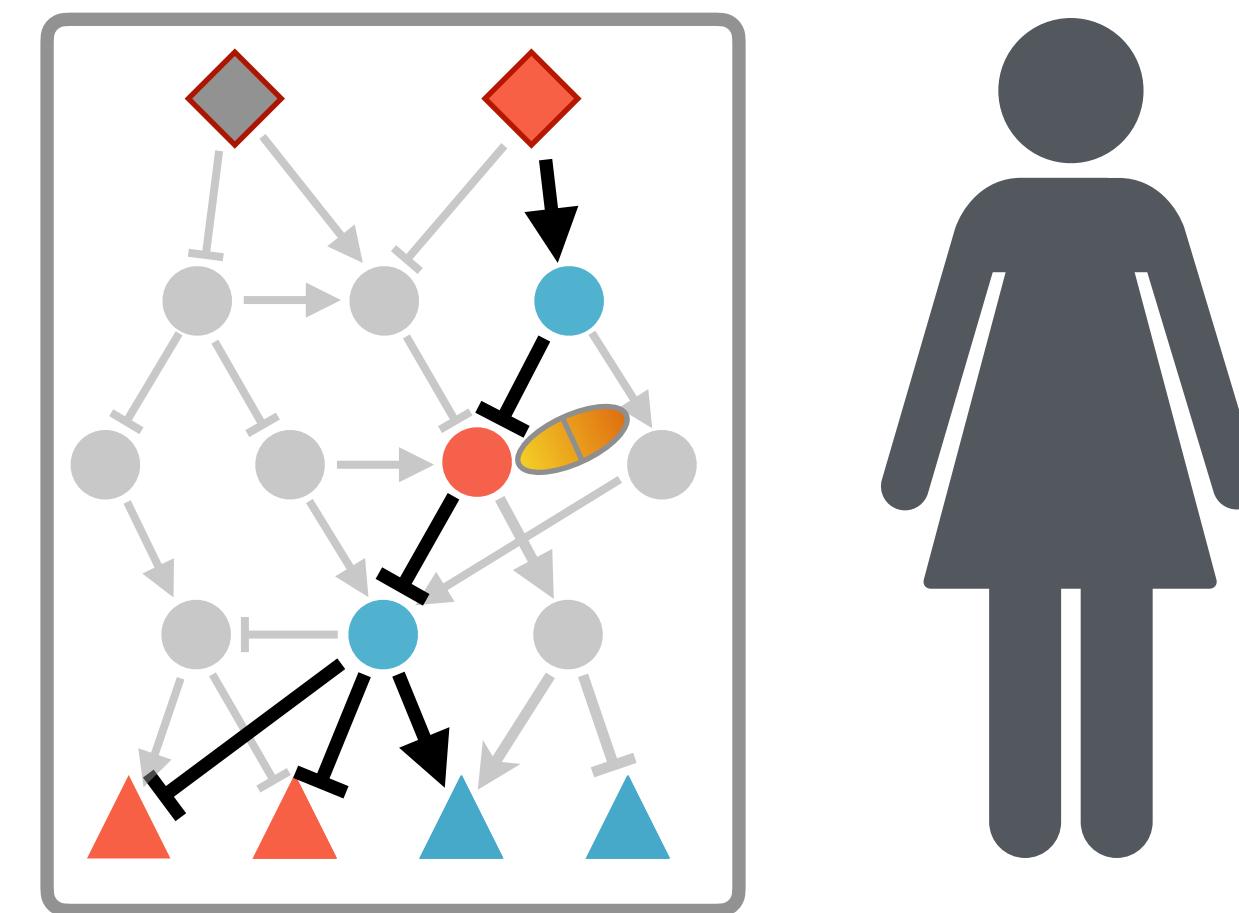
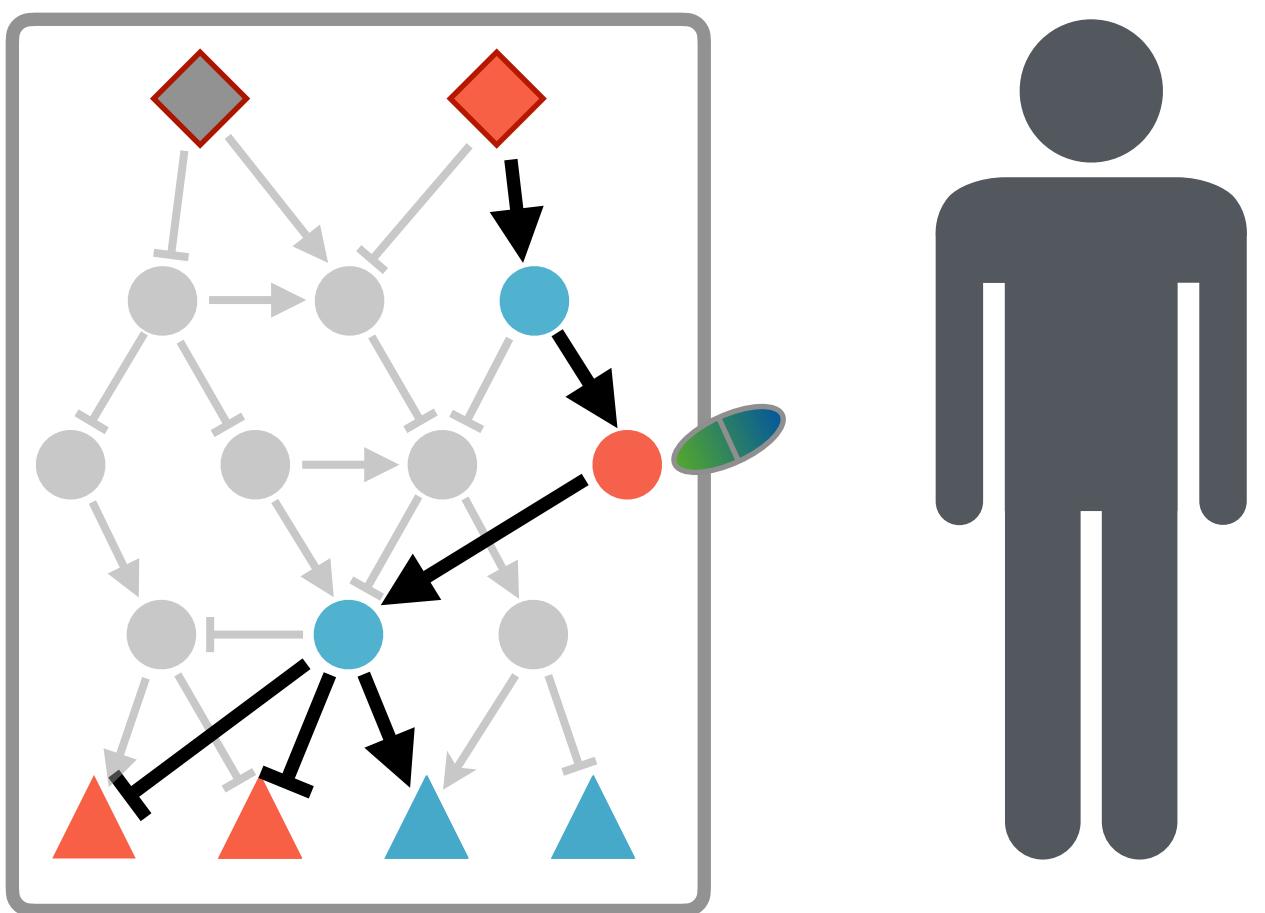


Footprint methods for functional analysis of omics data



Rosa Hernansaiz Ballesteros

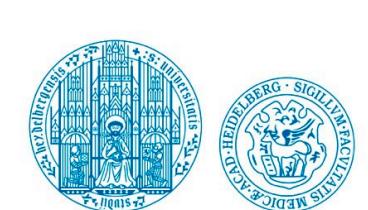


Institute for Computational Biomedicine
www.saezlab.org  [@sysbiomed](https://twitter.com/sysbiomed)





Who am I?

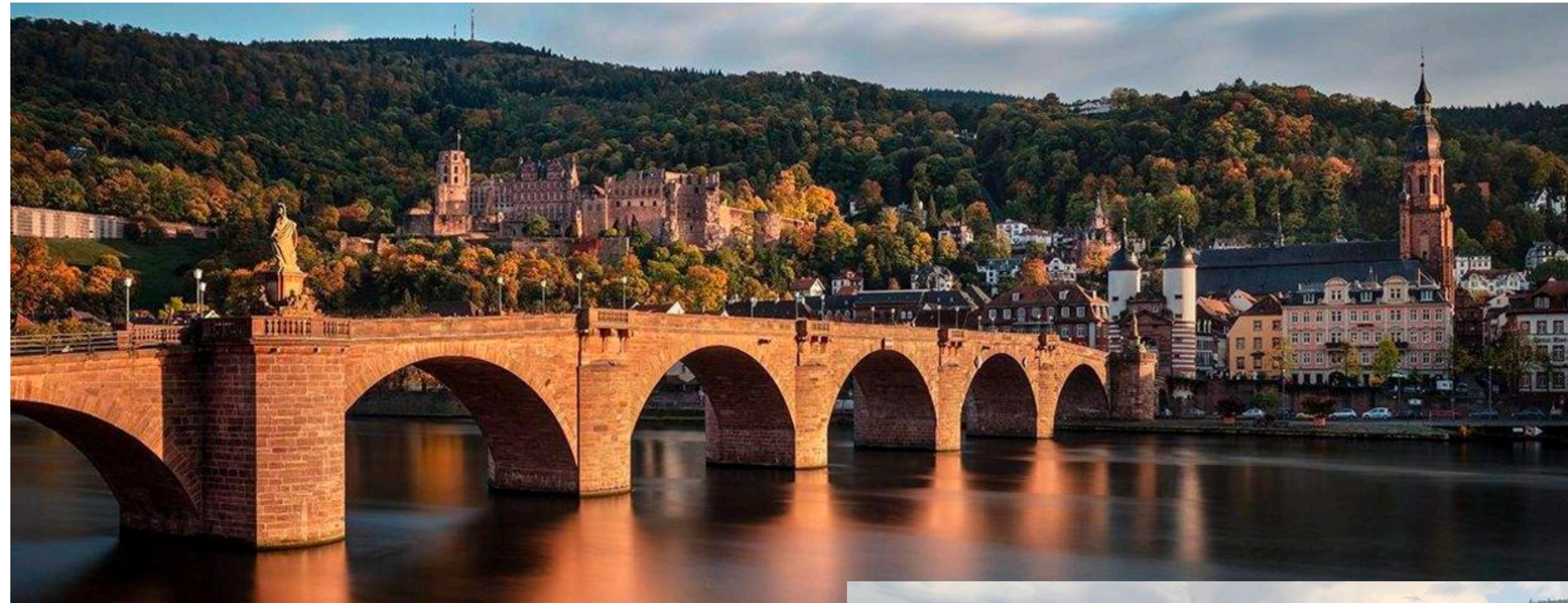


HEIDELBERG
UNIVERSITY
HOSPITAL





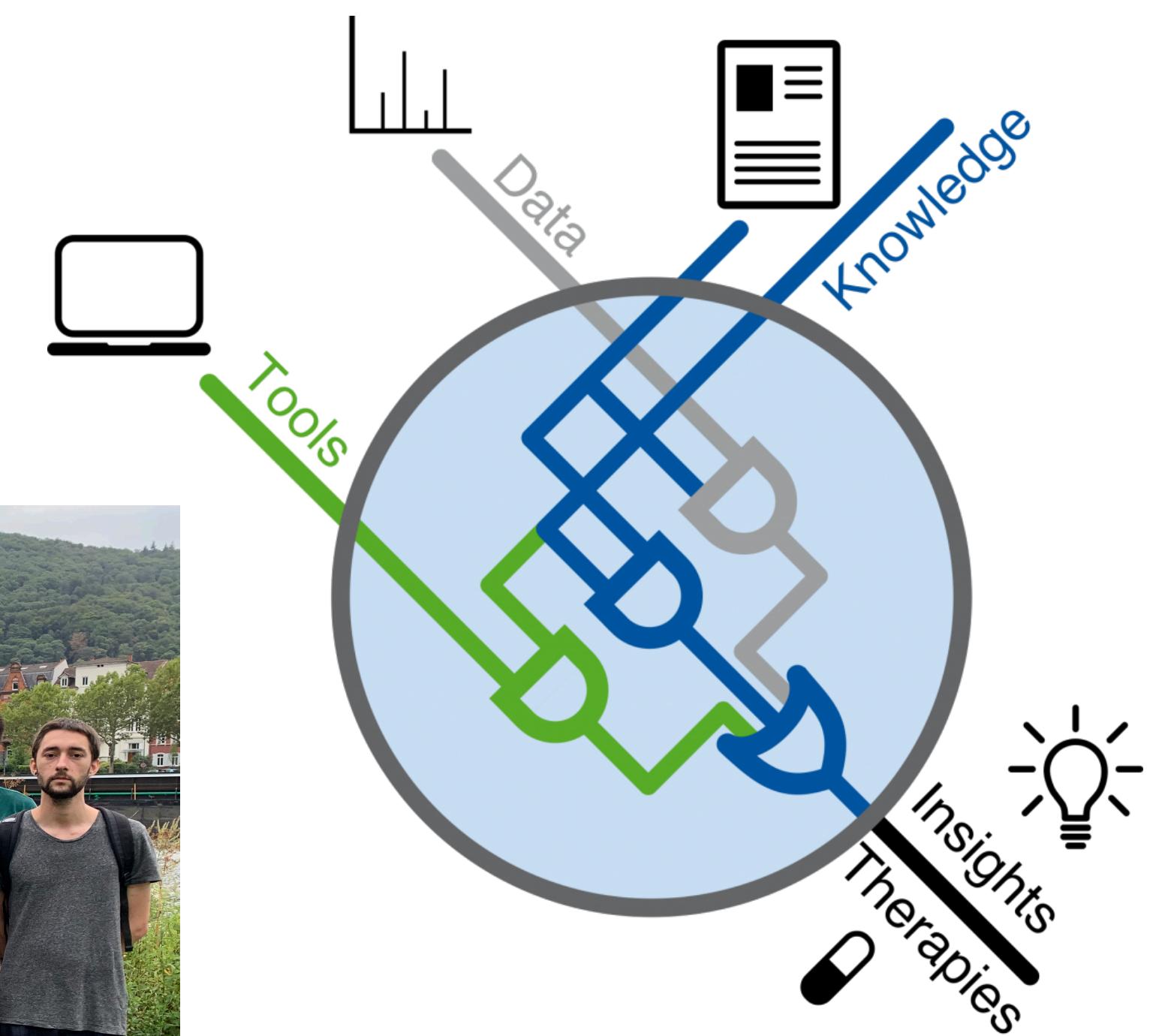
Who are we?



