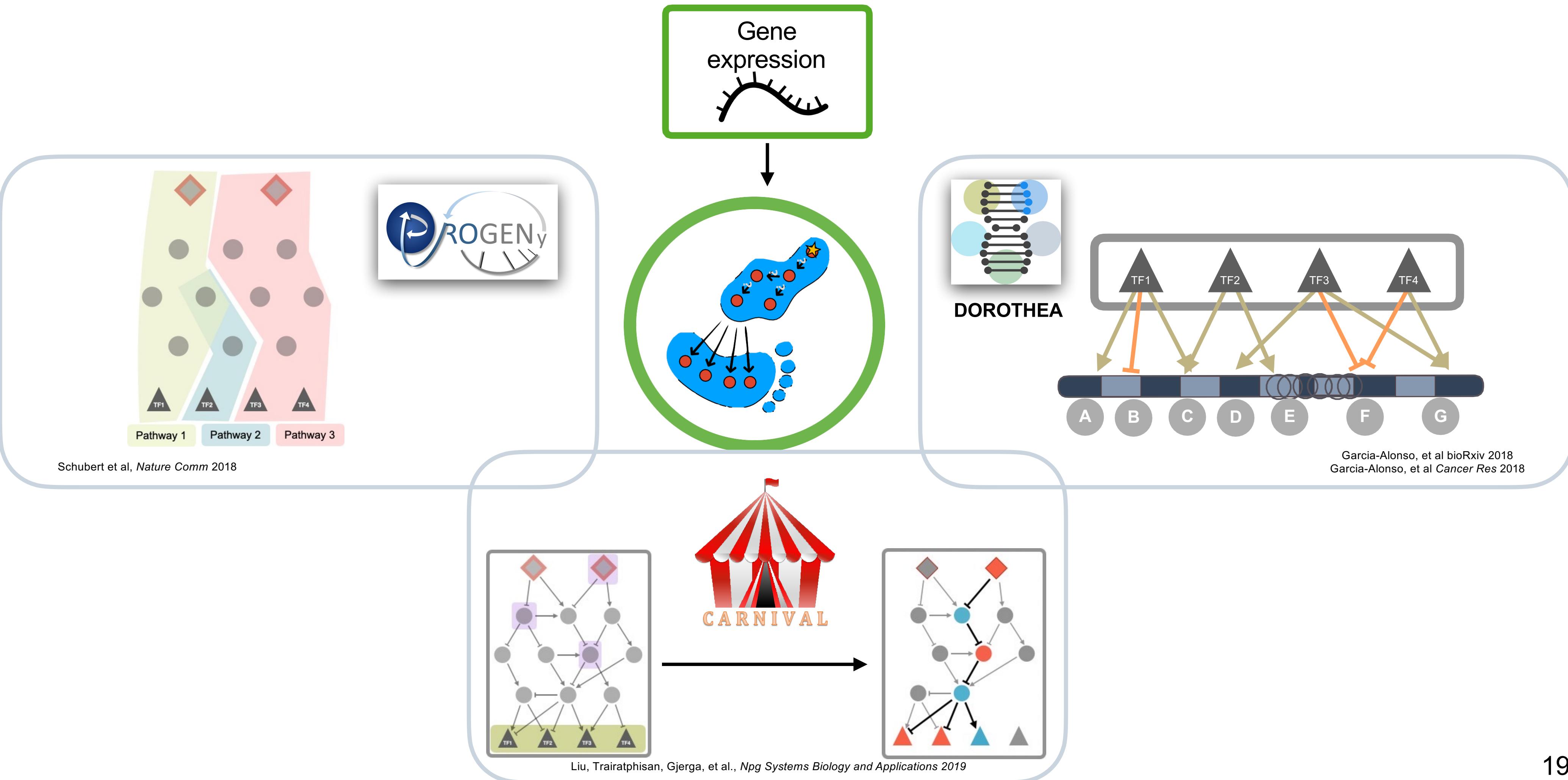


- X Protein's activity
- X Protein's abundance



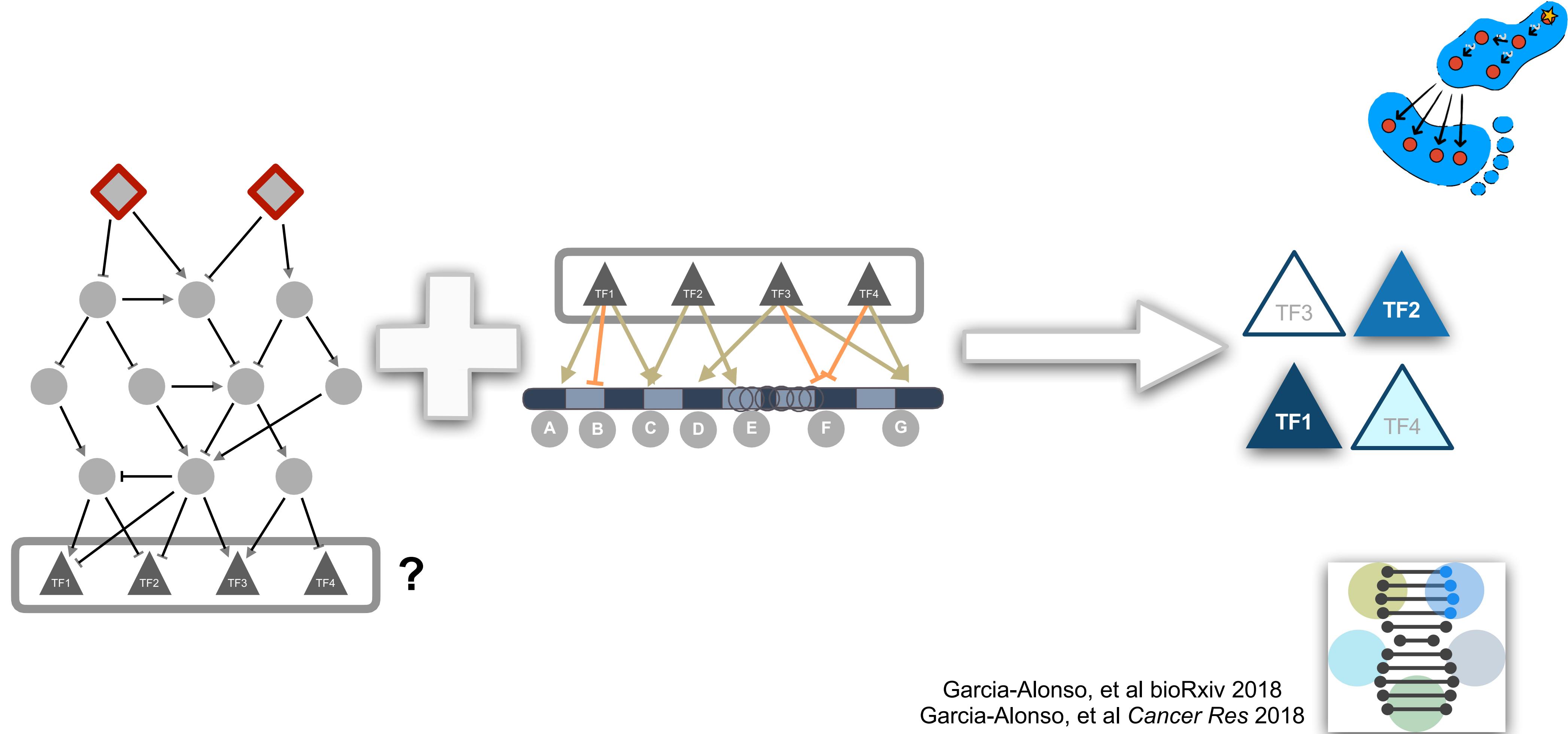


# Footprint methods



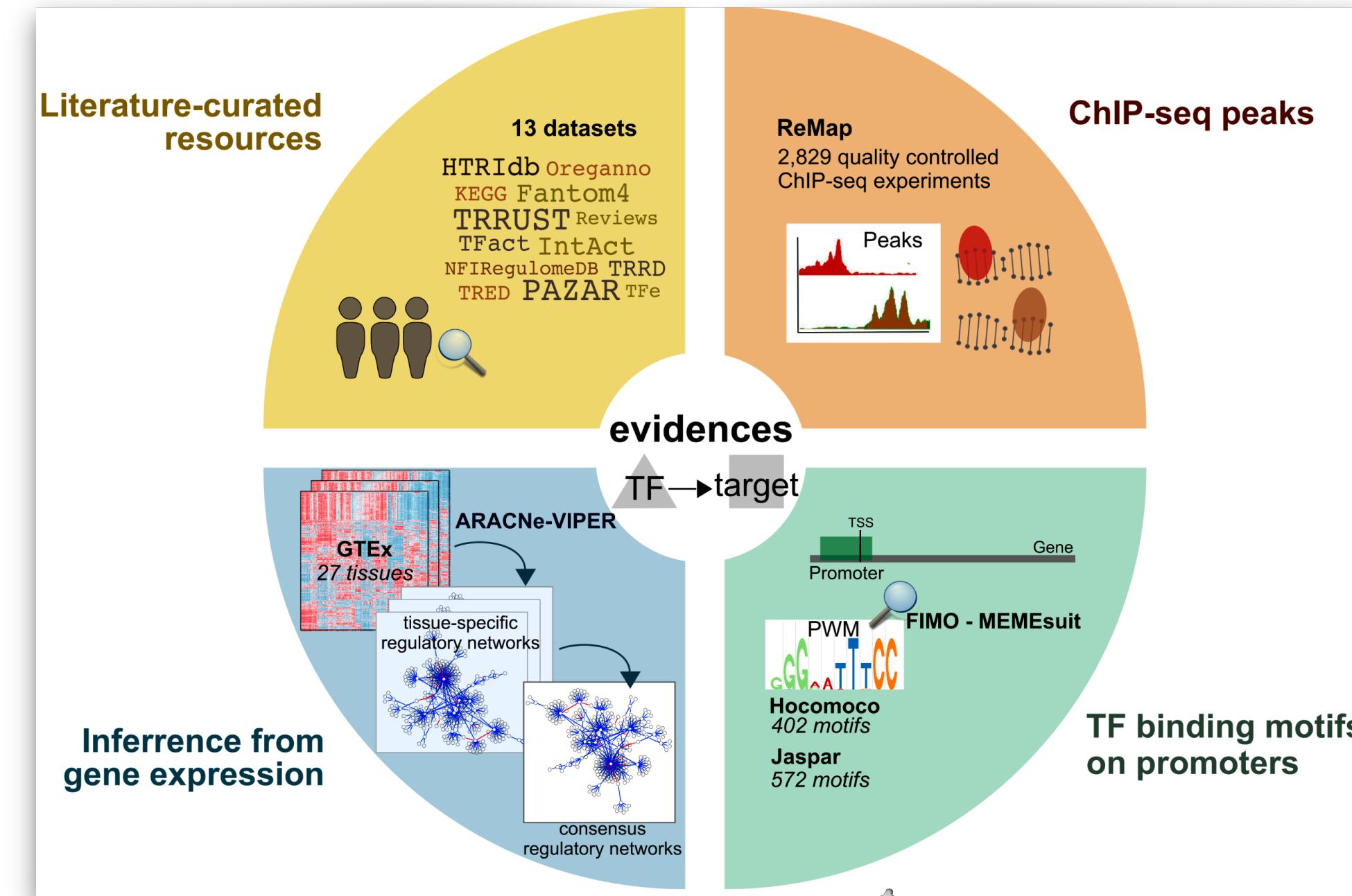
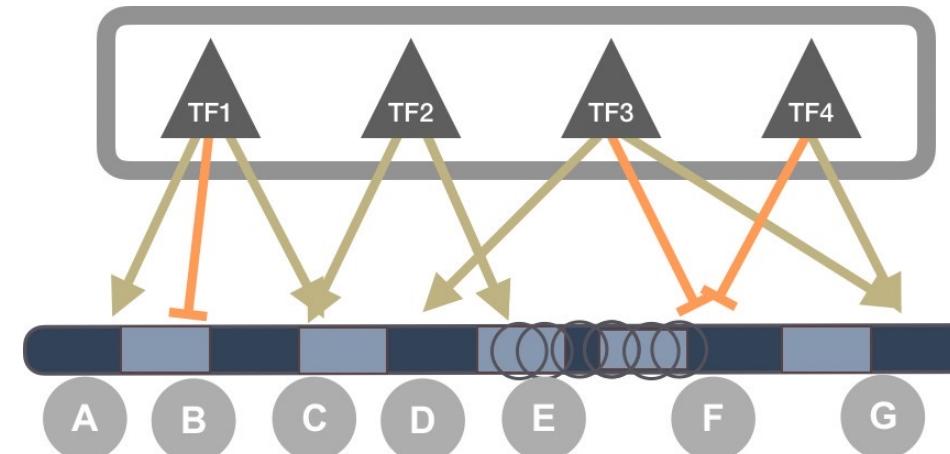