Heidelberg, Germany

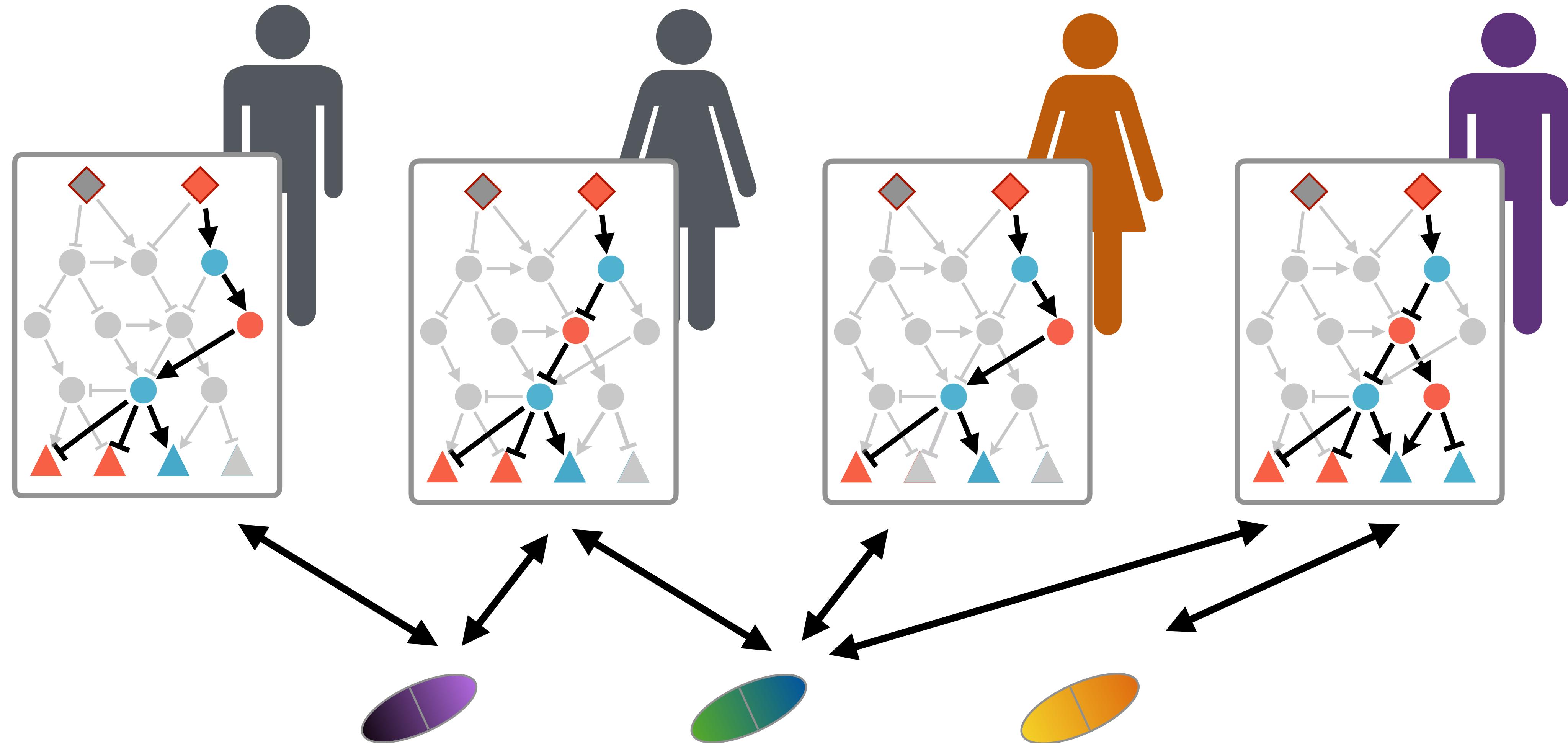


Saez-Rodriguez group





Personalise networks to find right drug to the right patient





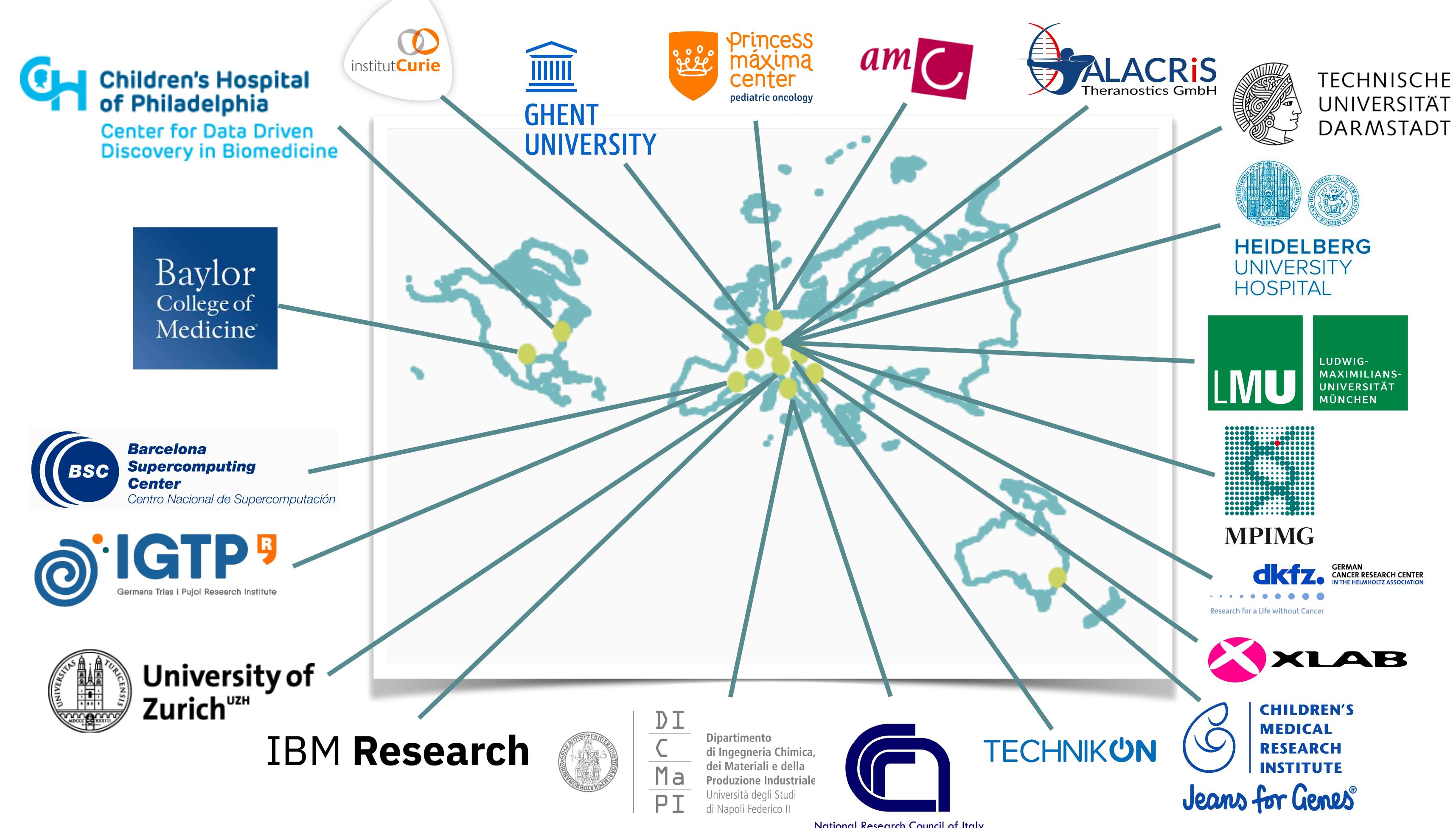
Motivation of the iPC project



- Paediatric cancer is rare
- High-dose administration with highly toxic profiles
- Current therapies have severe side effects
 - Developmental disorders
 - Autoimmune diseases



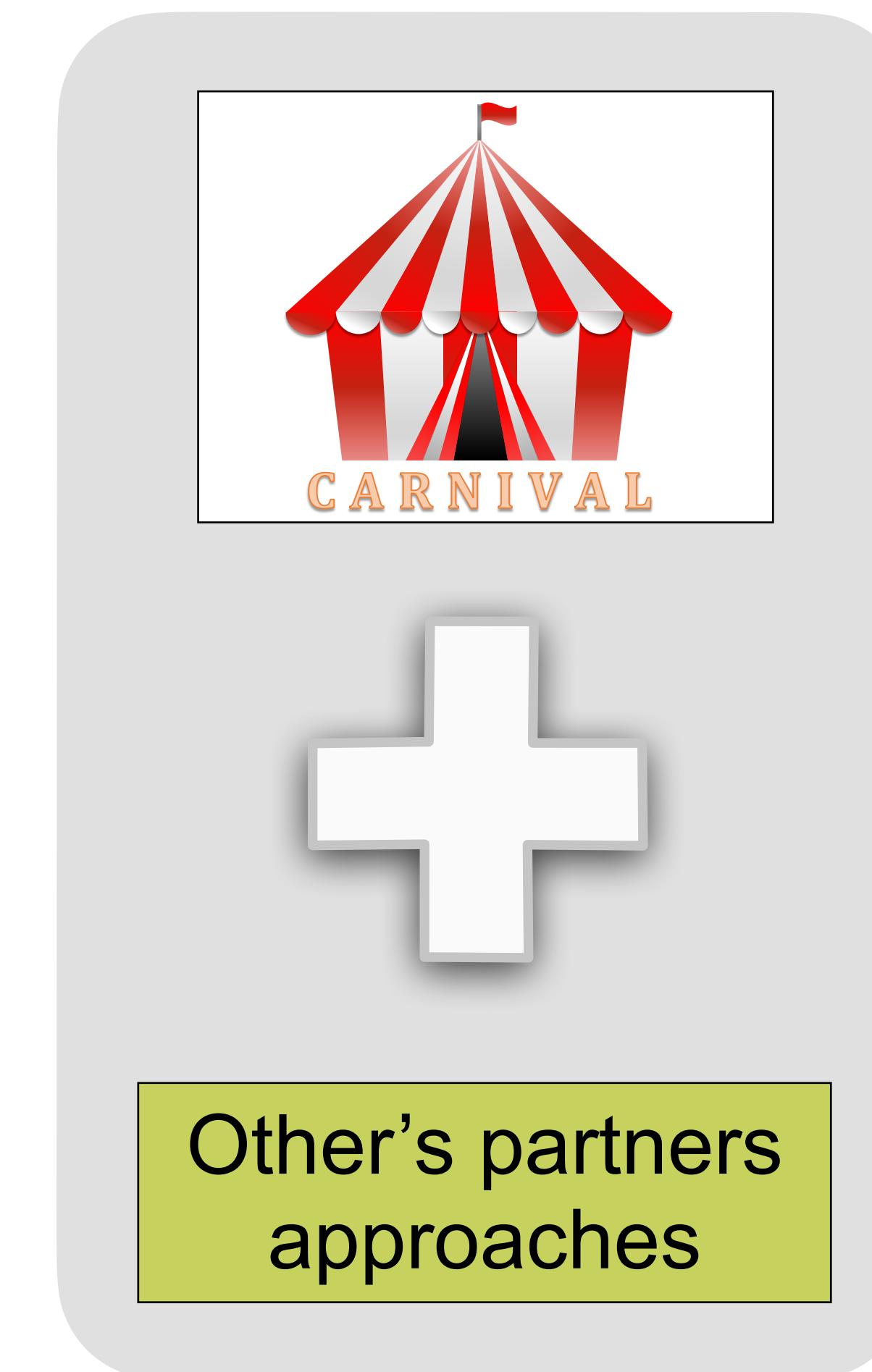
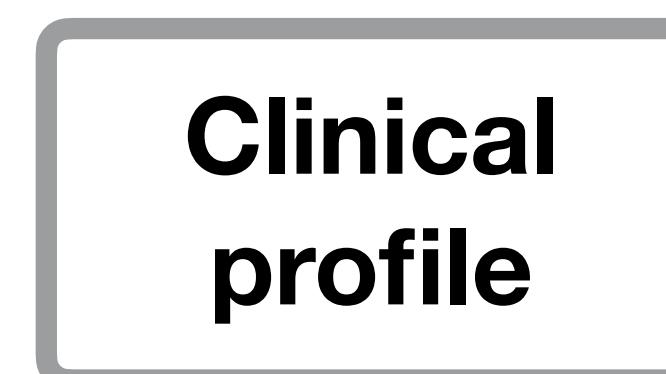
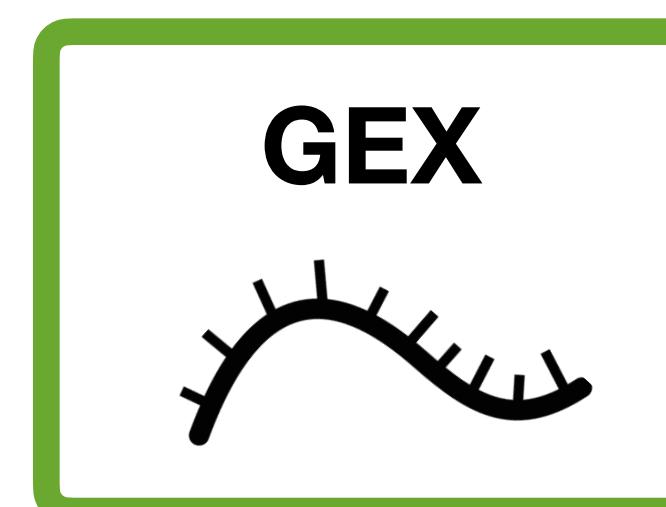
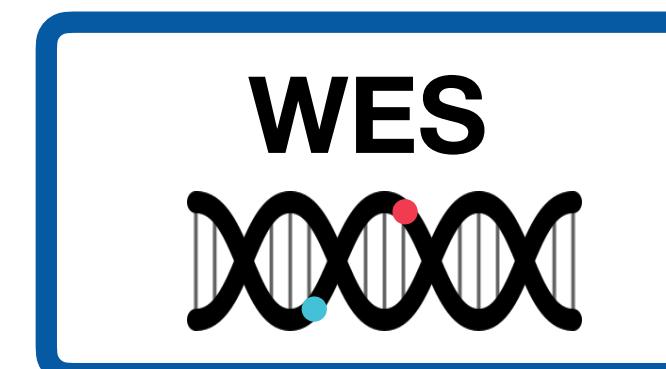
iPC Consortium





Pipelines integrated in a clinical report

Jane Doe



Drug	Efficacy	Side effects
Votrient	High	Low
Stivarga	Medium	Medium
Sorafenib Tosylate	Medium	Medium
5-fluorouracil	Medium	Medium
Doxorubicin	Medium	Medium
Cyclophosphamide	Medium	Medium
Halaven	Medium	Medium
Unituxin	Medium	Medium
Trabectedin	Medium	Medium
Methotrexate	Medium	Medium
Vincasar PFS	Medium	Medium
Lartruvo	Medium	Medium
Denosumab	Medium	Medium
Imatinib Mesylate	Medium	Medium
Cytoxan	Medium	Medium
Vincristine Sulfate	Medium	Medium
Regorafenib	Medium	Medium
Neosar	Medium	Medium
Clafen	Medium	Medium
Xgeva	Medium	Medium
Yondelis	Medium	Medium
Folex	Medium	Medium
Cisplatin	Medium	Medium
Nexavar	Medium	Medium
Gleevec	Medium	Medium
Dinutuximab	Medium	Medium
Dactinomycin	Medium	Medium
Abitrexate	Medium	Medium
Eribulin Mesylate	Medium	Medium
Folex PFS	Medium	Medium
Cosmegen	Medium	Medium
Pazopanib Hydrochloride	Medium	Medium
Mexate	Medium	Medium
Olaratumab	Medium	Medium

Suggested drug combinations

- 5-fluorouracil Cisplatin
- 5-fluorouracil Vincasar
- Doxorubicin Cyclophosphamide
- Unituxin Gleevec

Suggested Experimental therapies

- AZD6738
- Metaformin
- MTX, cisplatin, and ifosfamide
- EGFR-specific CAR T cells
- Glypican 3-specific CAR T cells
- GD2-specific NKTs
- EGFR-specific RNA therapy