# DOROTHEA: Discriminant Regulon Expression Analysis

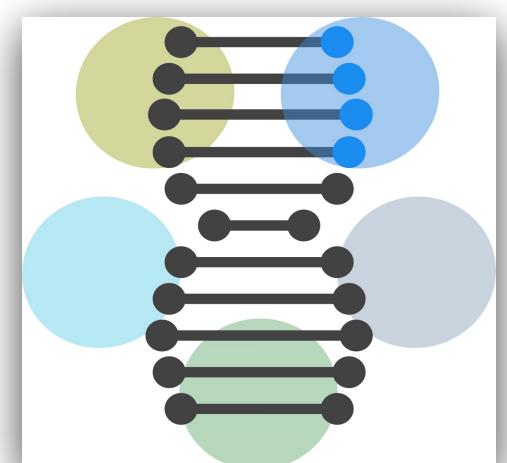




# DOROTHEA: Discriminant Regulon Expression Analysis

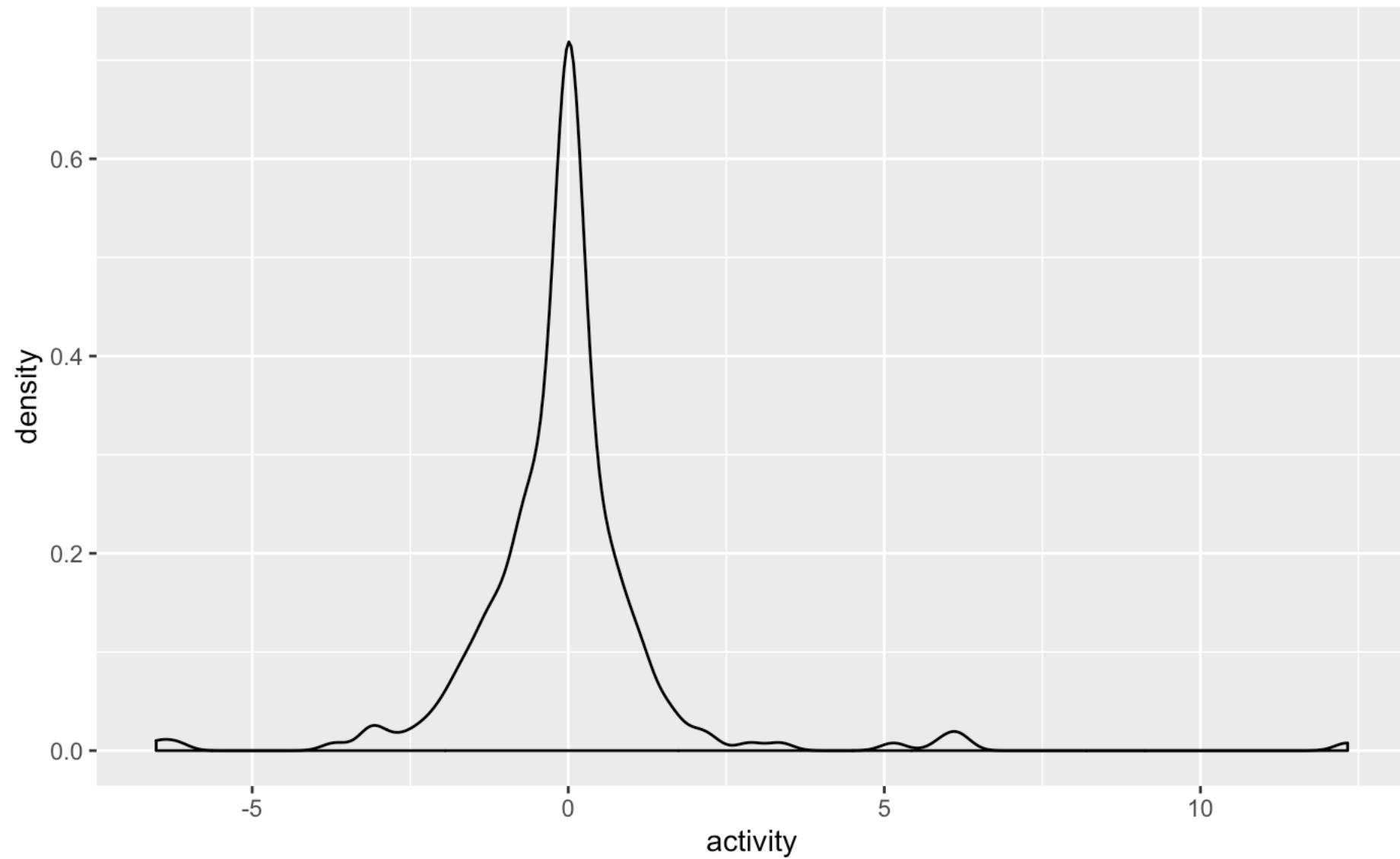


Garcia-Alonso, et al bioRxiv 2018  
Garcia-Alonso, et al Cancer Res 2018

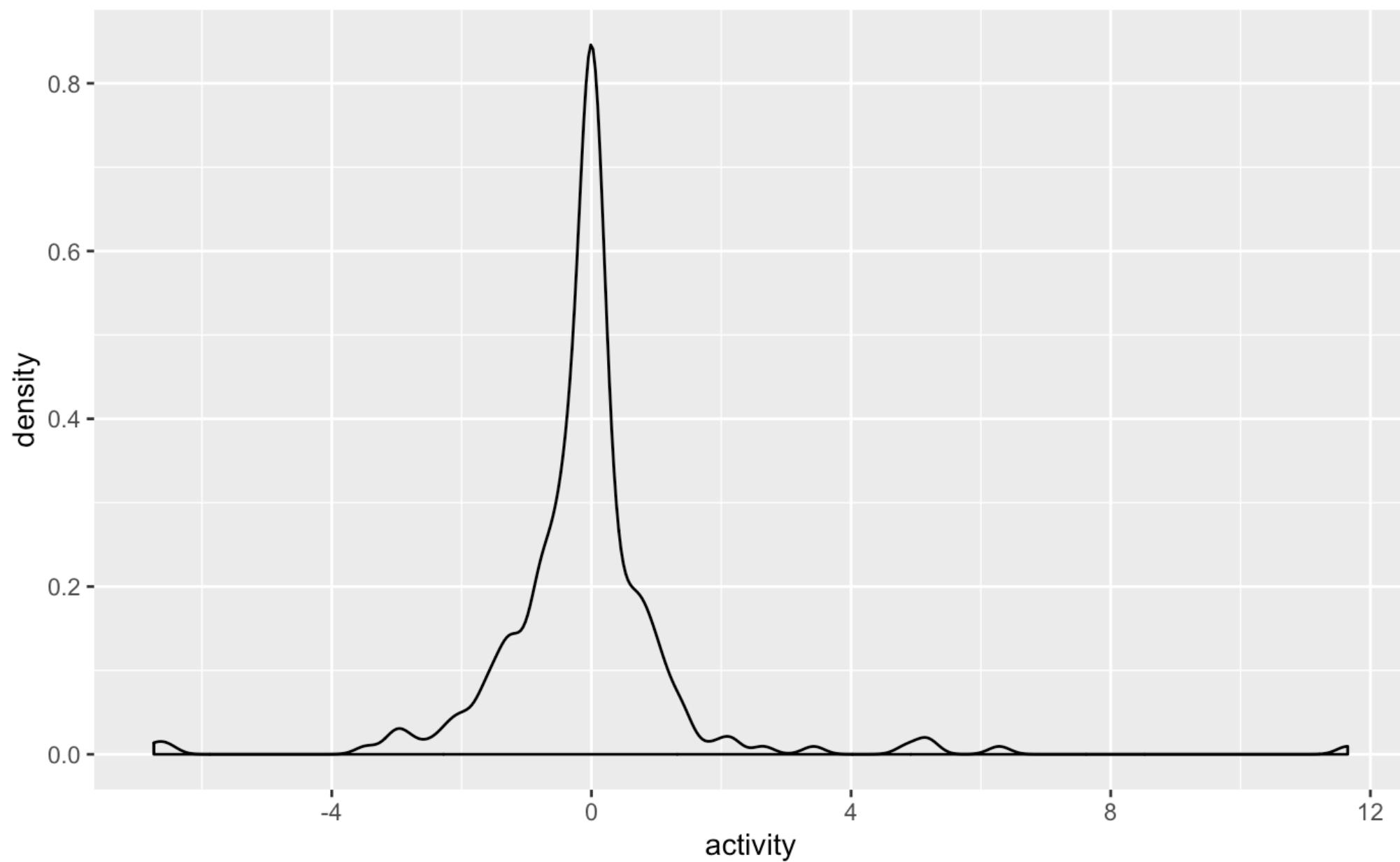




# DOROTHEA: Discriminant Regulon Expression Analysis



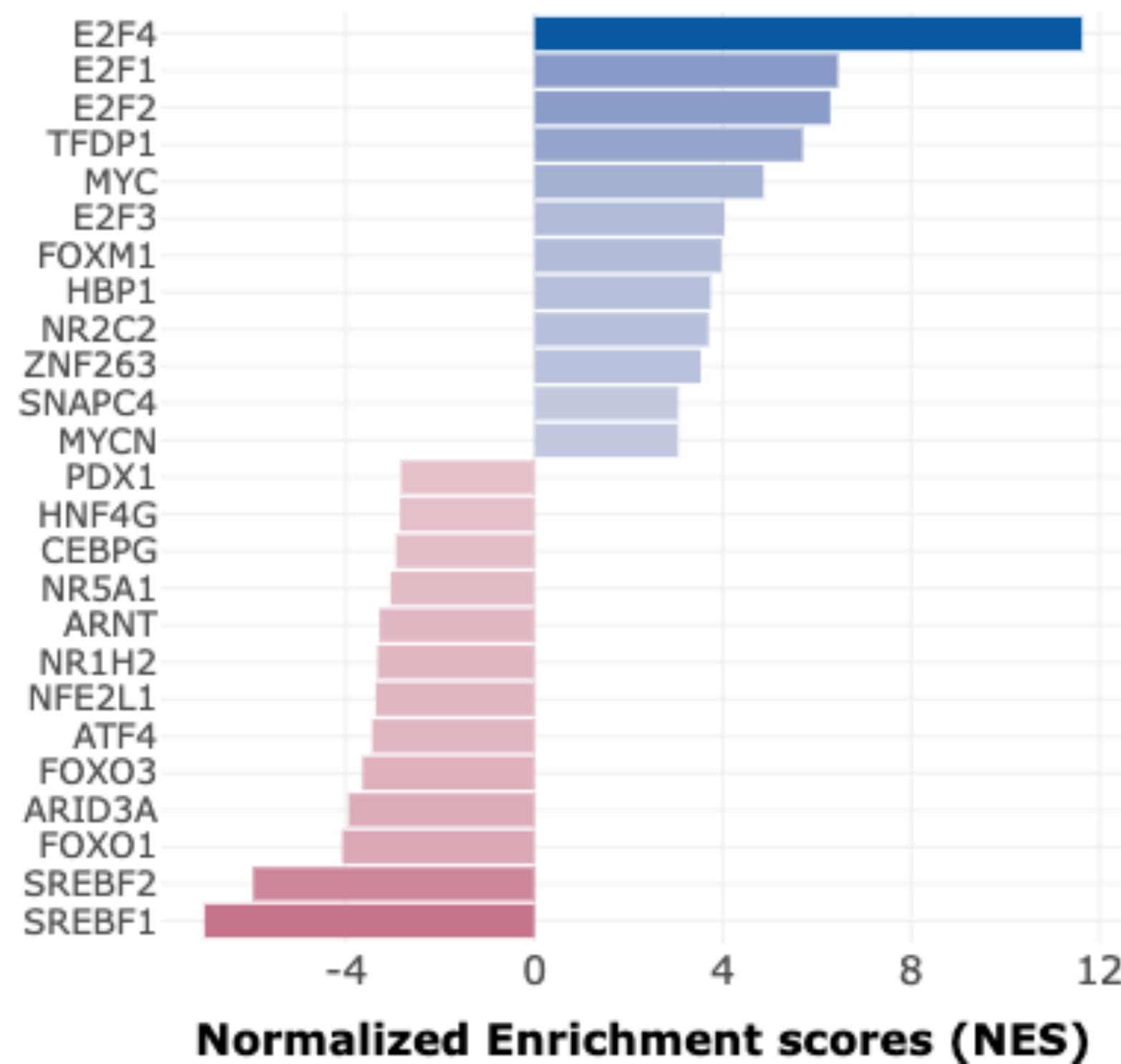
**eset.filter:** whether the dataset should be limited only to the genes represented in the interactome