Short-term risks

- Metastasis
- Anemia
- Kidney failure

Long-term risks

- Organ loss
- Breast cancer
- Hearing loss
- Lower IQ

Genetic predisposition

- PMS2 mutation

Clinical Report



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

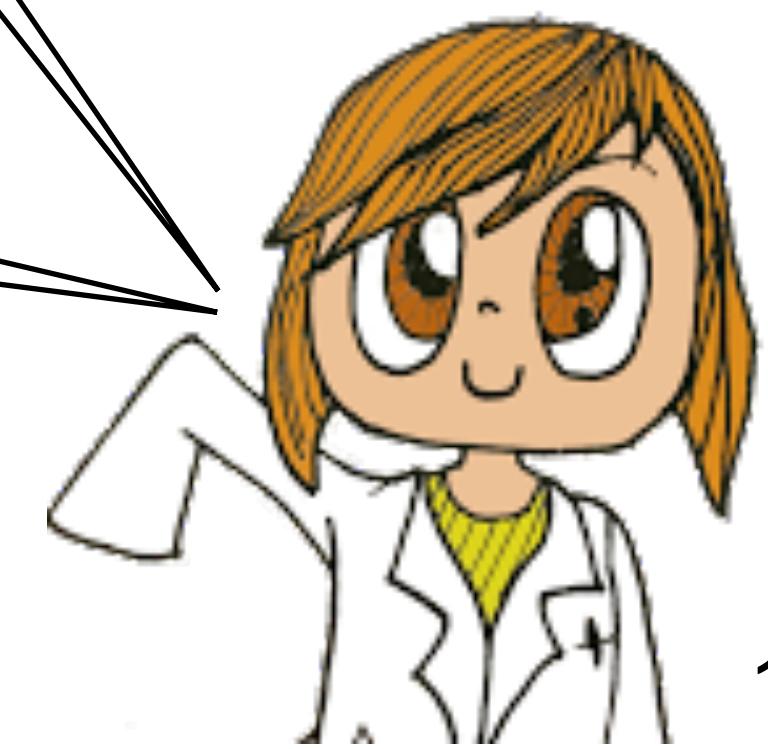




Framework of research

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

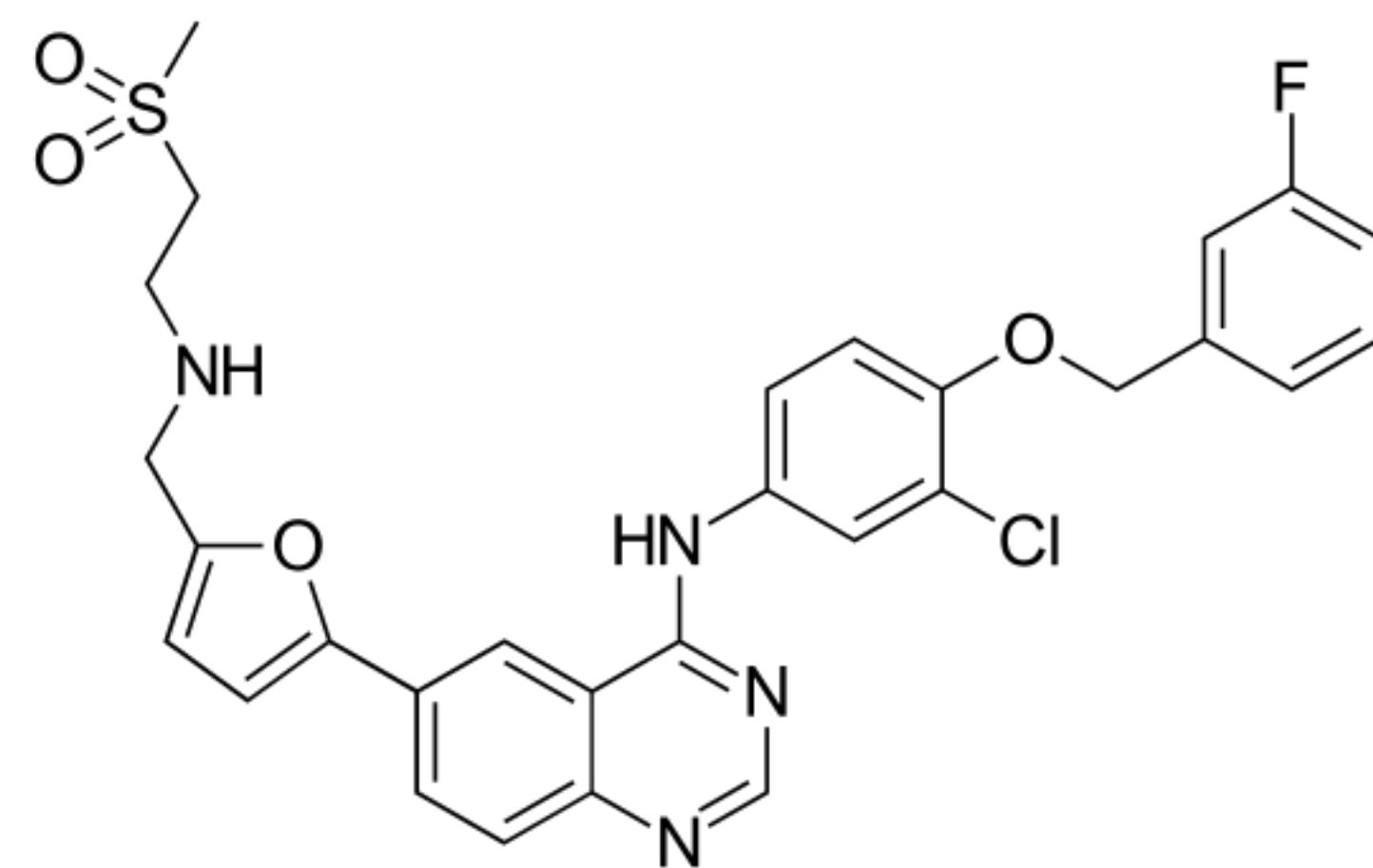
Is there any effect on the response
of lung cancer cell lines when
treated with lapatinib?





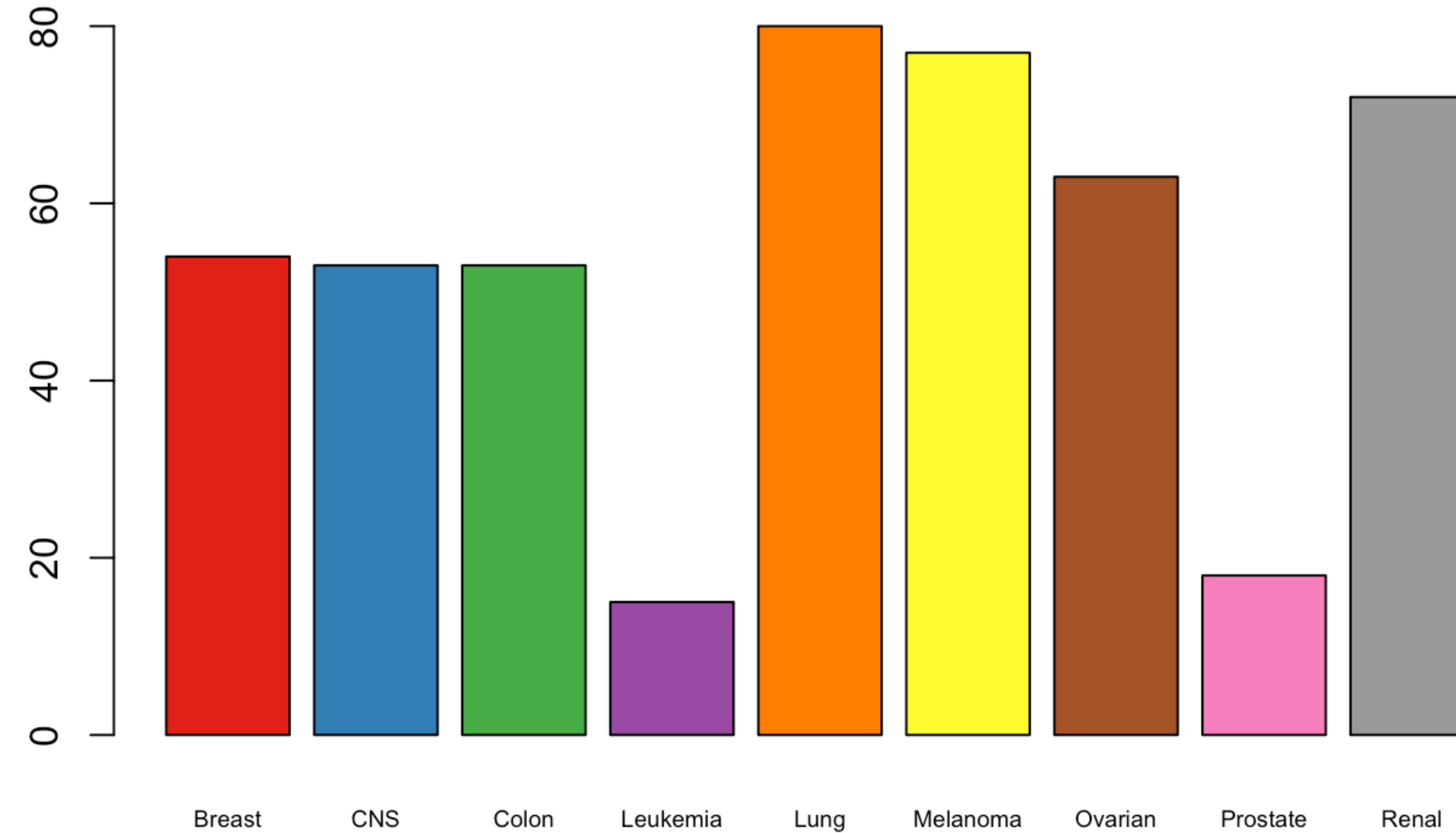
Lapatinib in cancer

- 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



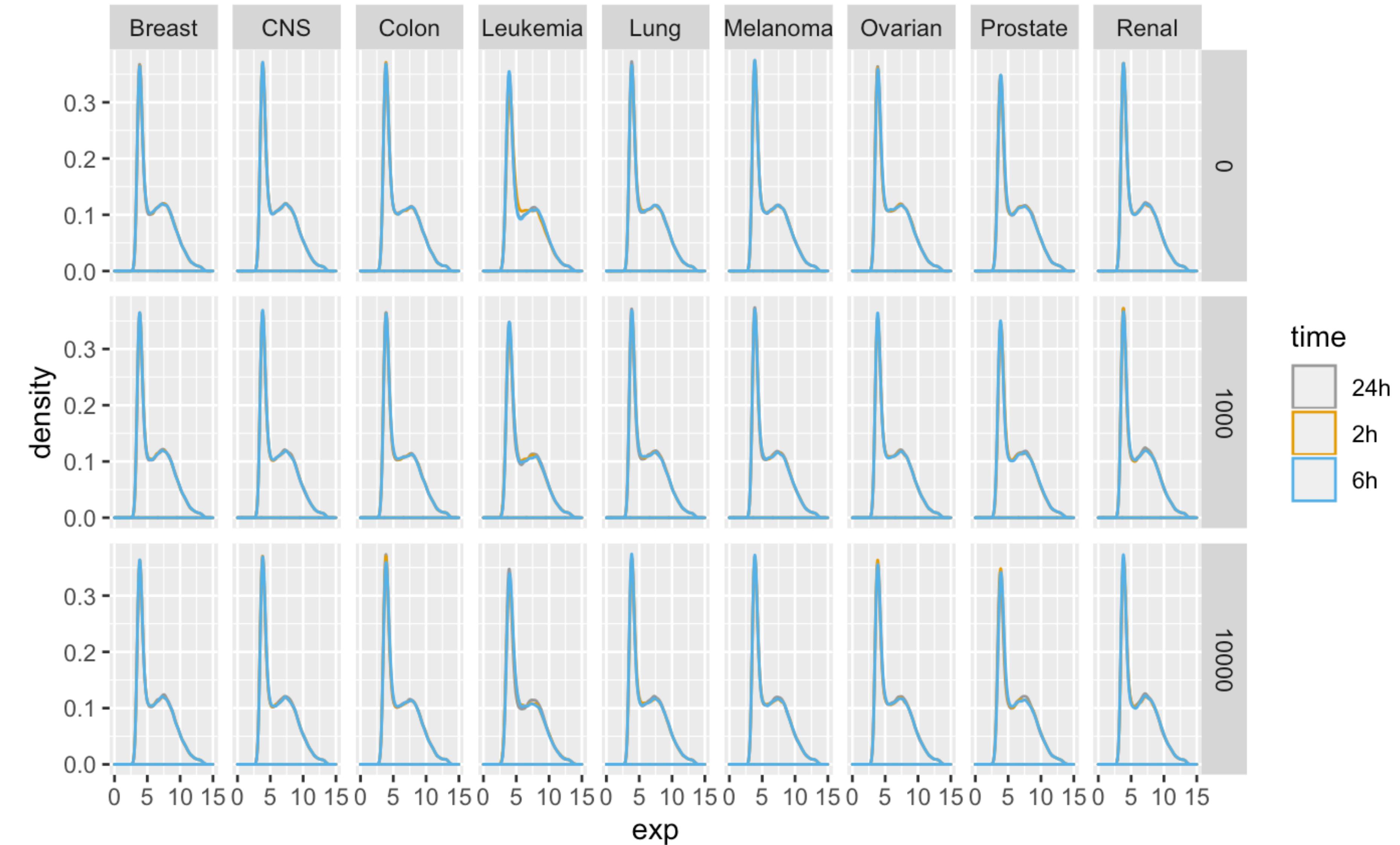


Samples' distribution





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.

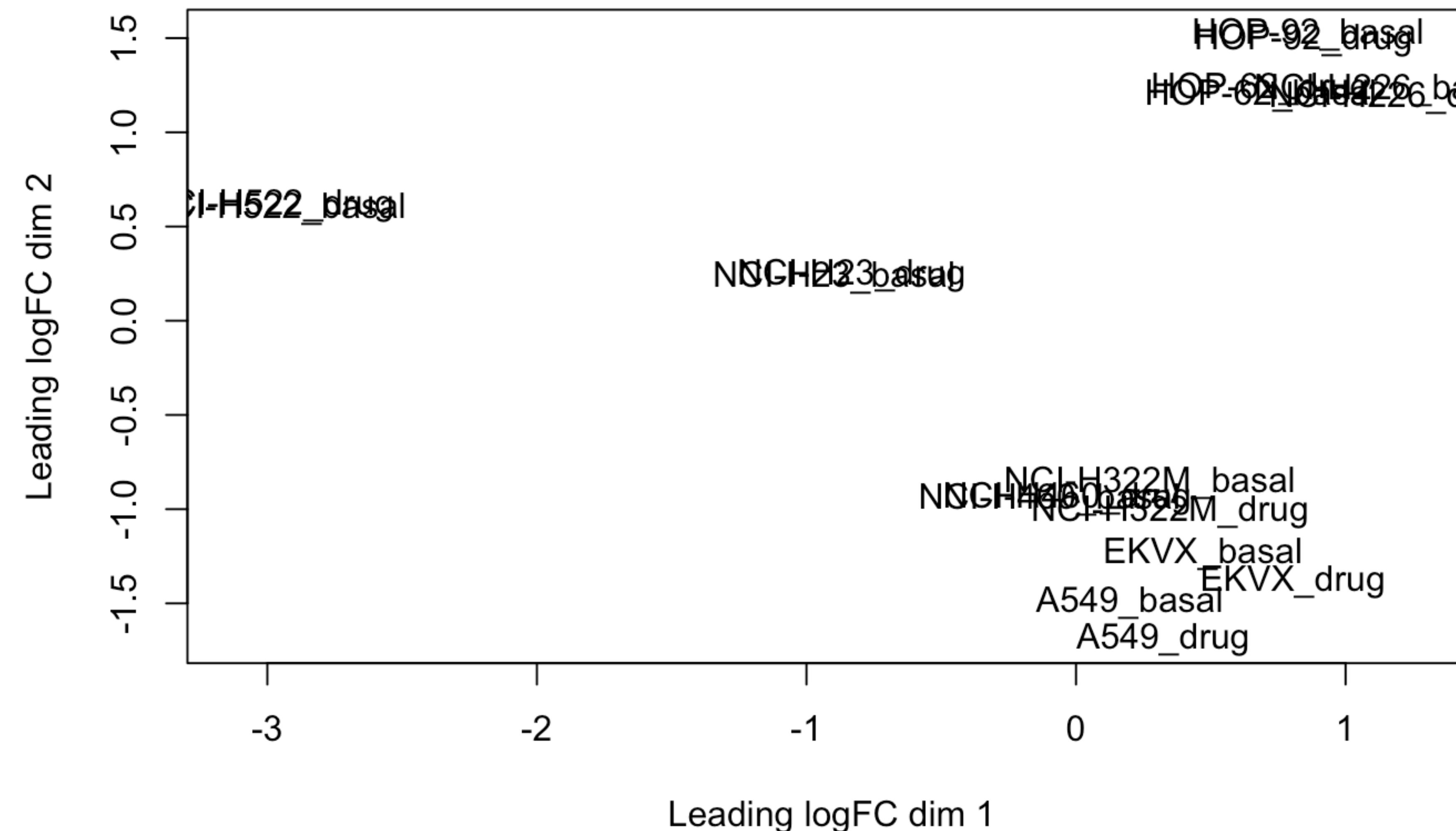
- Multidimensional scaling (MDS)

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

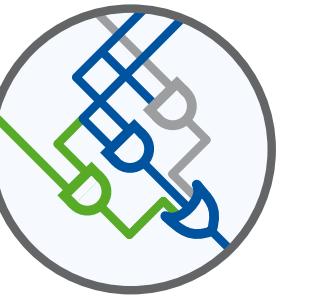
Average log2-expression for the probe over all arrays and channels

Moderated t-statistic

Raw p-value and adjusted p-value

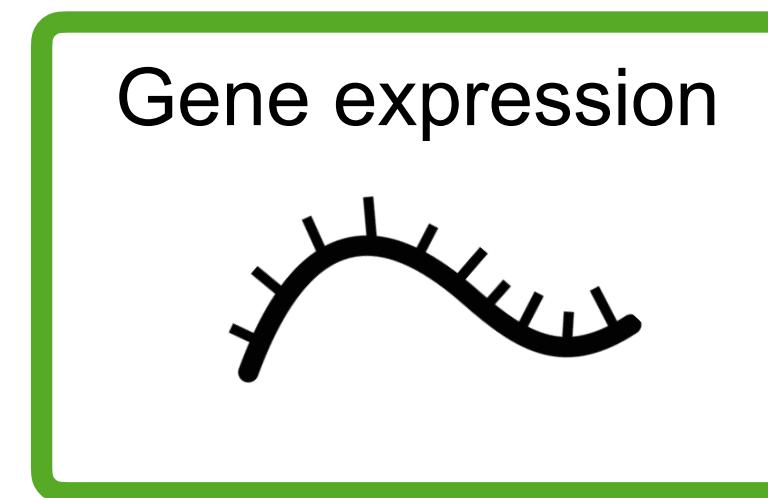
log-odds that the gene is differentially expressed

Footprint methods

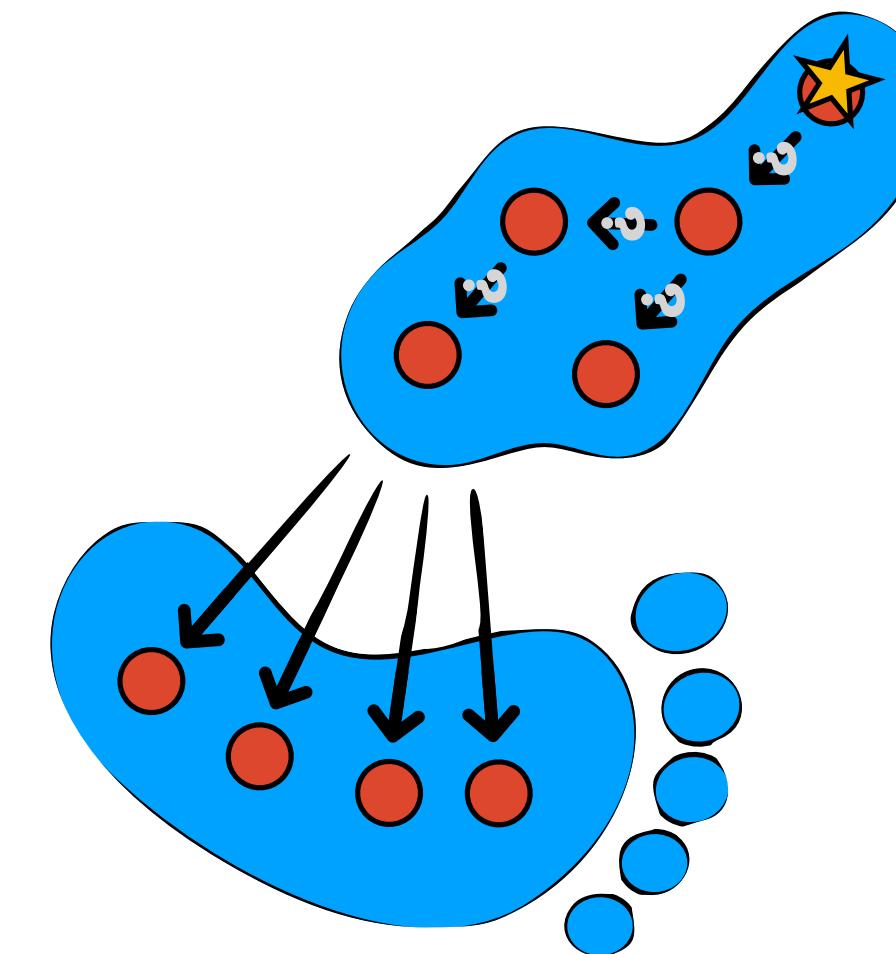




Why use footprint methods?

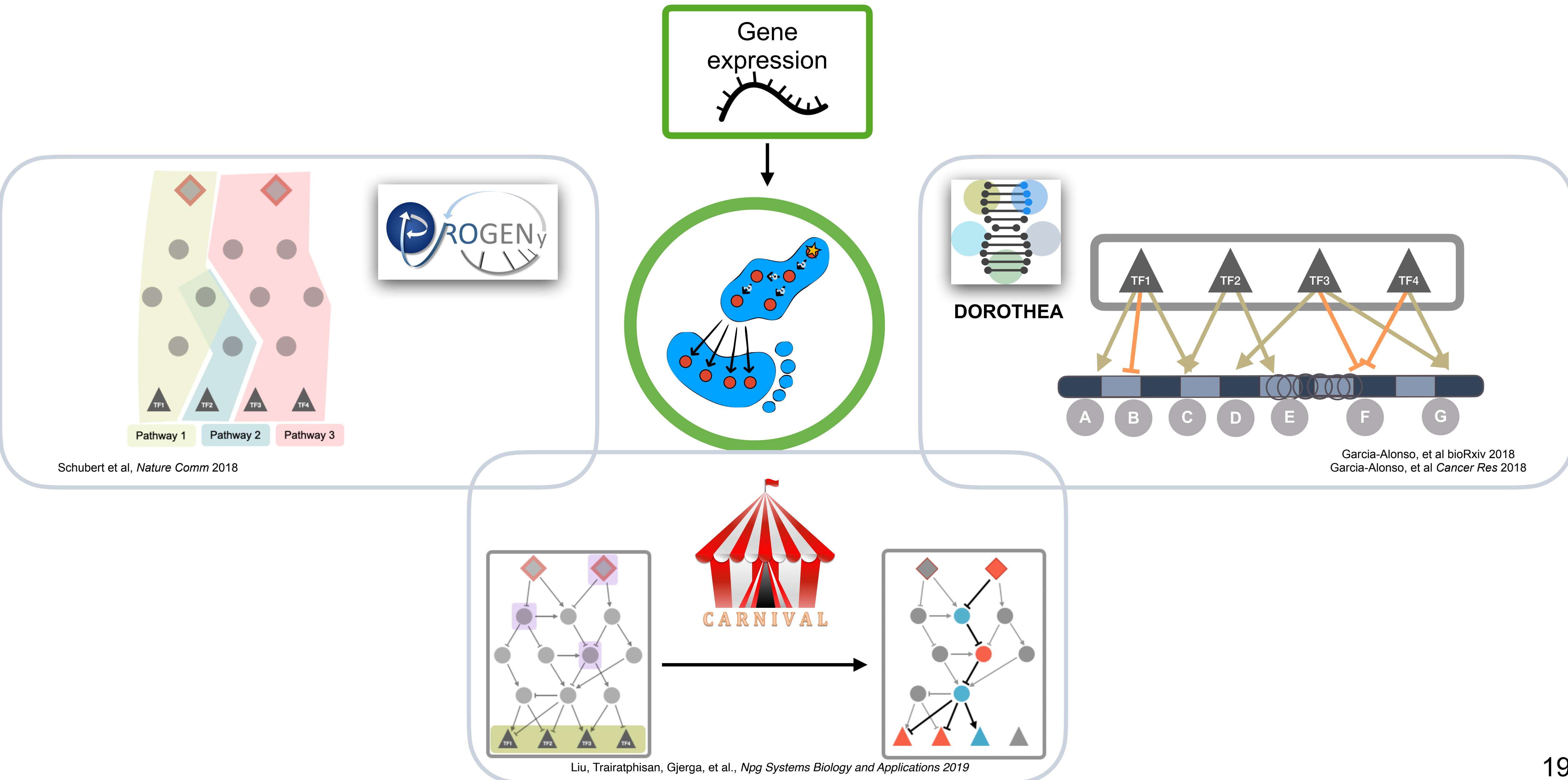


- ✗ Protein's activity
- ✗ Protein's abundance



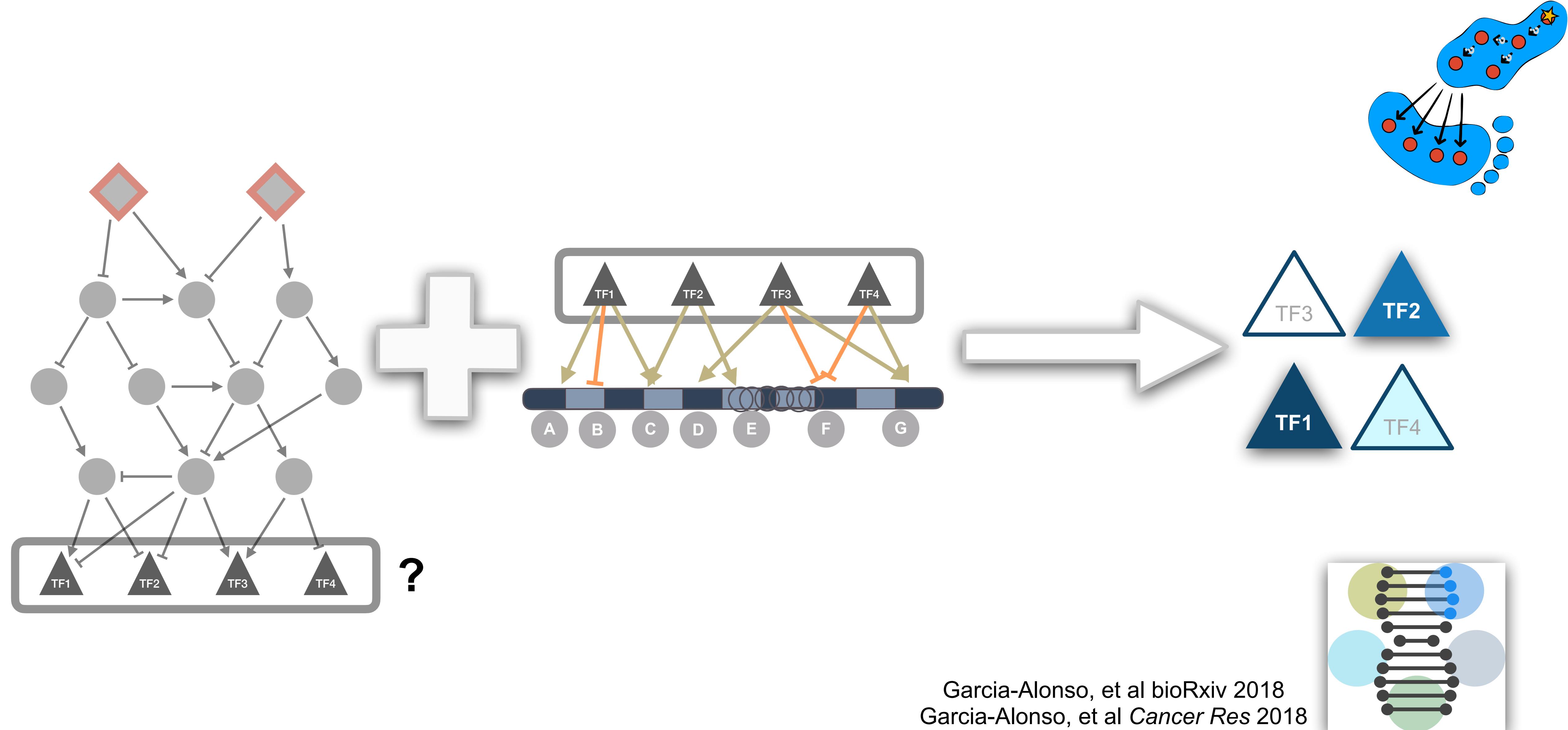


Footprint methods



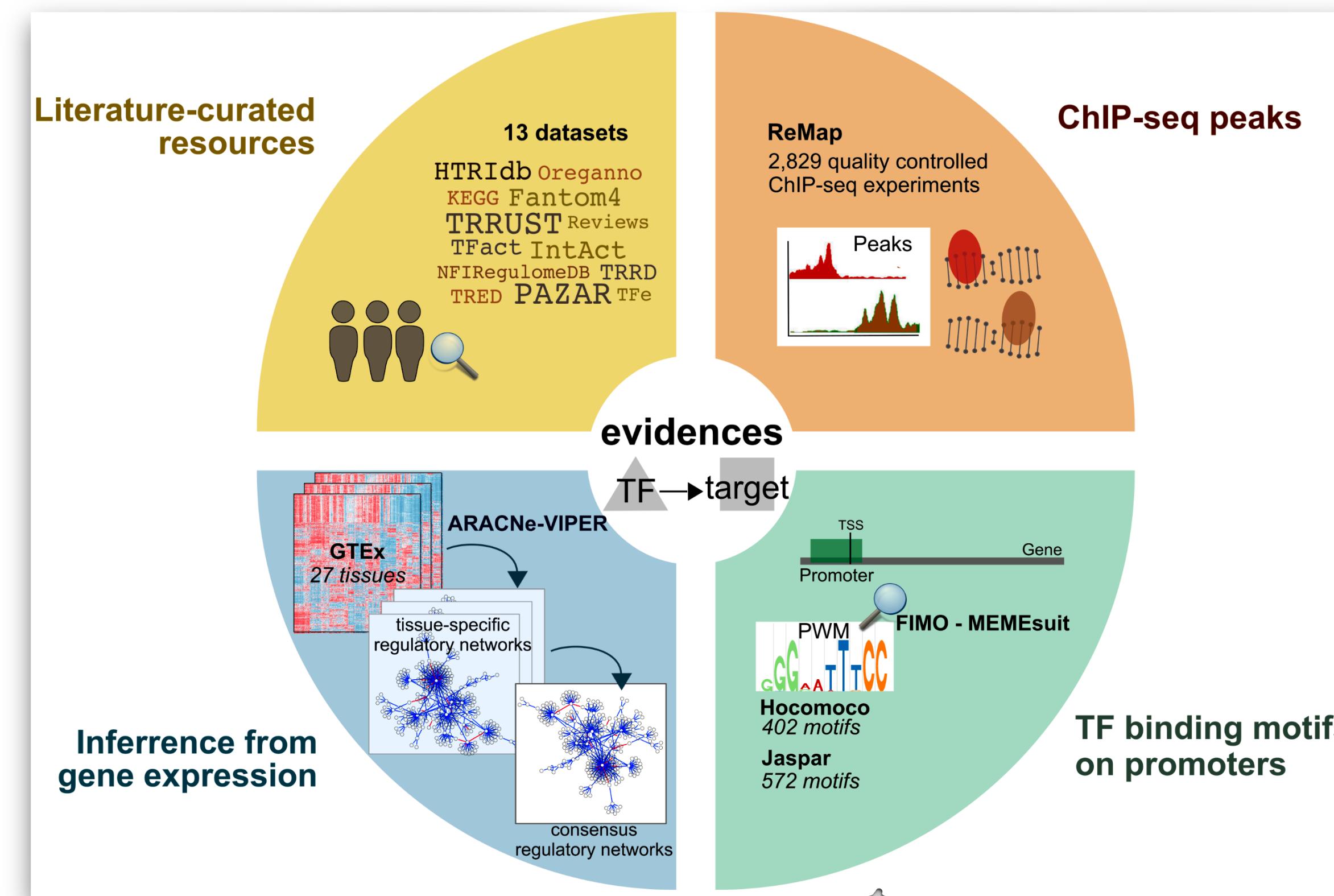
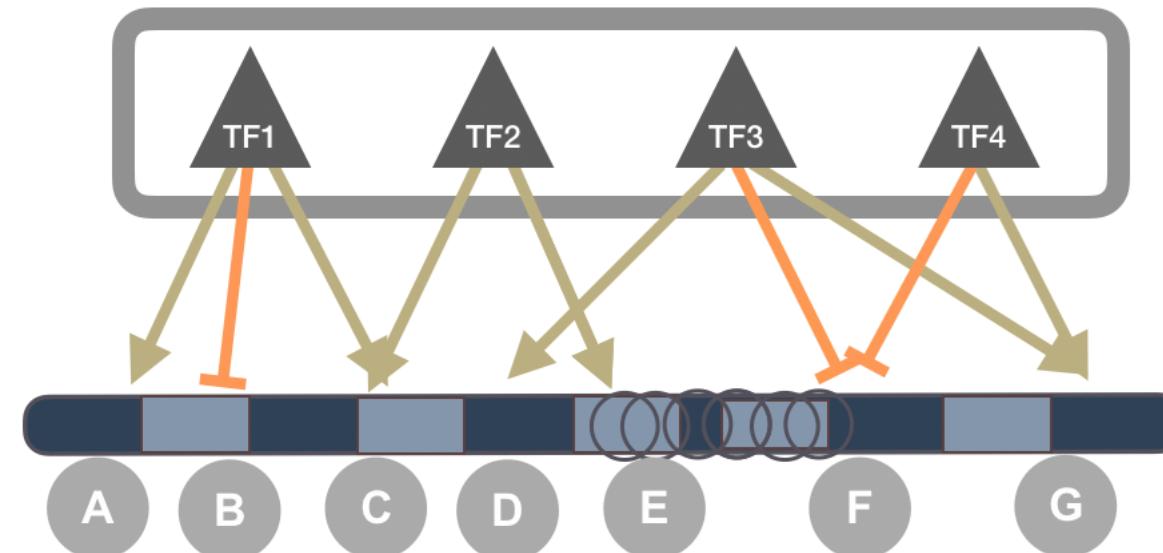