# DOROTHEA: Discriminant Regulon Expression Analysis

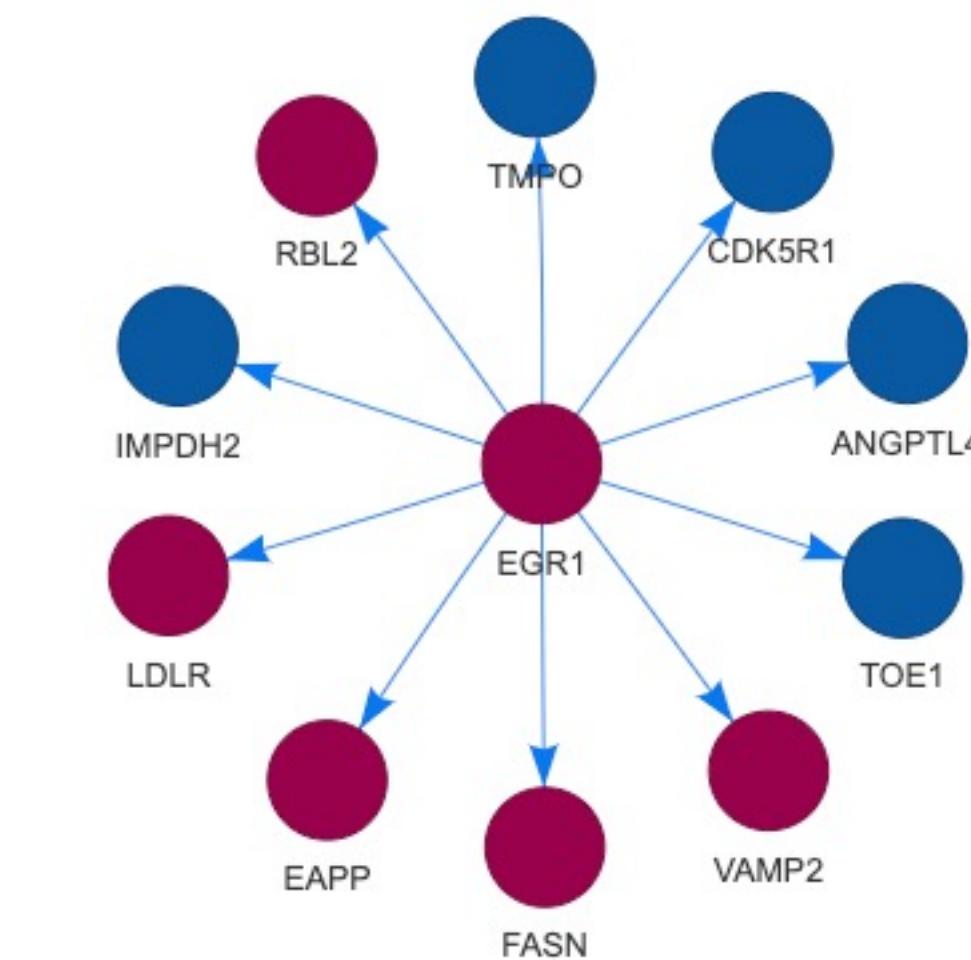
Sample/Contrast: t



NES

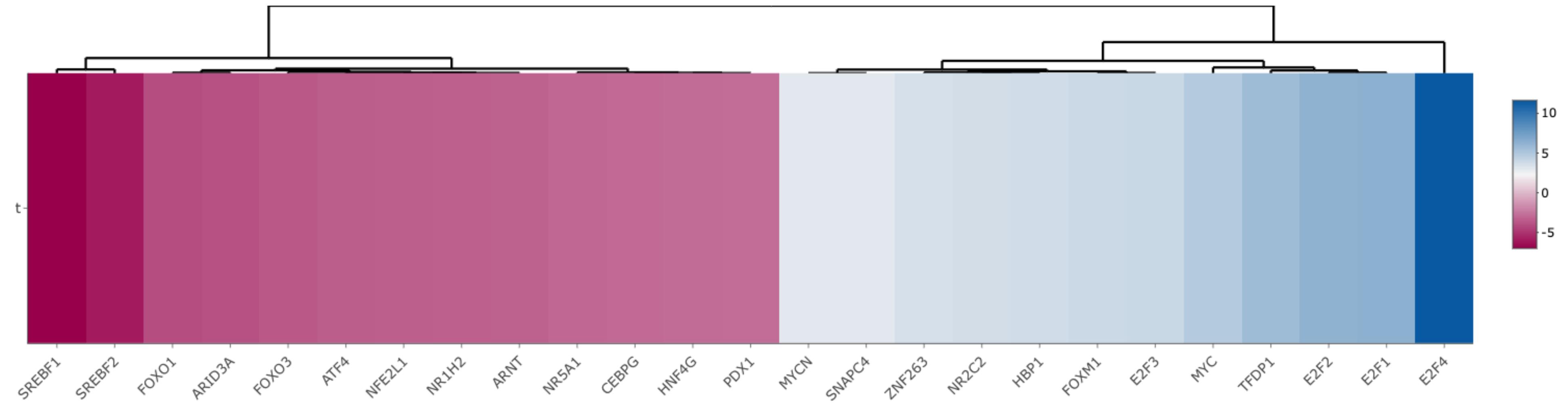


**EGR1 for t**



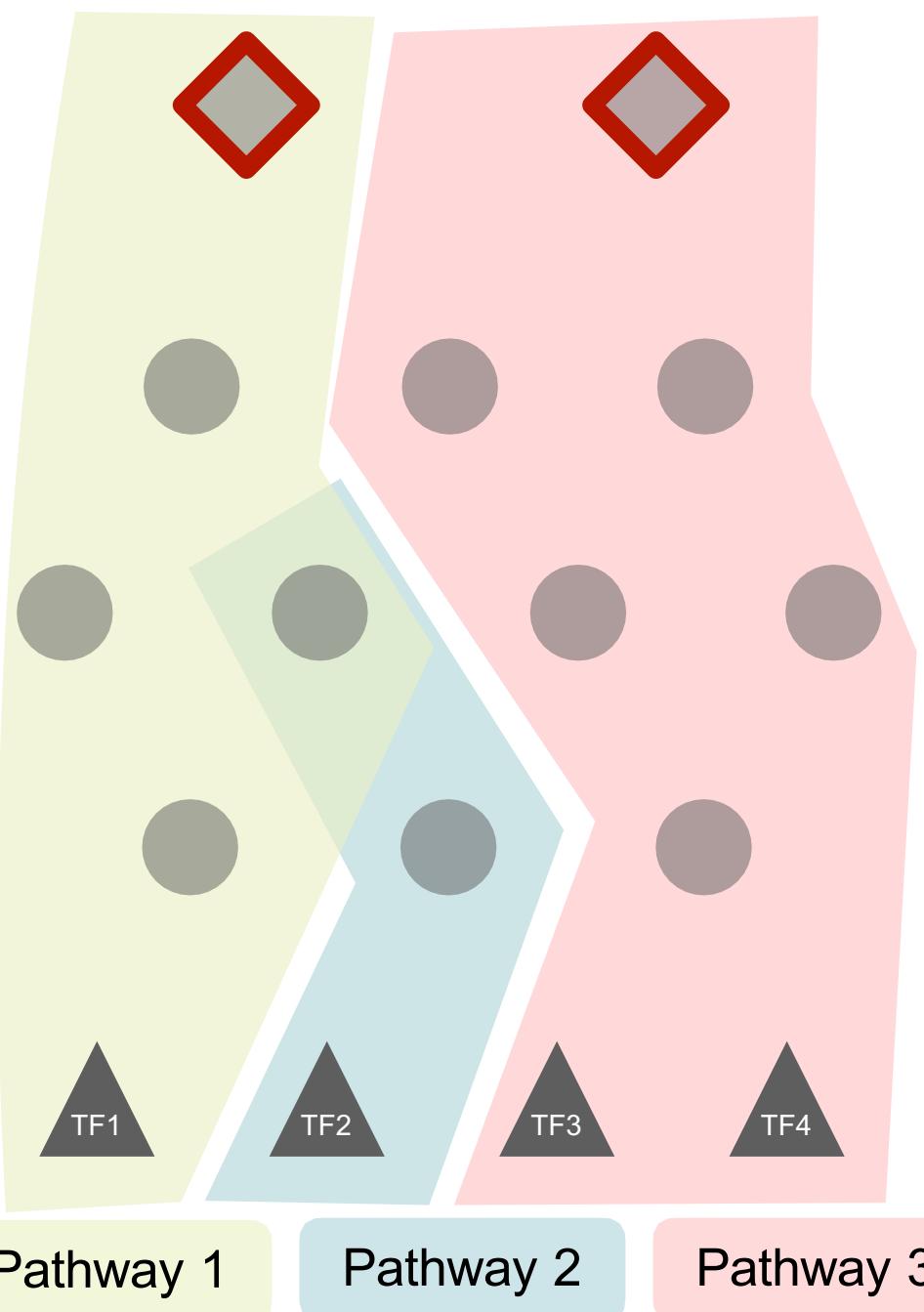
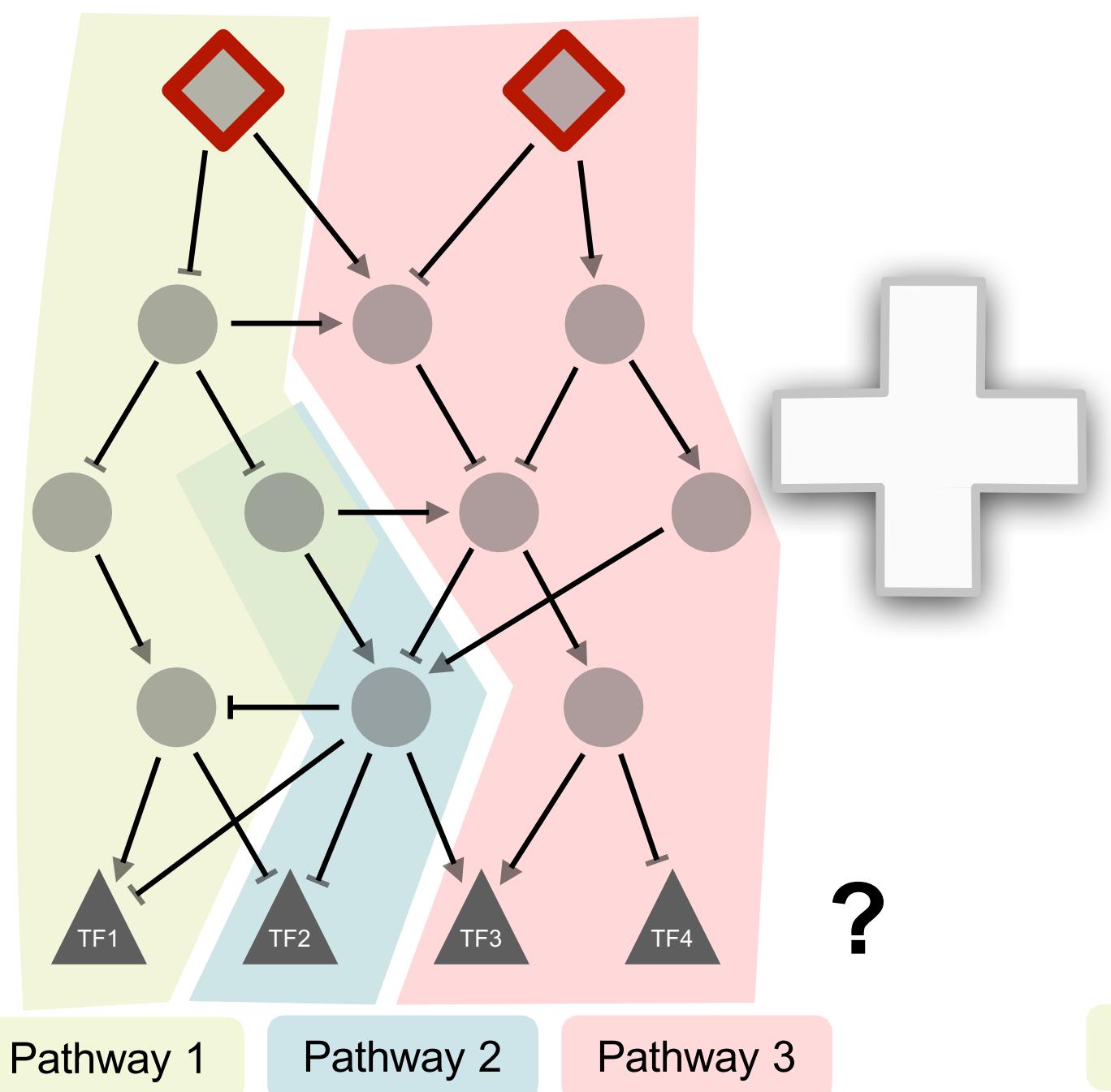