DOROTHEA: Discriminant Regulon Expression Analysis





DOROTHEA: Discriminant Regulon Expression Analysis

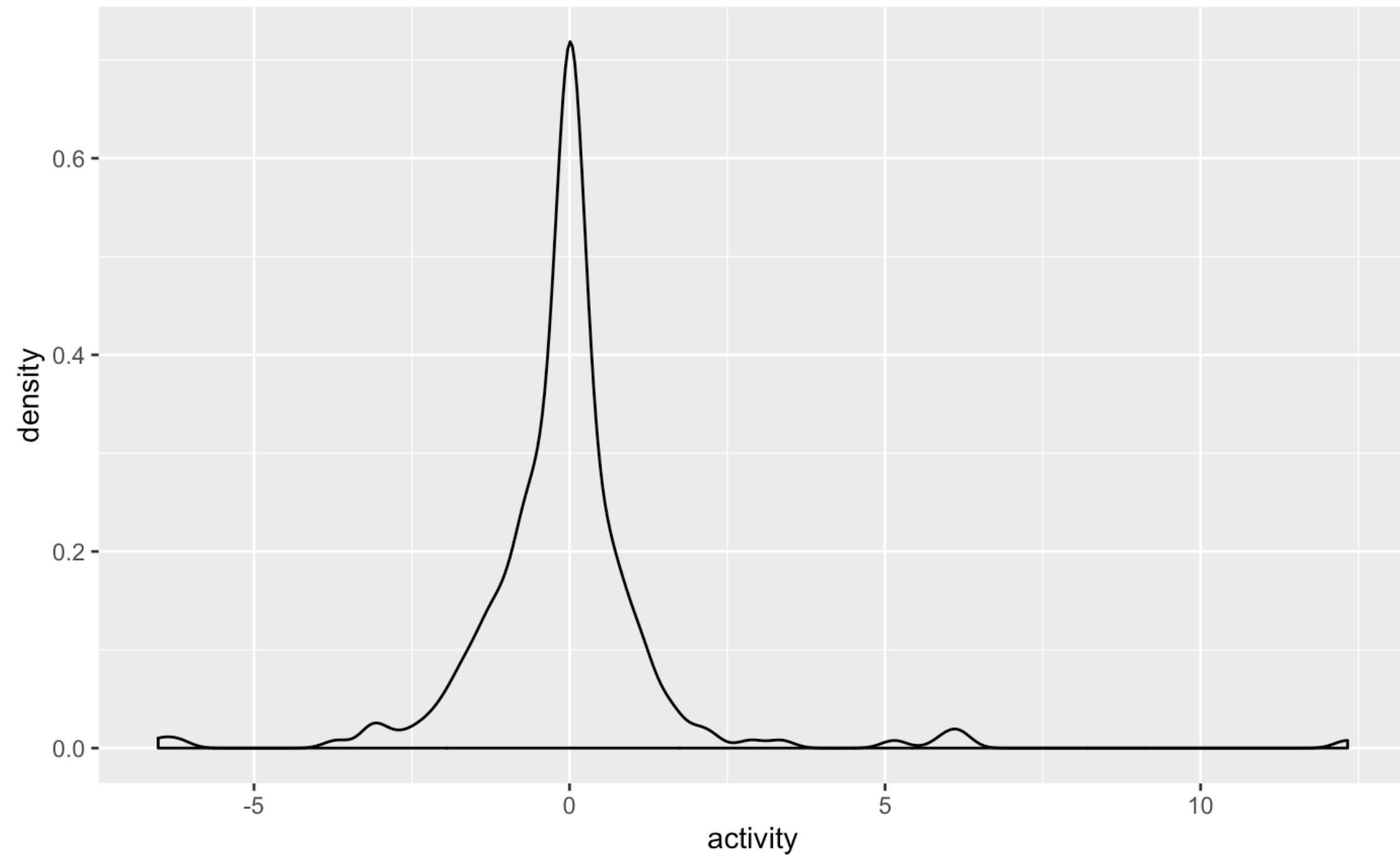


Garcia-Alonso, et al bioRxiv 2018
Garcia-Alonso, et al Cancer Res 2018

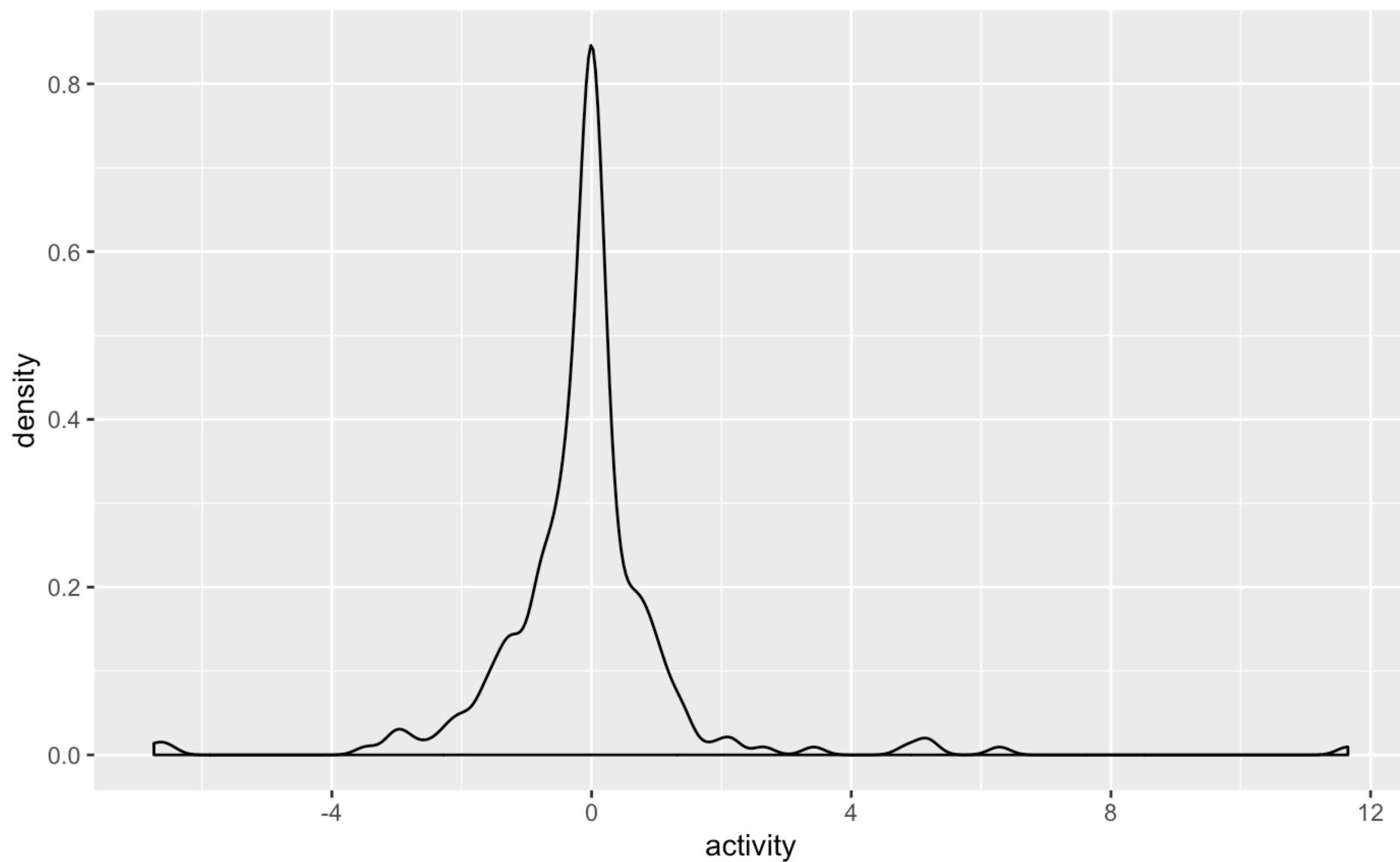




DOROTHEA: Discriminant Regulon Expression Analysis

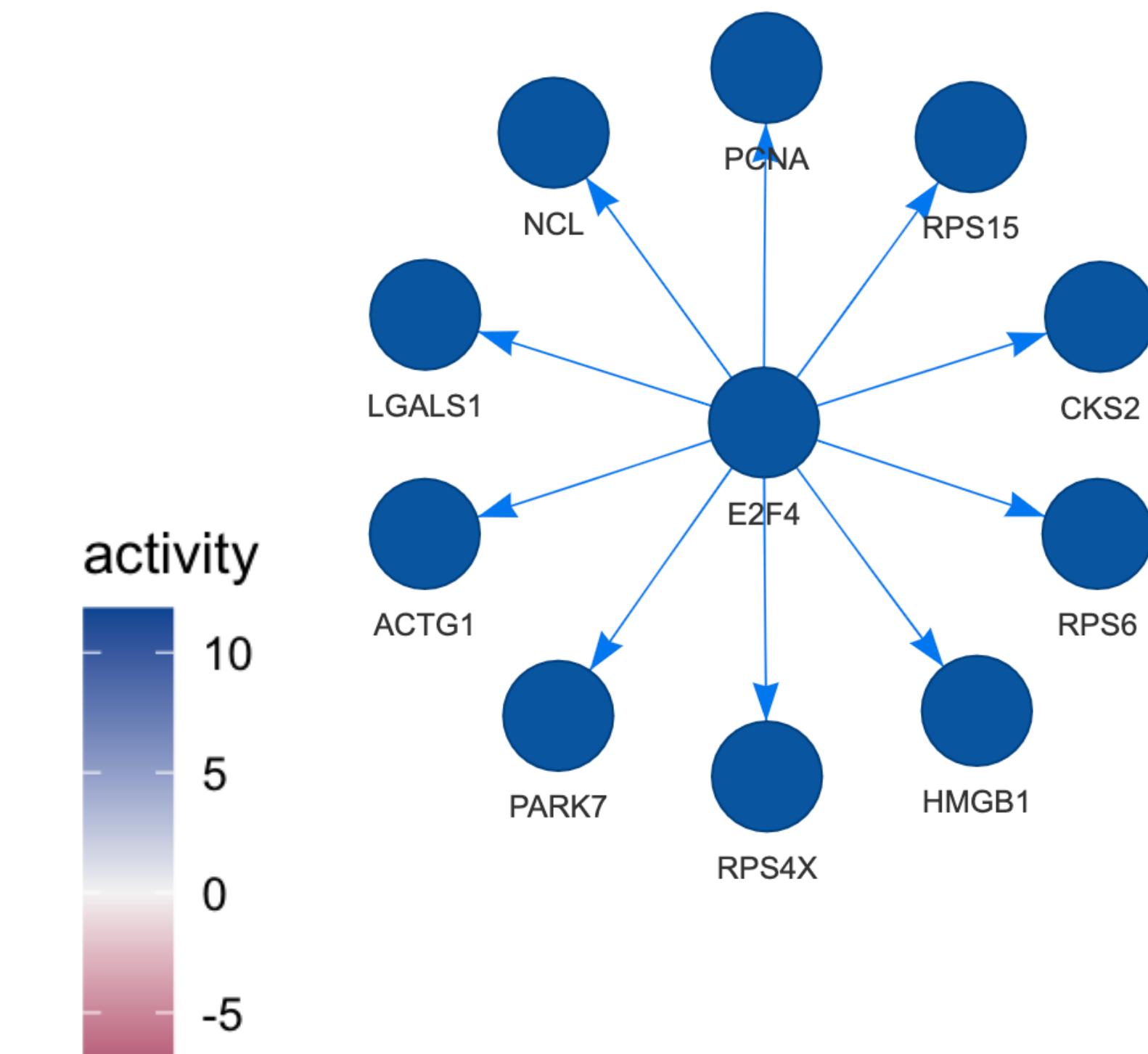
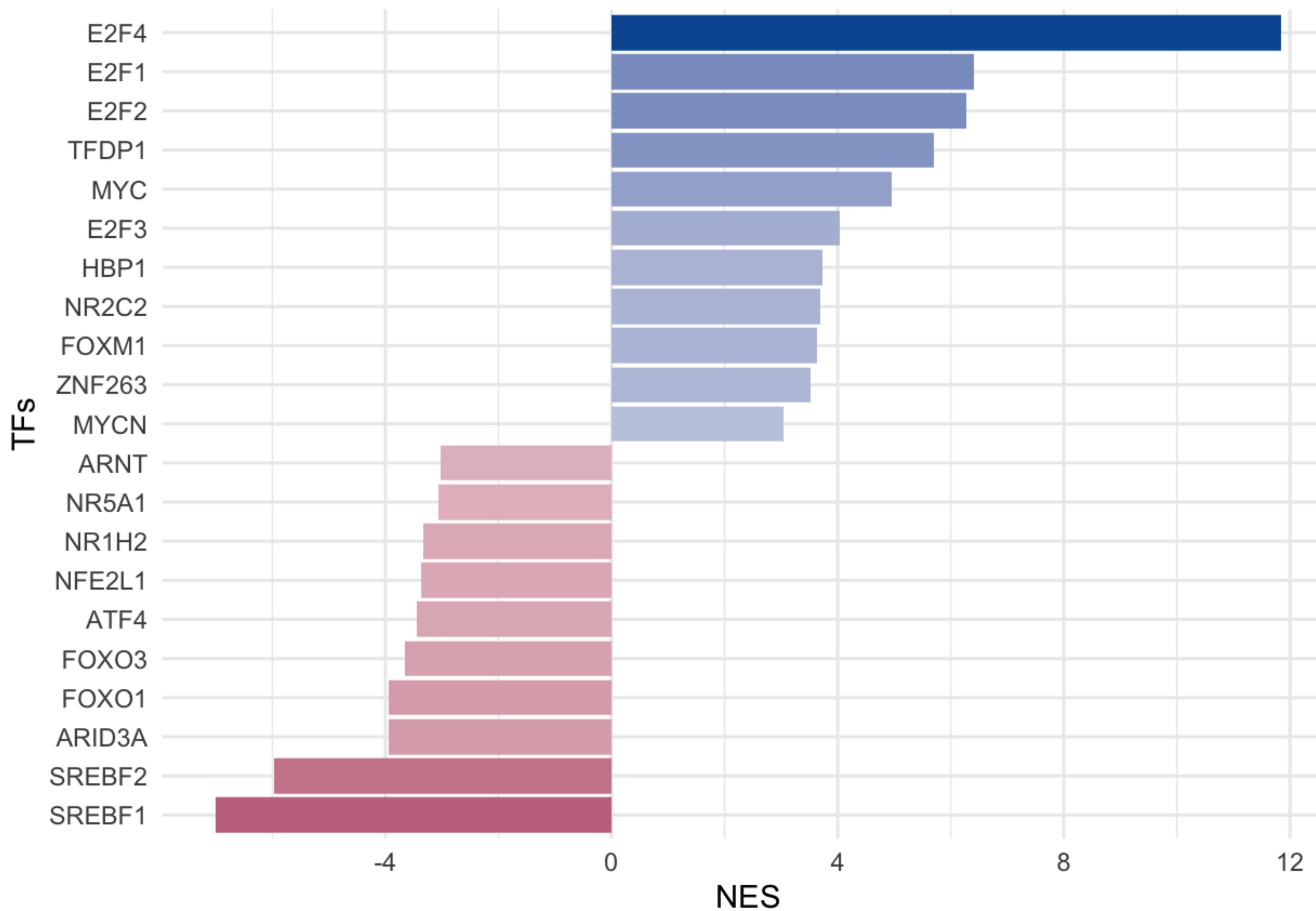


eset.filter: whether the dataset should be limited only to the genes represented in the interactome