# User interface using FUNKI: <https://saezlab.shinyapps.io/funki/>

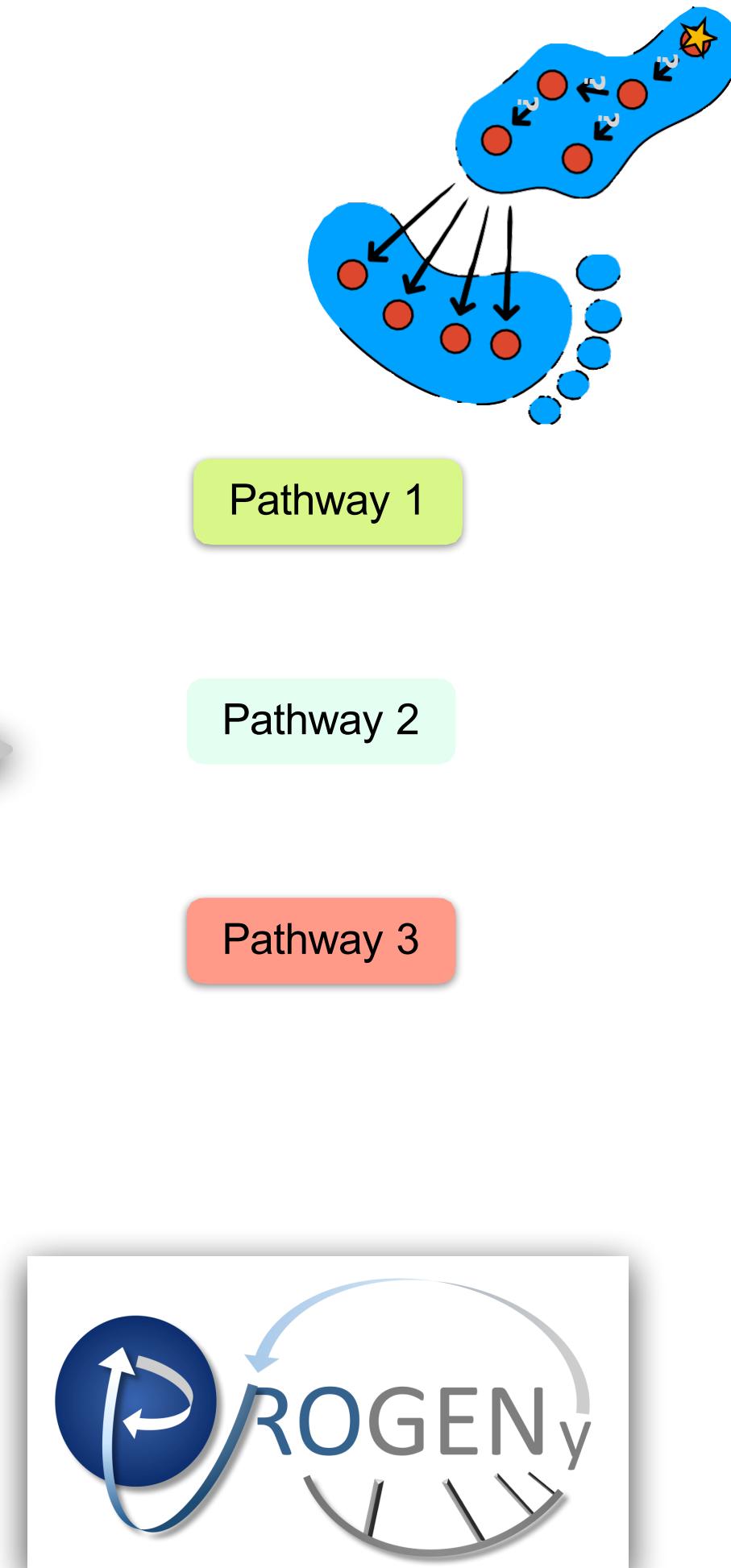




# PROGENy: Pathway RespOnsive GENes

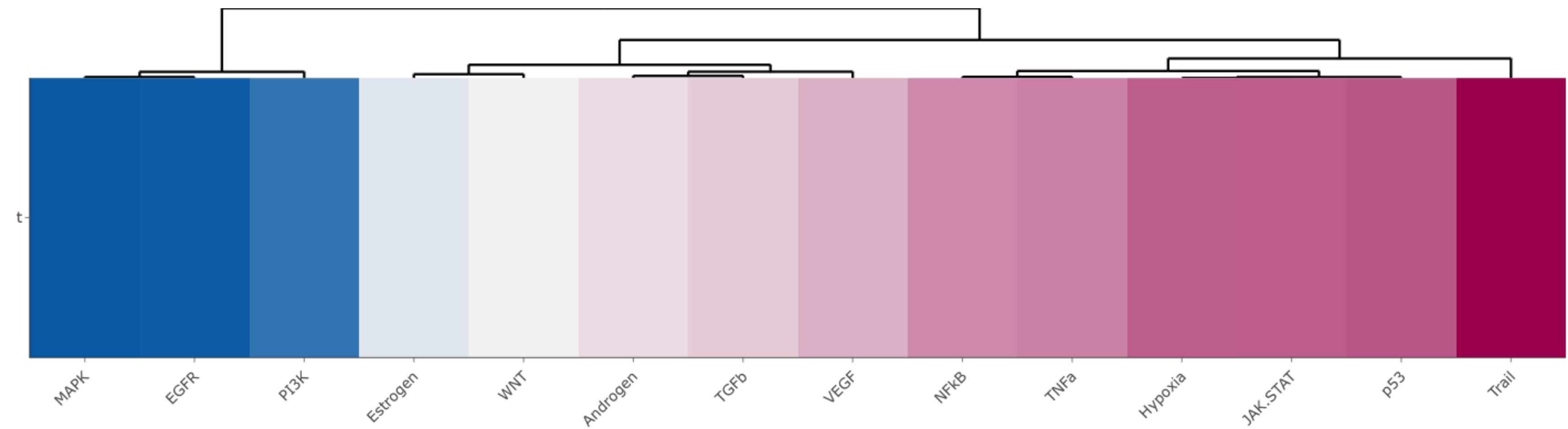


Schubert et al, *Nature Comm* 2018



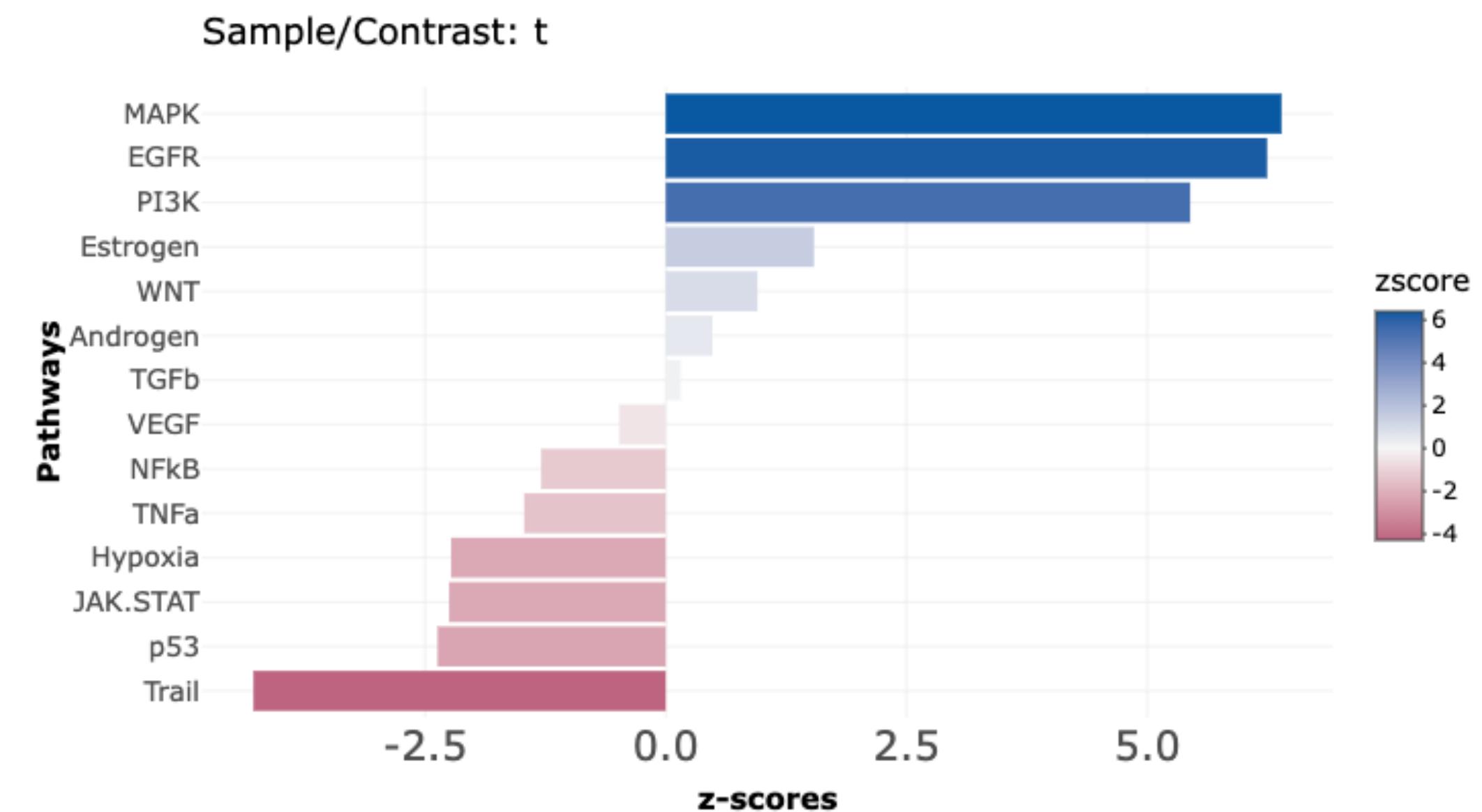
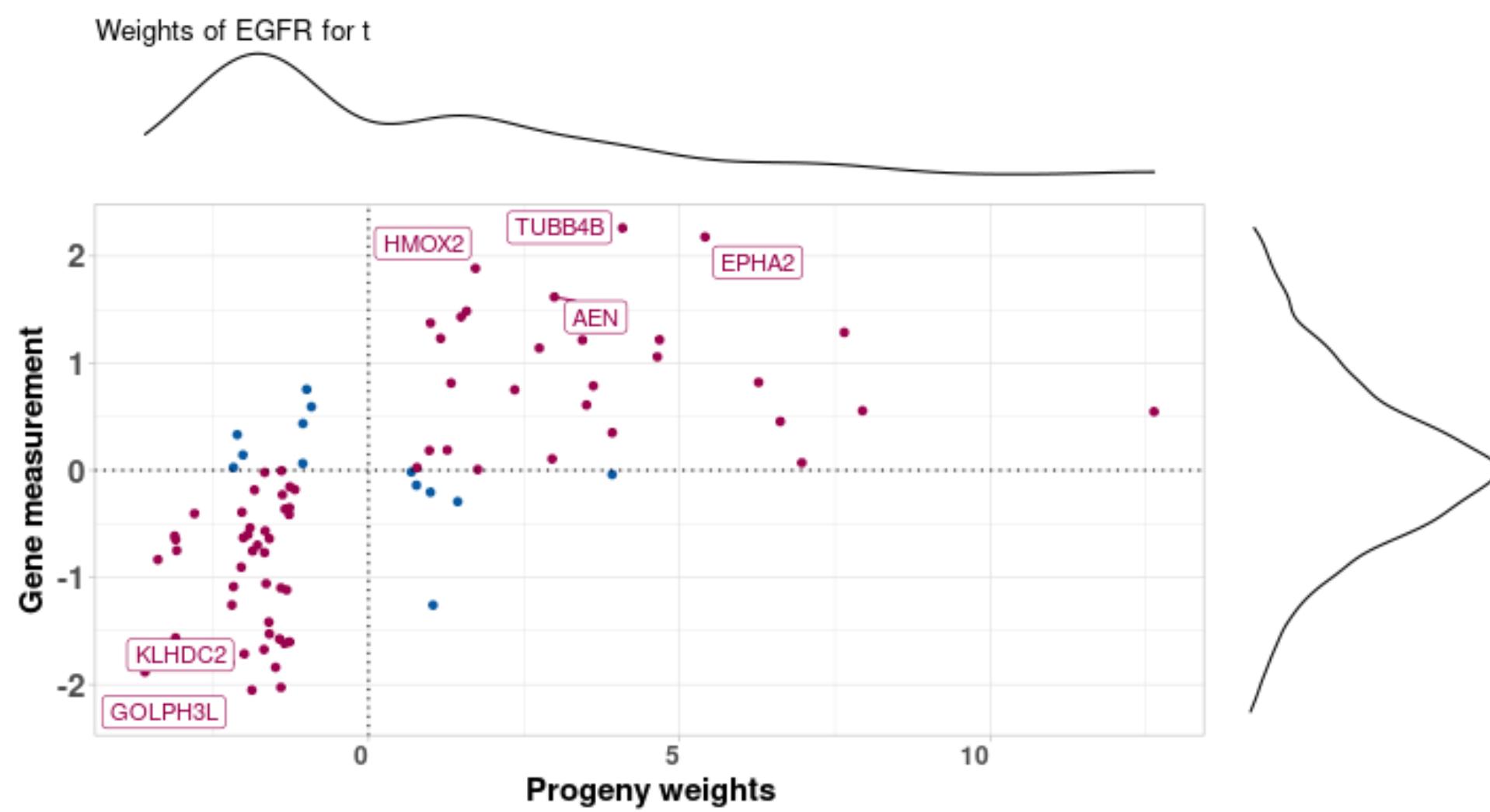