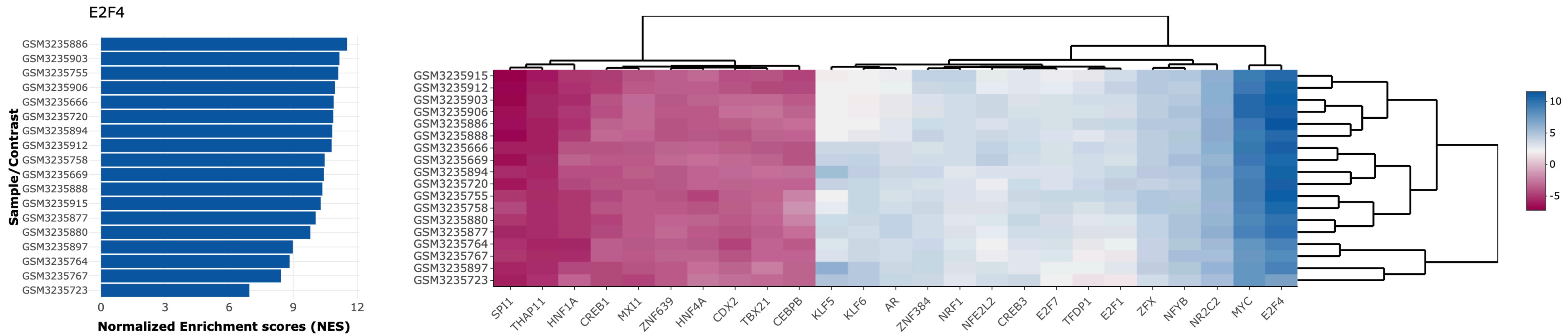


DOROTHEA: Discriminant Regulon Expression Analysis



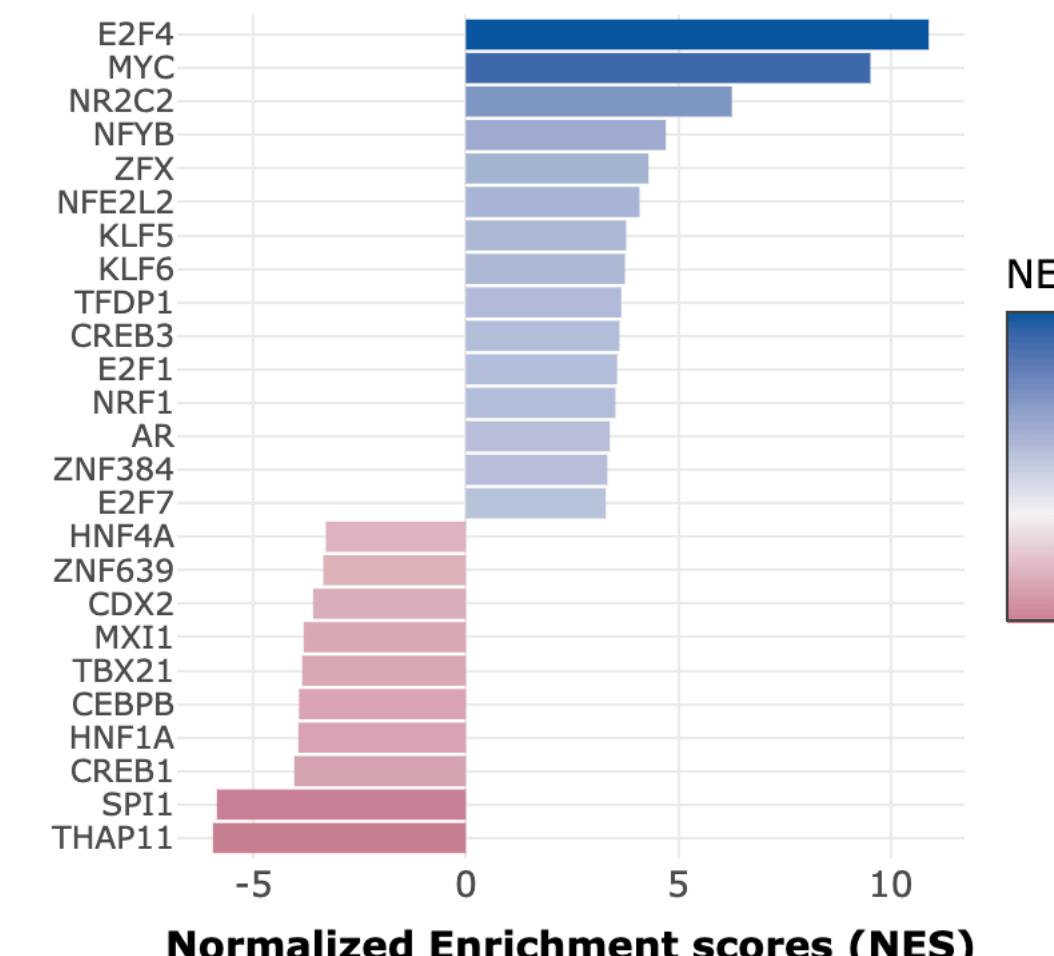


User interface using FUNKI: <https://saezlab.shinyapps.io/funki/>



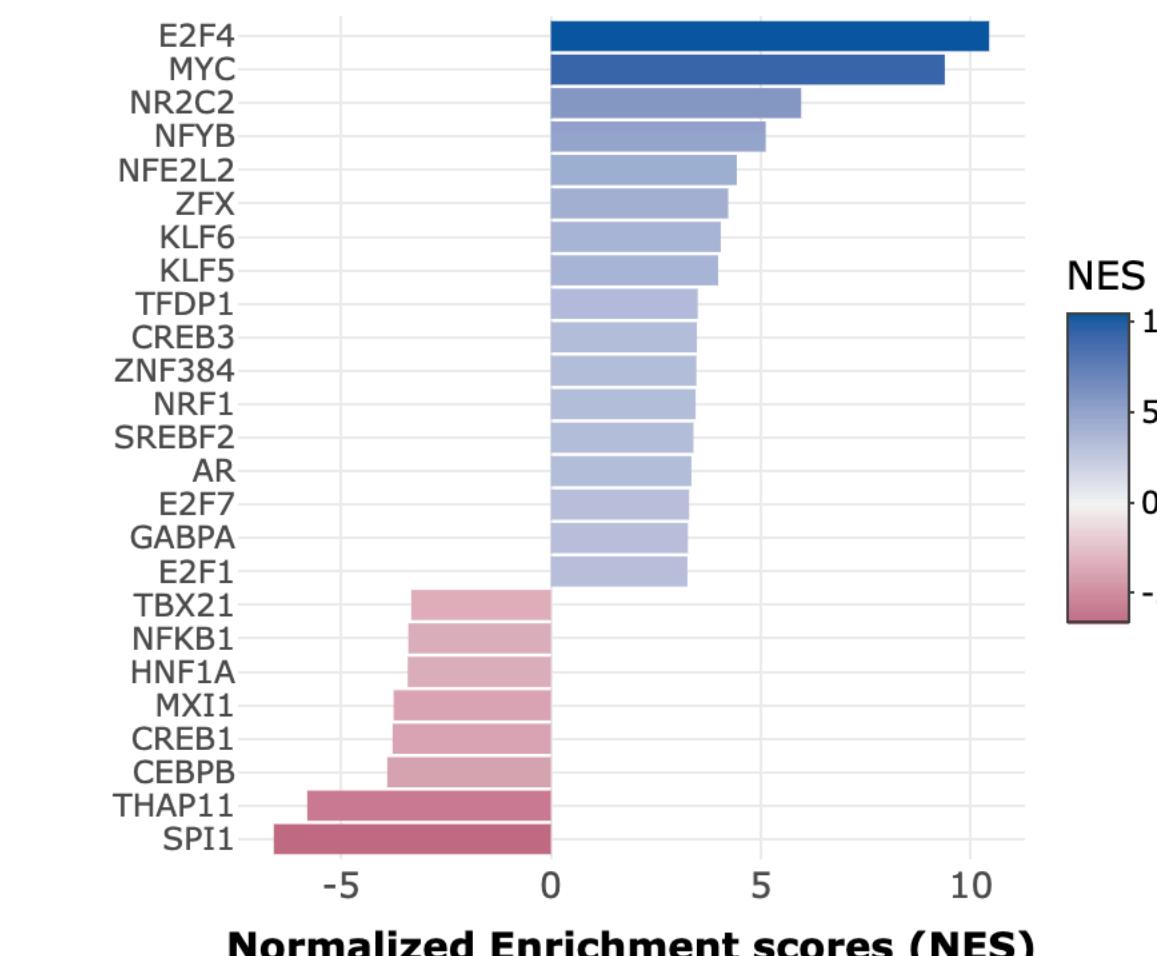
A549 Basal

Sample/Contrast: GSM3235666



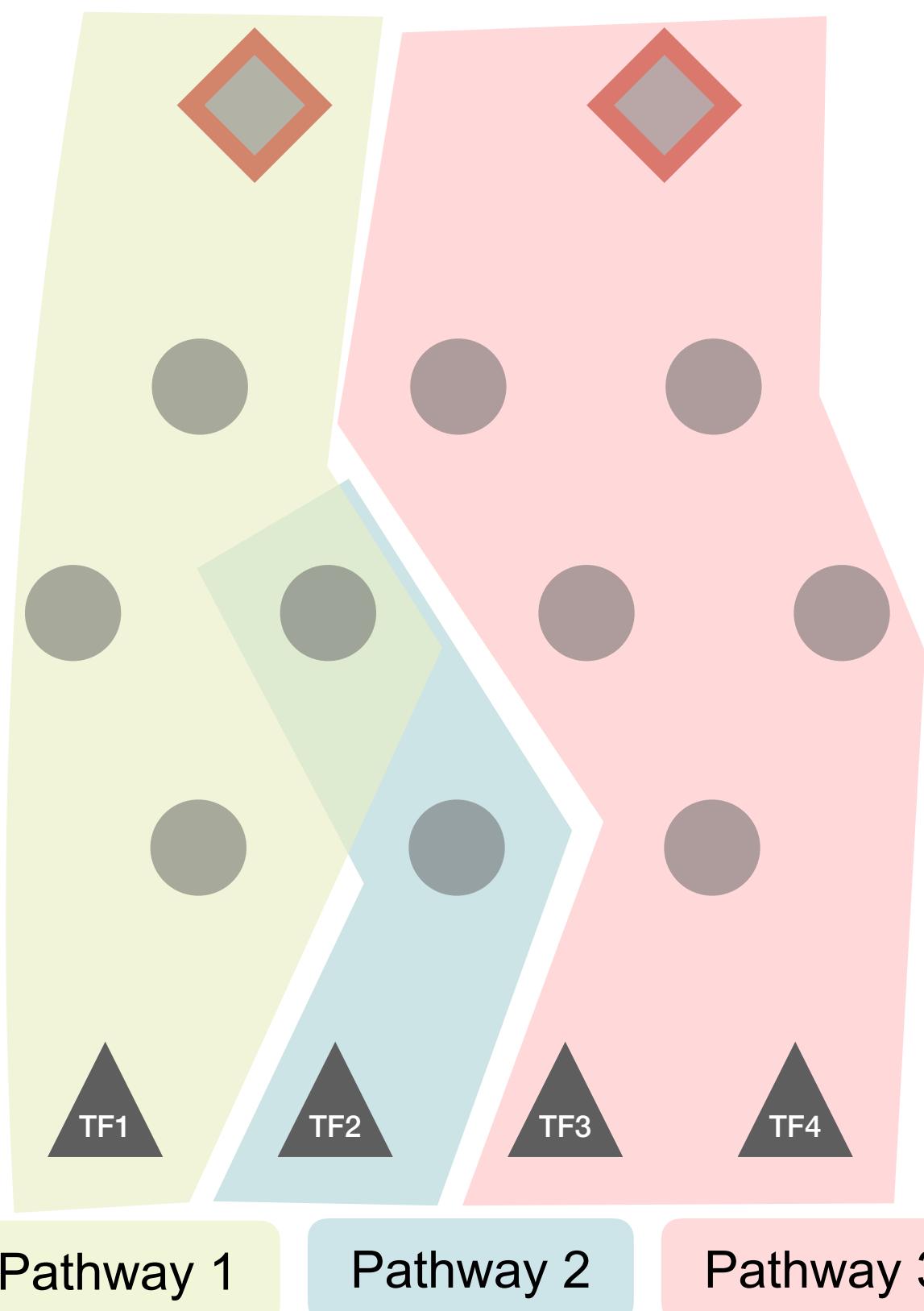
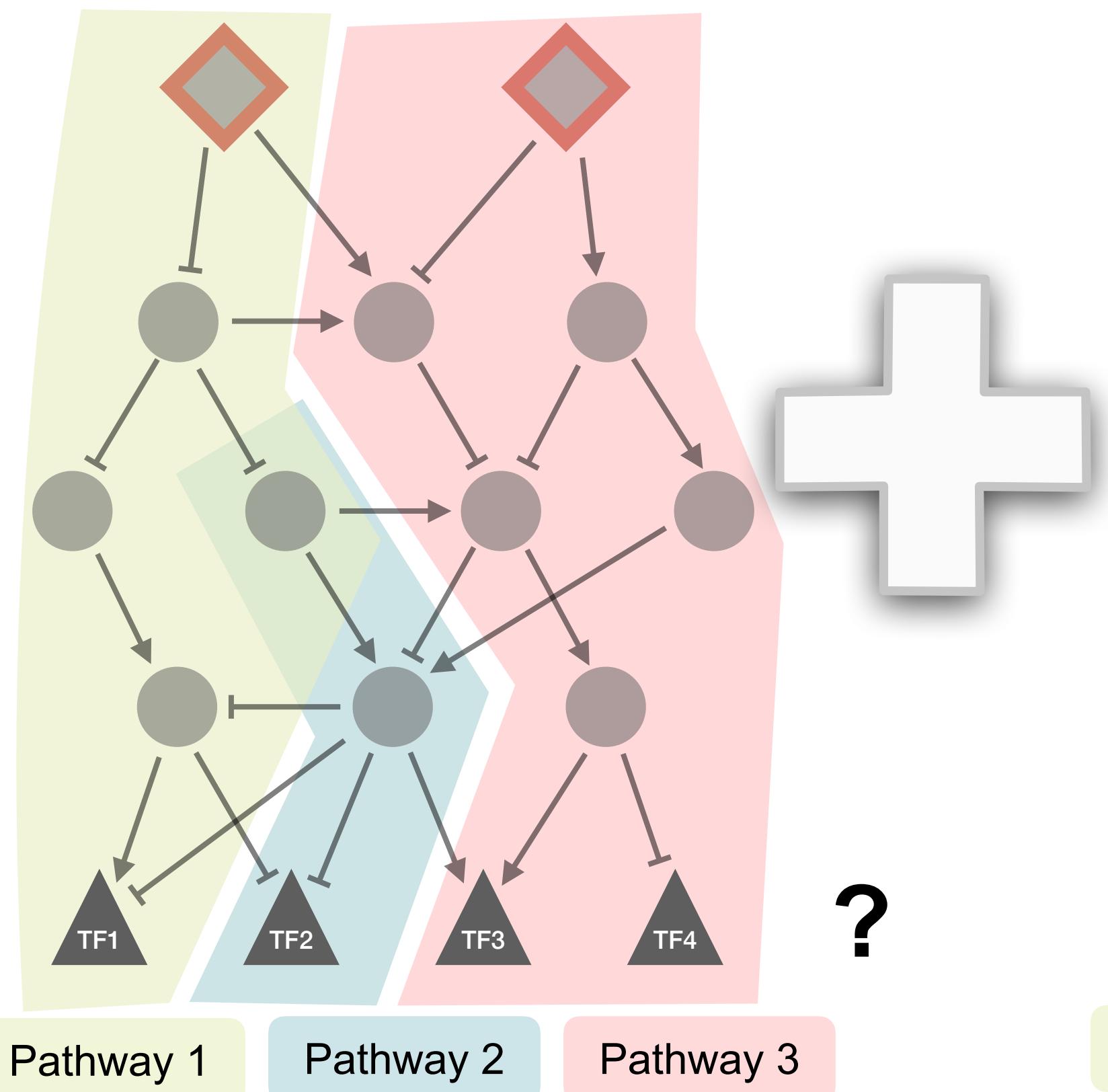
A549 Drug