# PROGENy: Pathway RespOnsive GENes

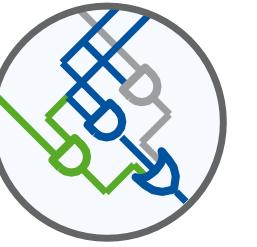




# User interface using FUNKI: <https://saezlab.shinyapps.io/funki/>

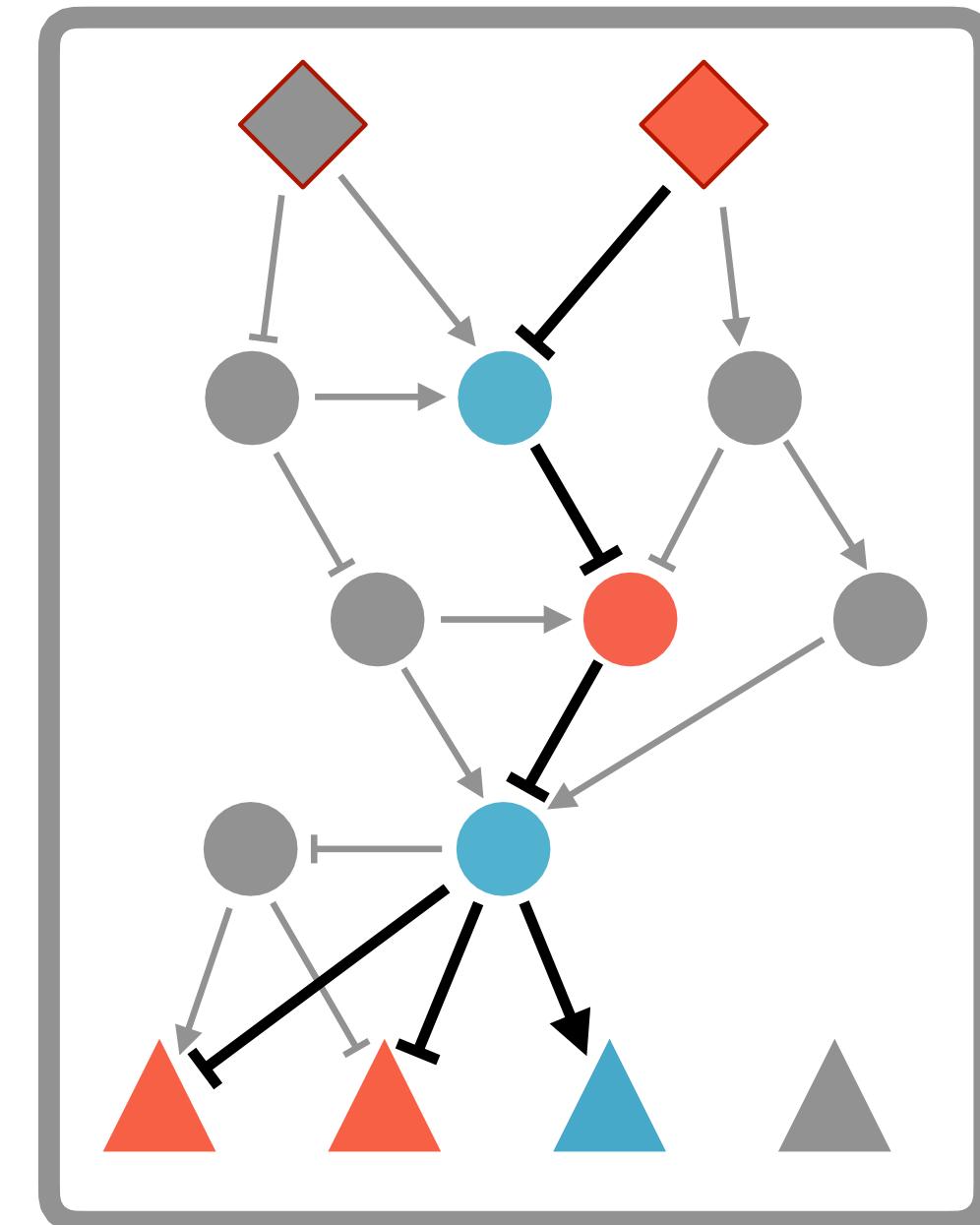
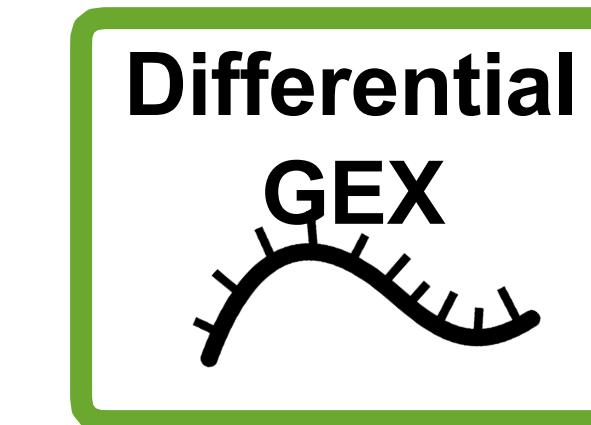
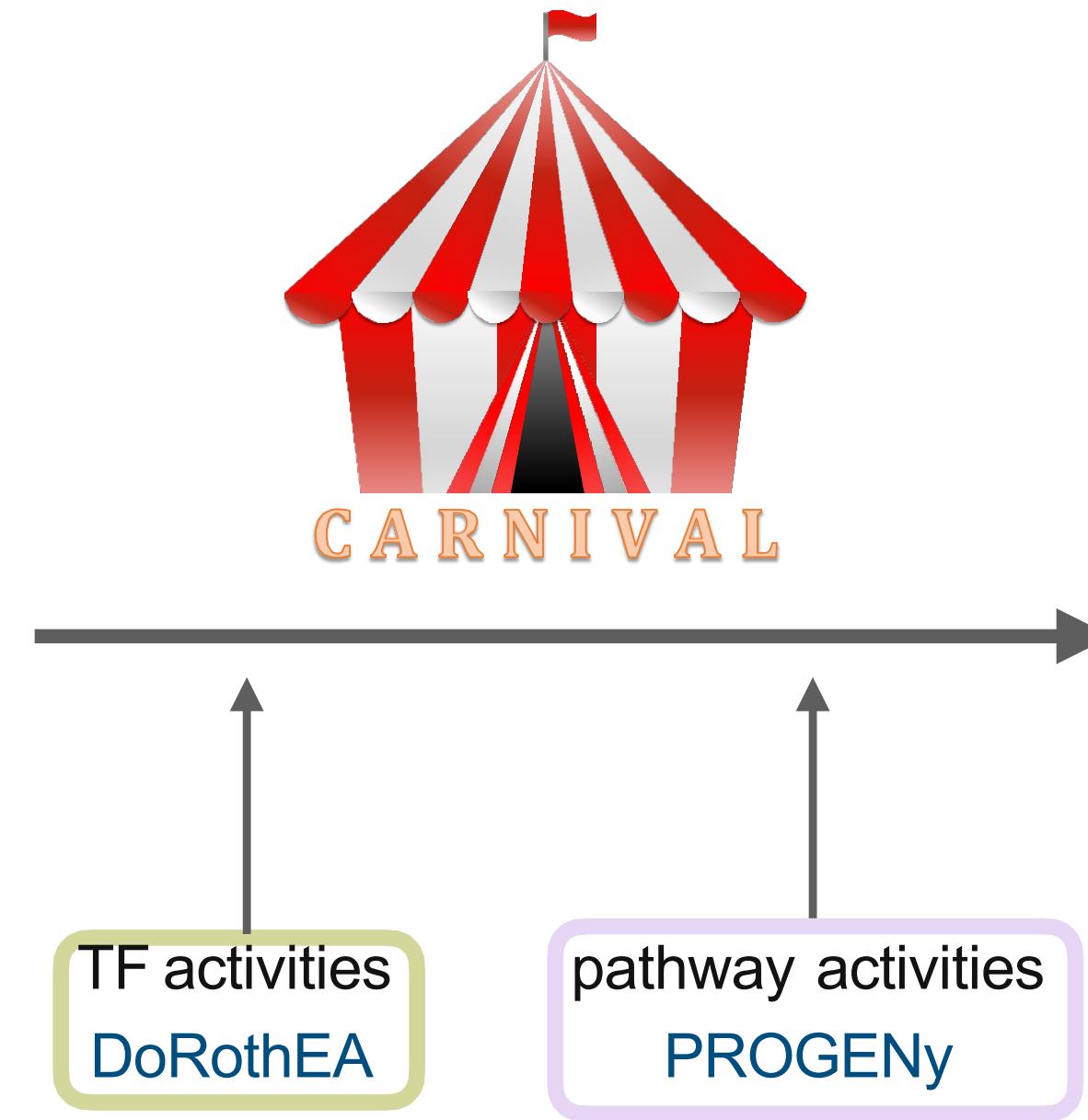
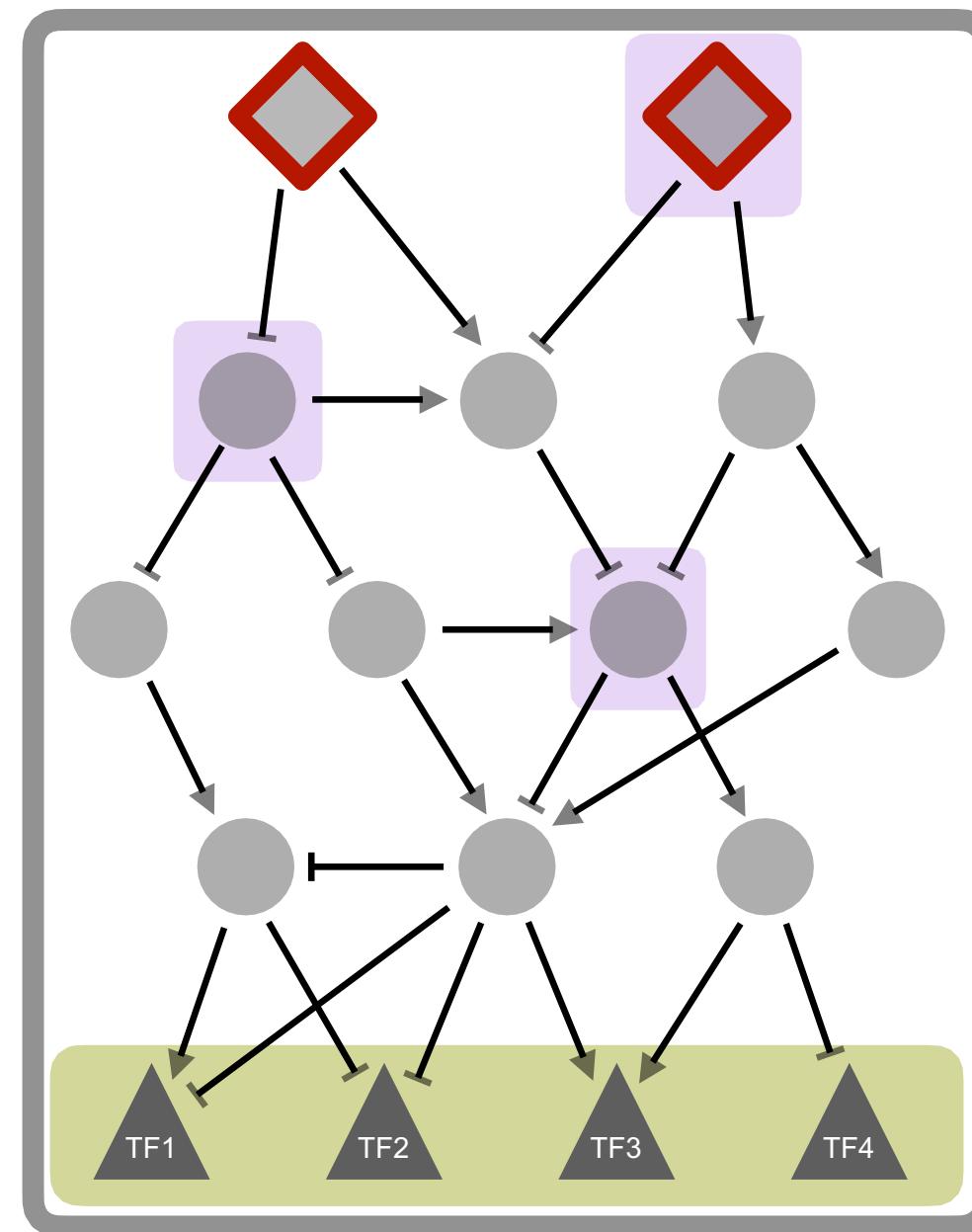