Sample/Contrast: GSM3235669





PROGENy: Pathway RespOnsive GENes

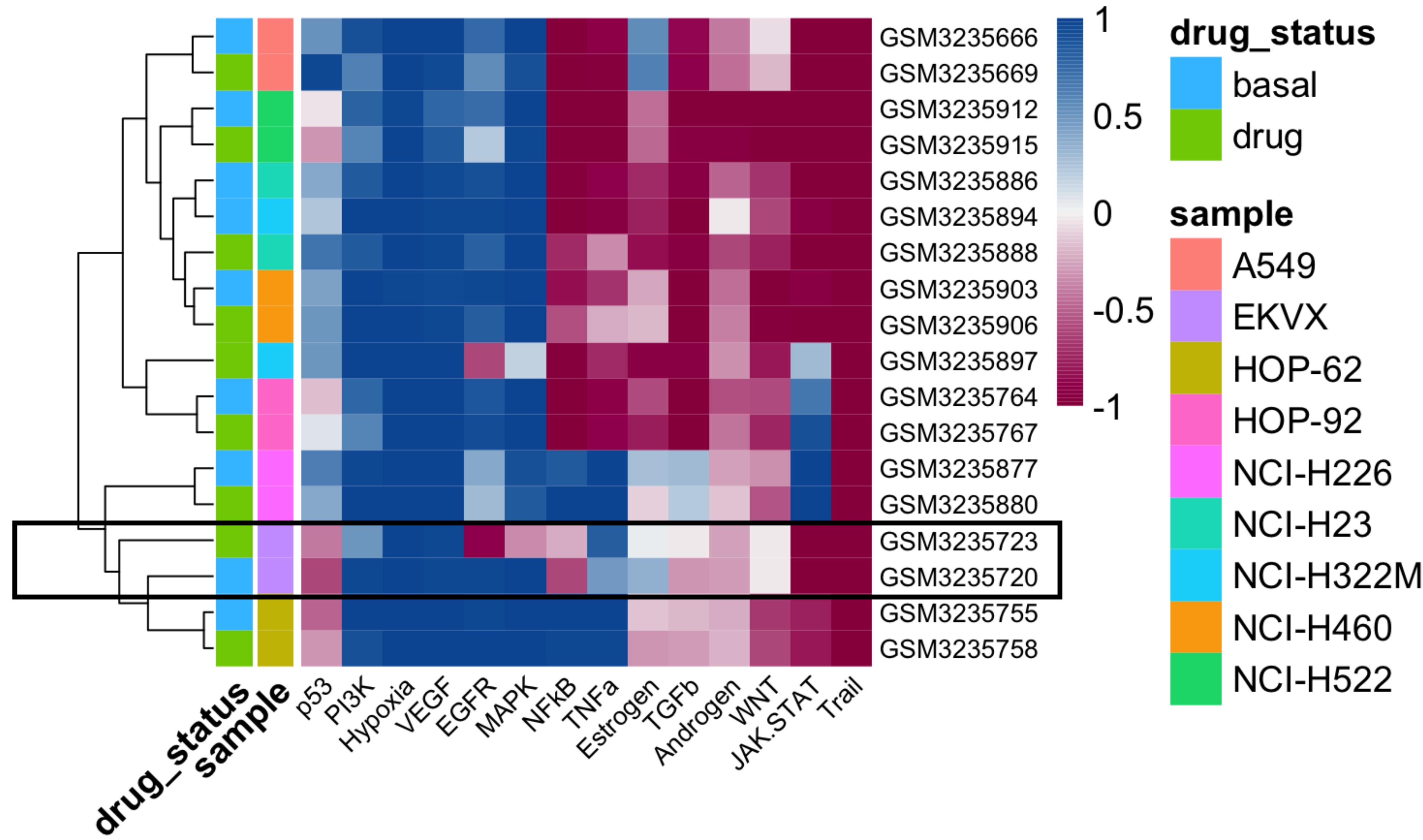


Schubert et al, *Nature Comm* 2018





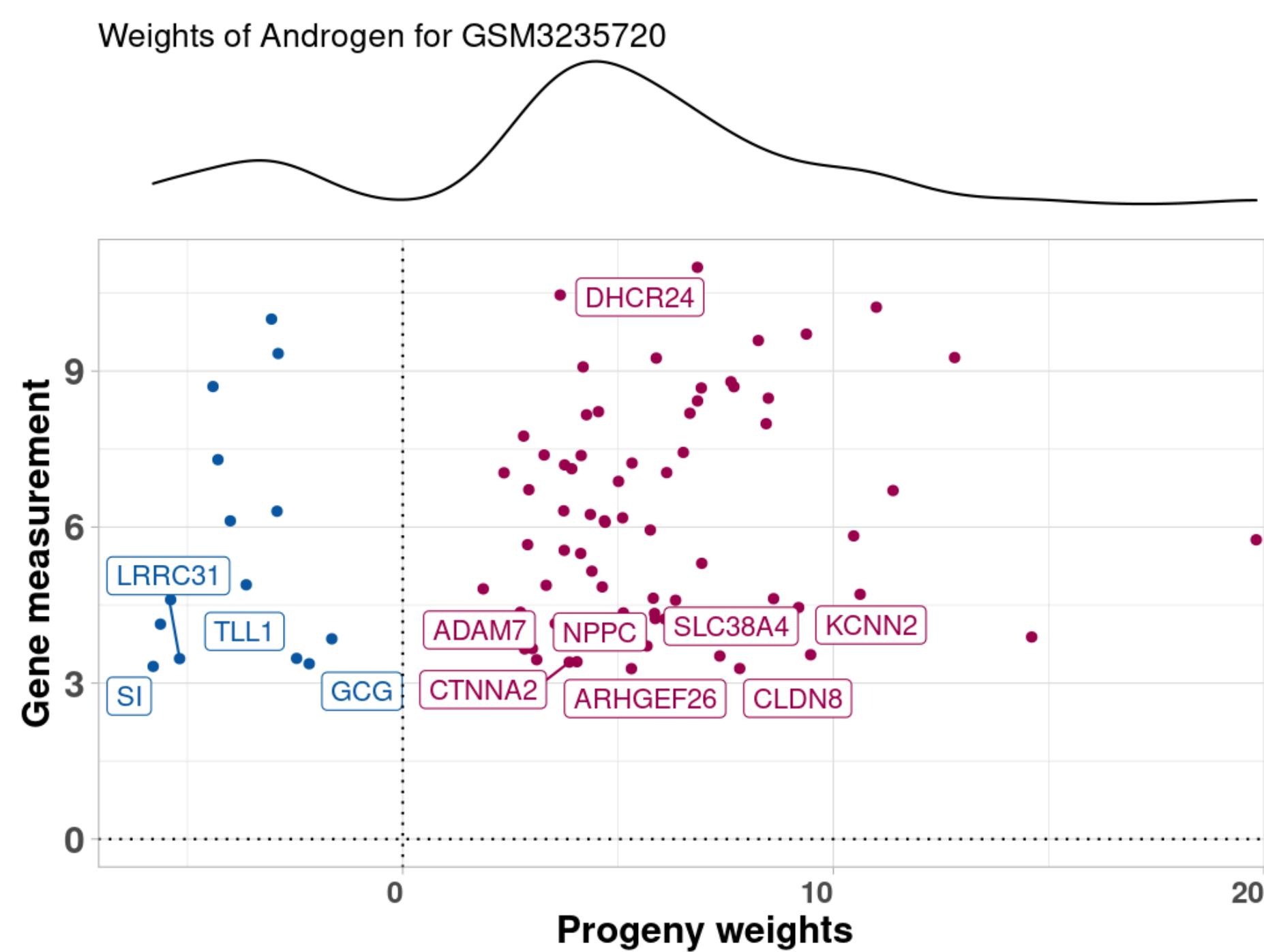
PROGENy: Pathway RespOnsive GENes



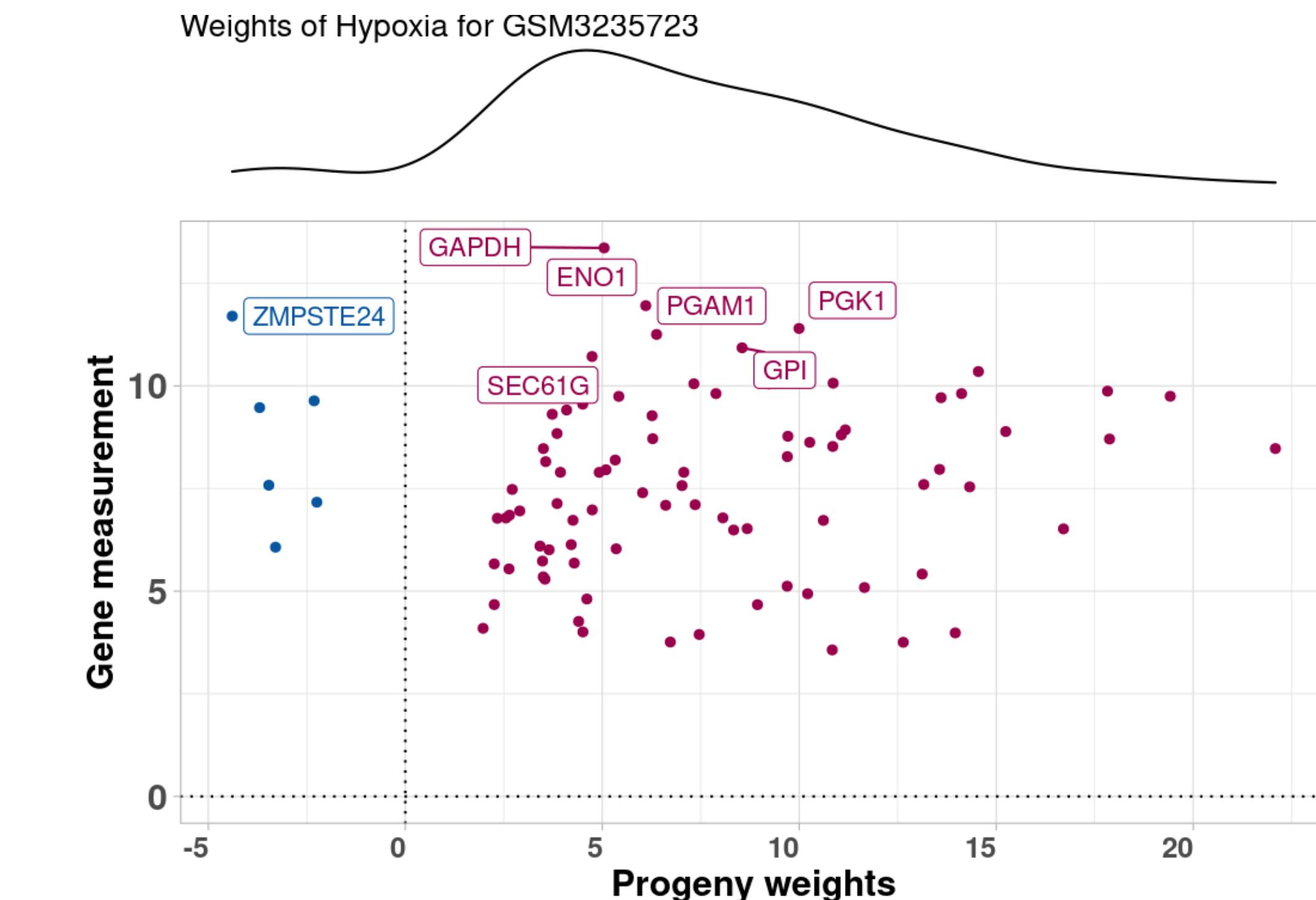


User interface using FUNKI: <https://saezlab.shinyapps.io/funki/>

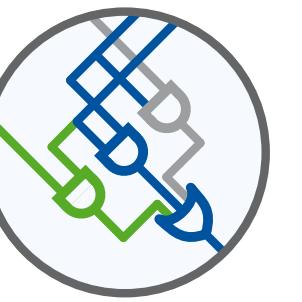