# **From footprints to networks**





# Causal networks explain gene expression



Validated in cell lines  
with phosphoproteomic



# Omnipath: Integration of over 100 knowledge resources

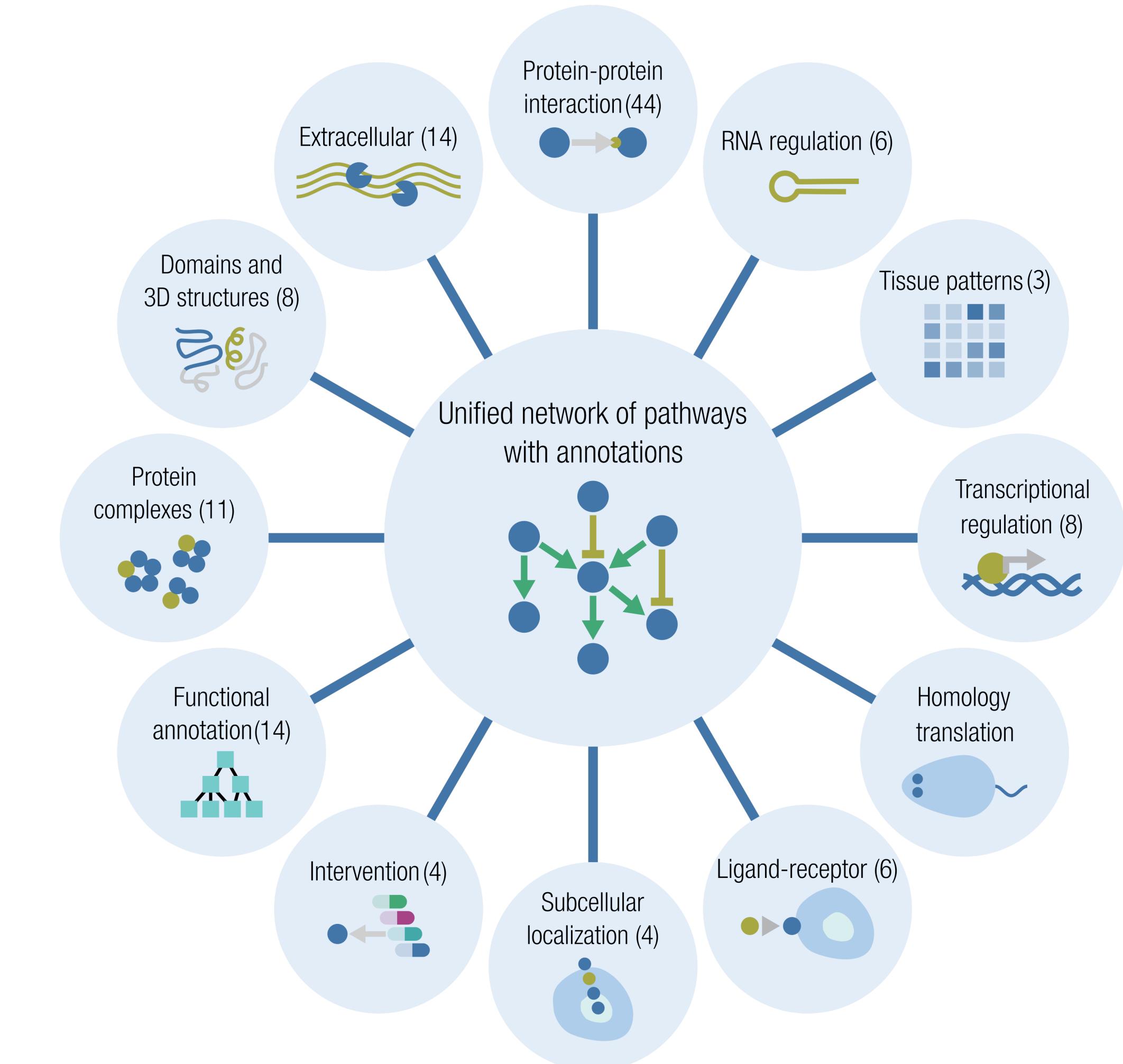
2,200,000 annotation entries for 20,000 human proteins and 16,500 complexes



[www.omnipathdb.org](http://www.omnipathdb.org)

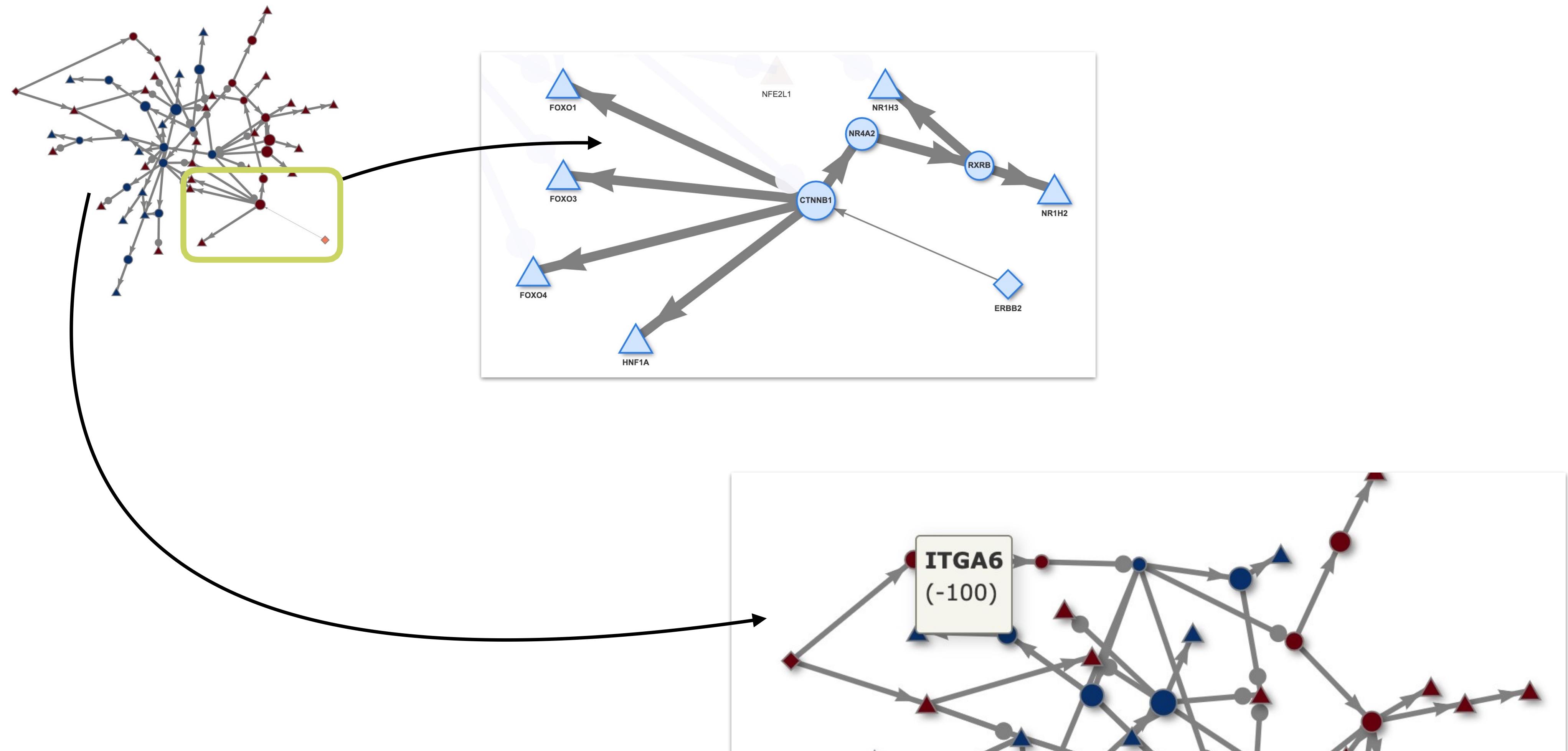


omnipathdb



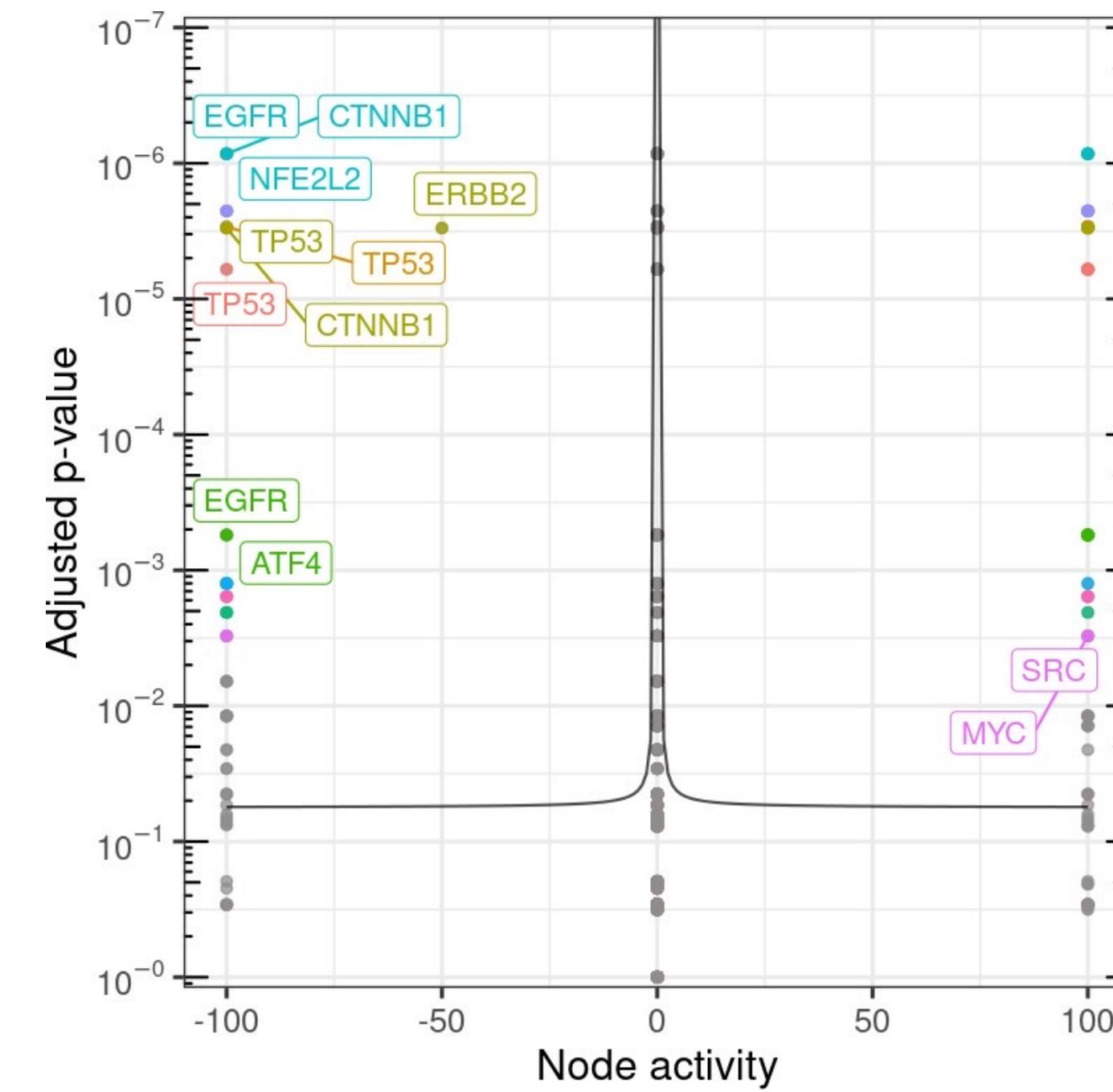
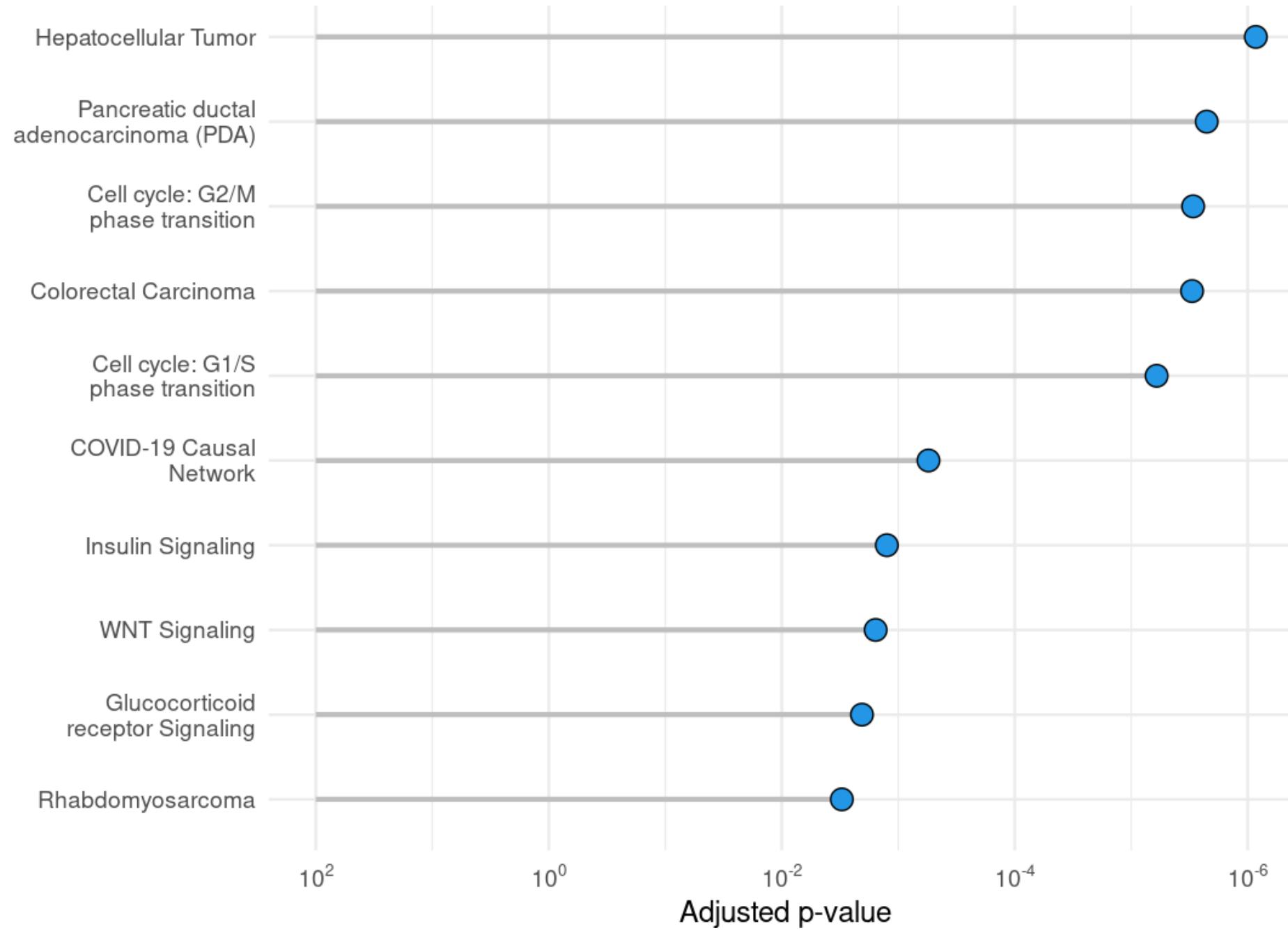


# What can CARNIVAL tell us?





# What can CARNIVAL tell us?



pathway

- Cell cycle: G1/S phase transition
- Cell cycle: G2/M phase transition
- Colorectal Carcinoma
- COVID-19 Causal Network
- Glucocorticoid receptor Signaling
- Hepatocellular Tumor
- Insulin Signaling
- Pancreatic ductal adenocarcinoma (PDA)
- Rhabdomyosarcoma
- WNT Signaling