EKVX Basal



EKVX Drug

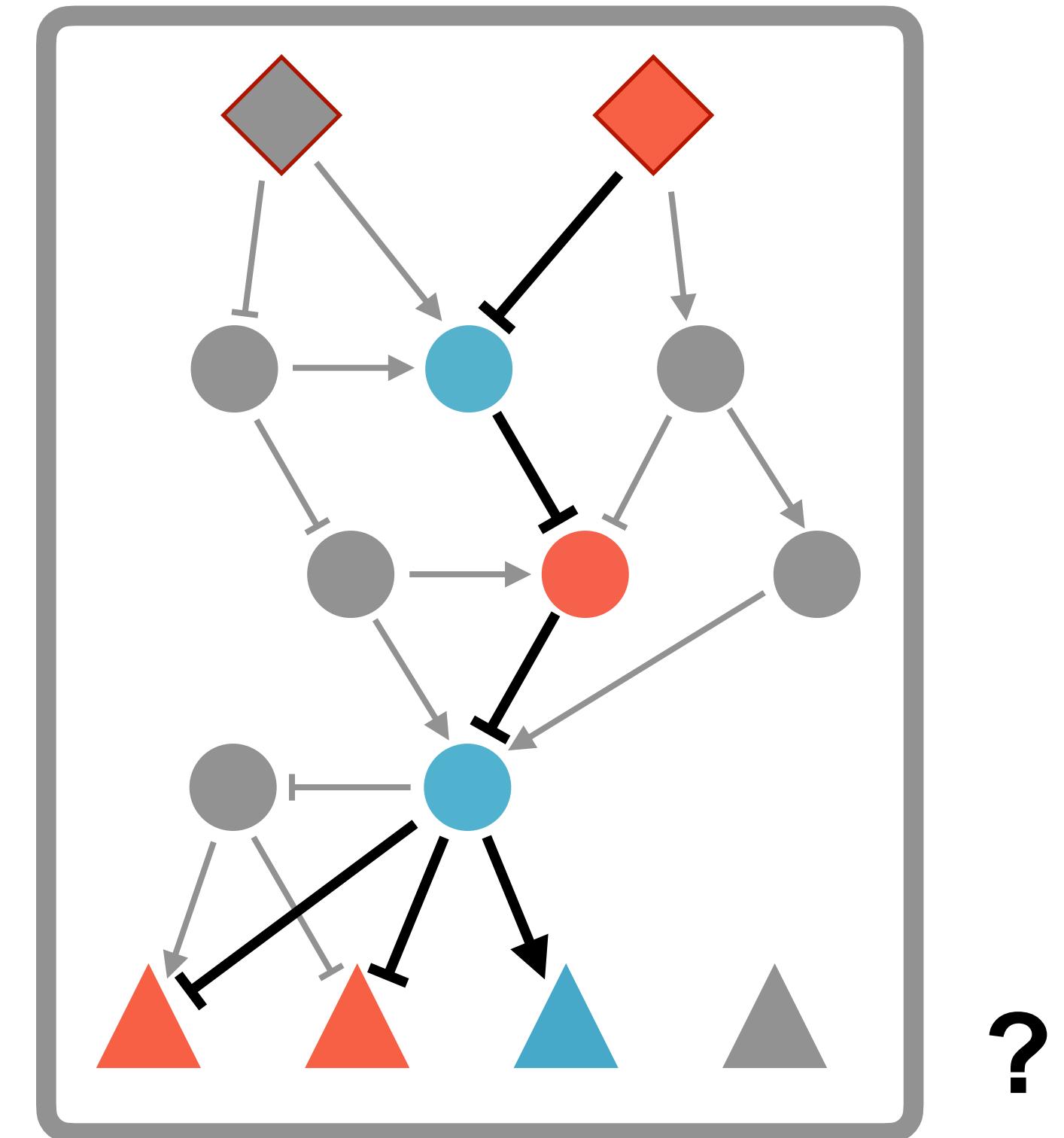
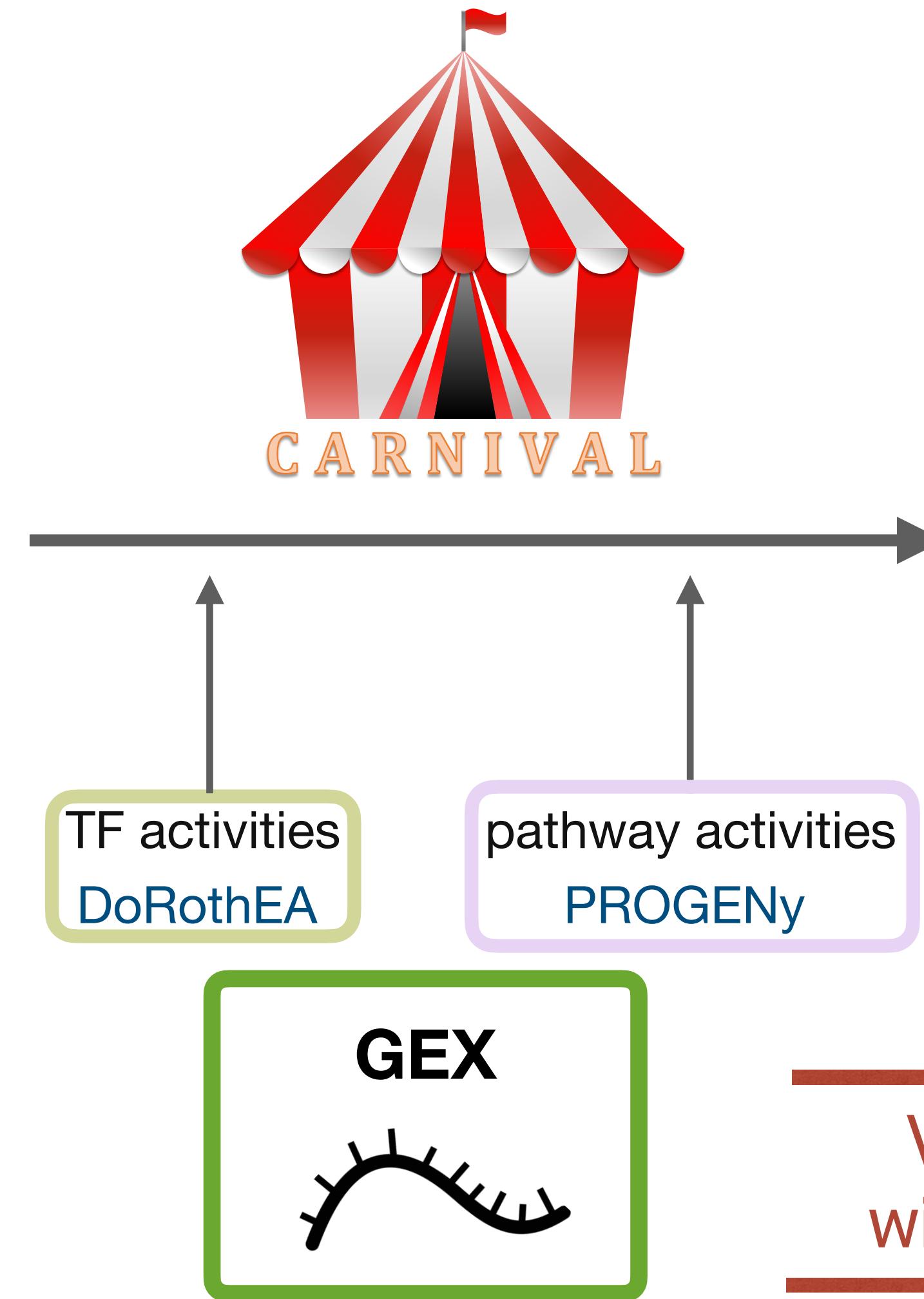
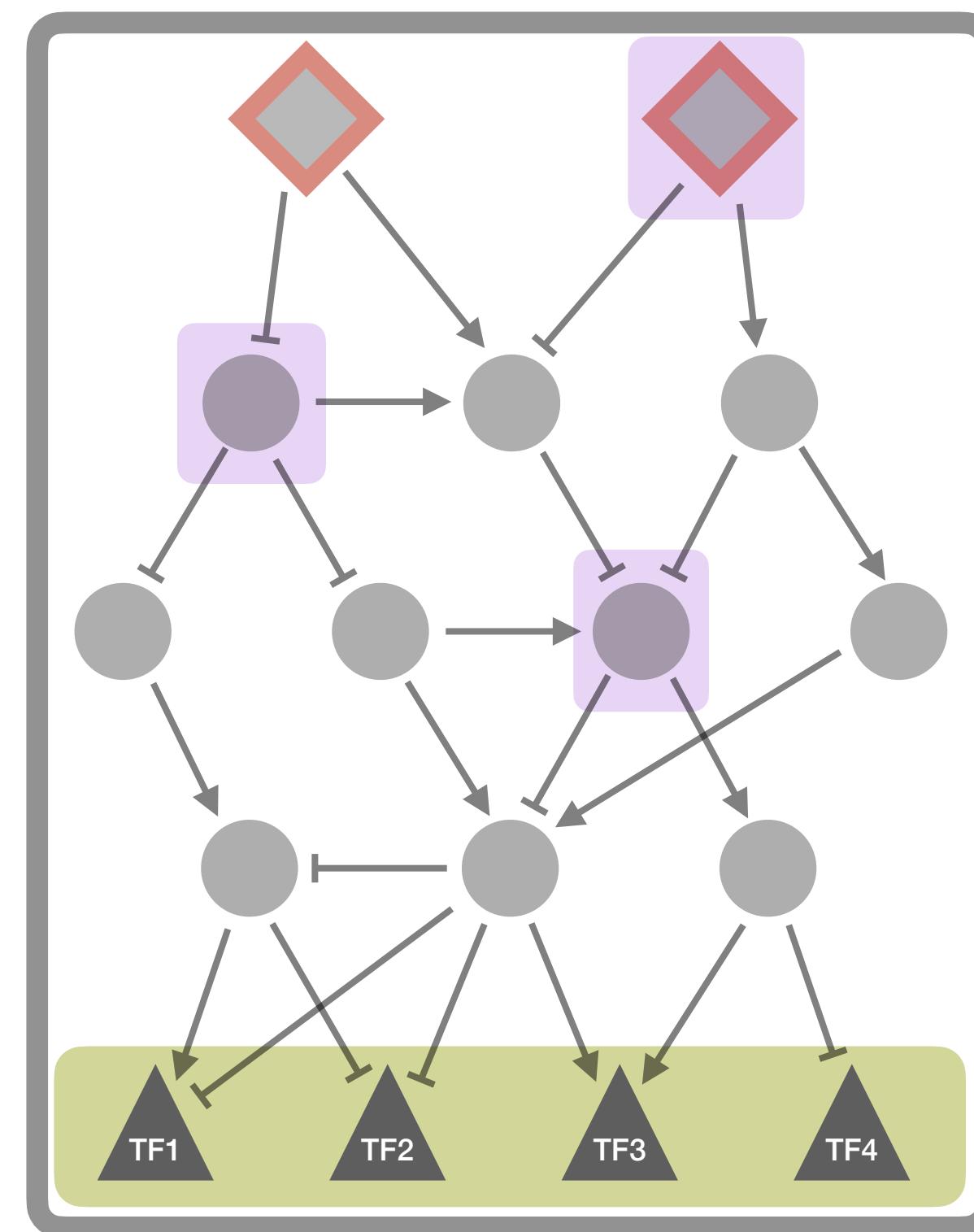


From footprints to networks





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



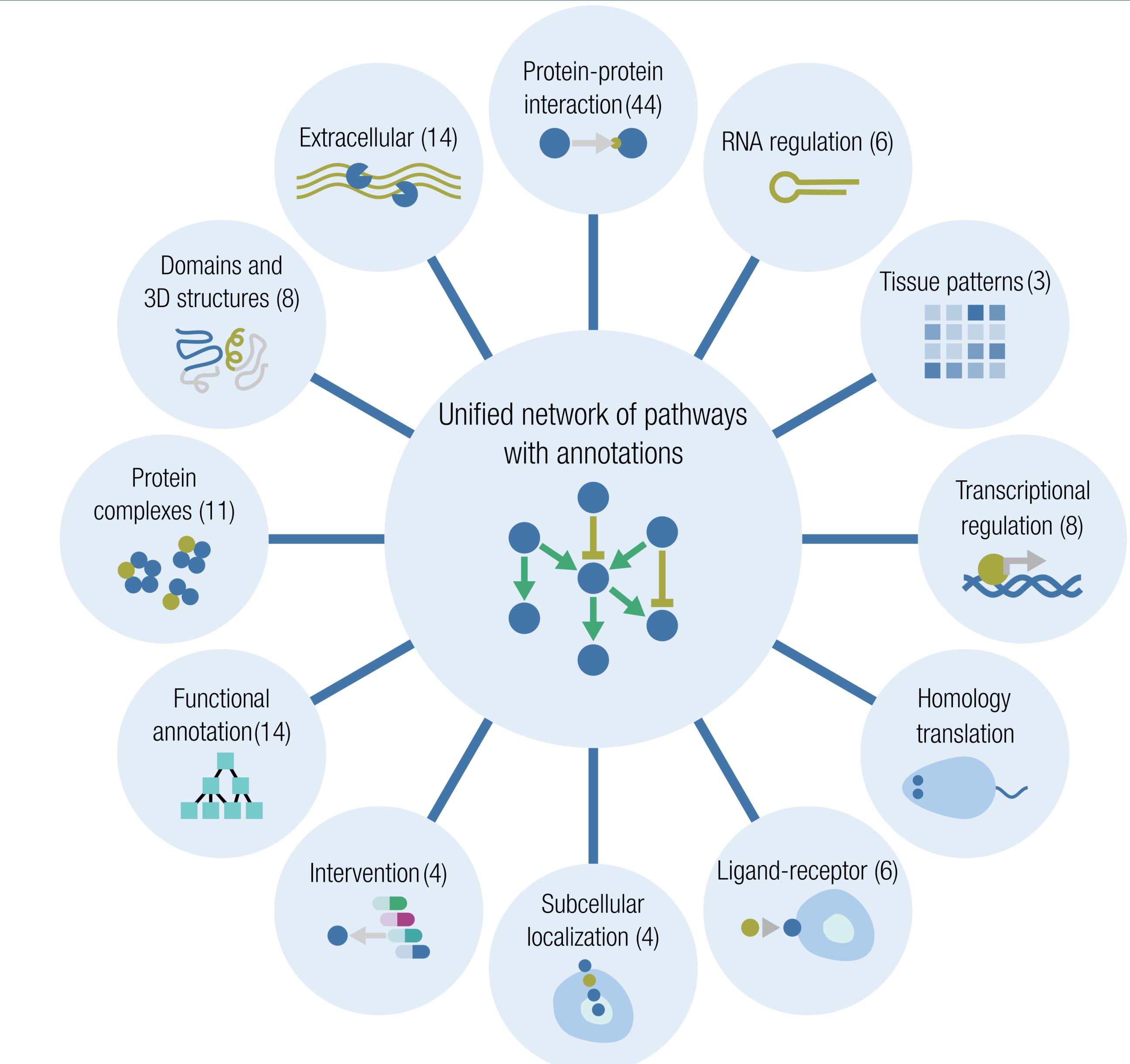
www.omnipathdb.org



python™

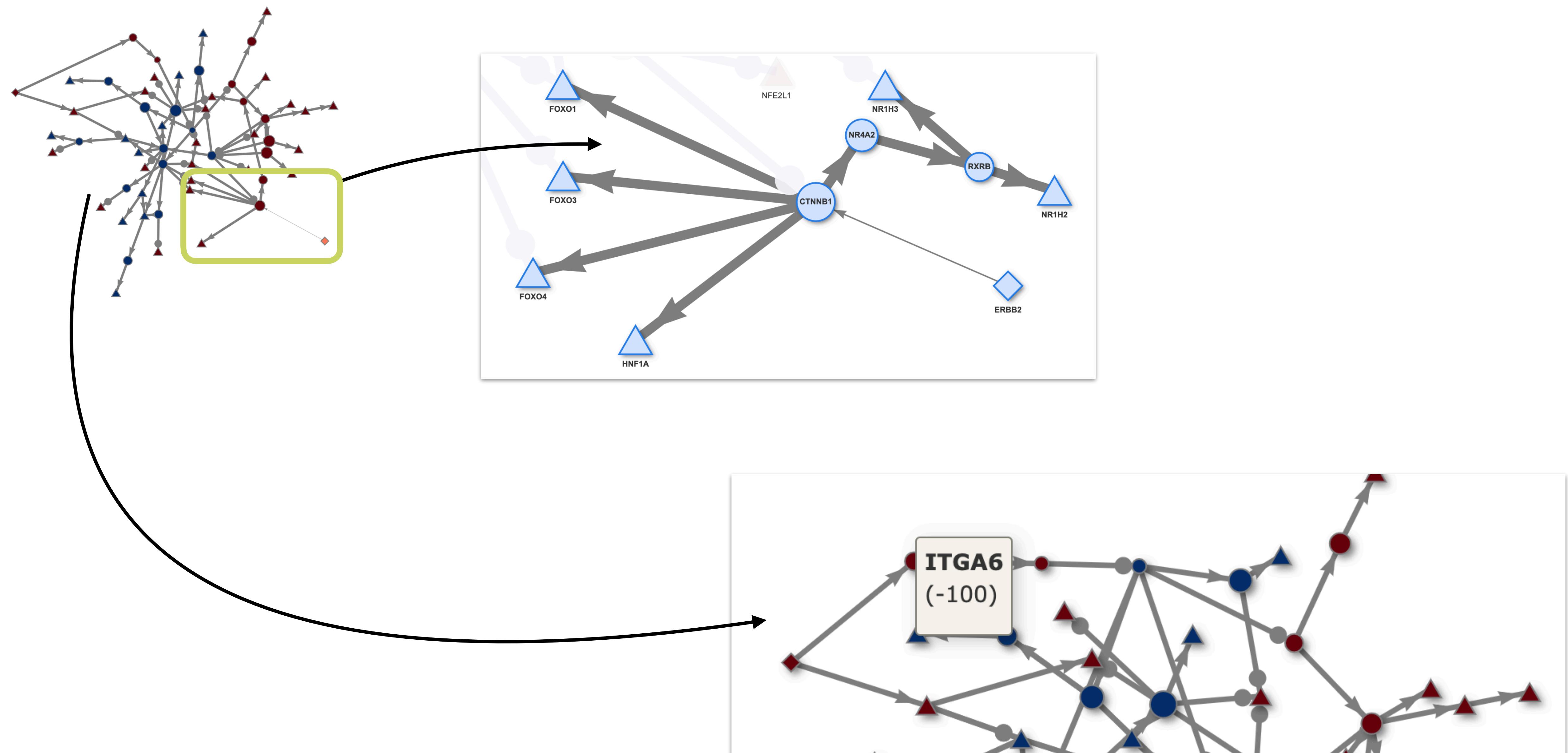


omnipathdb



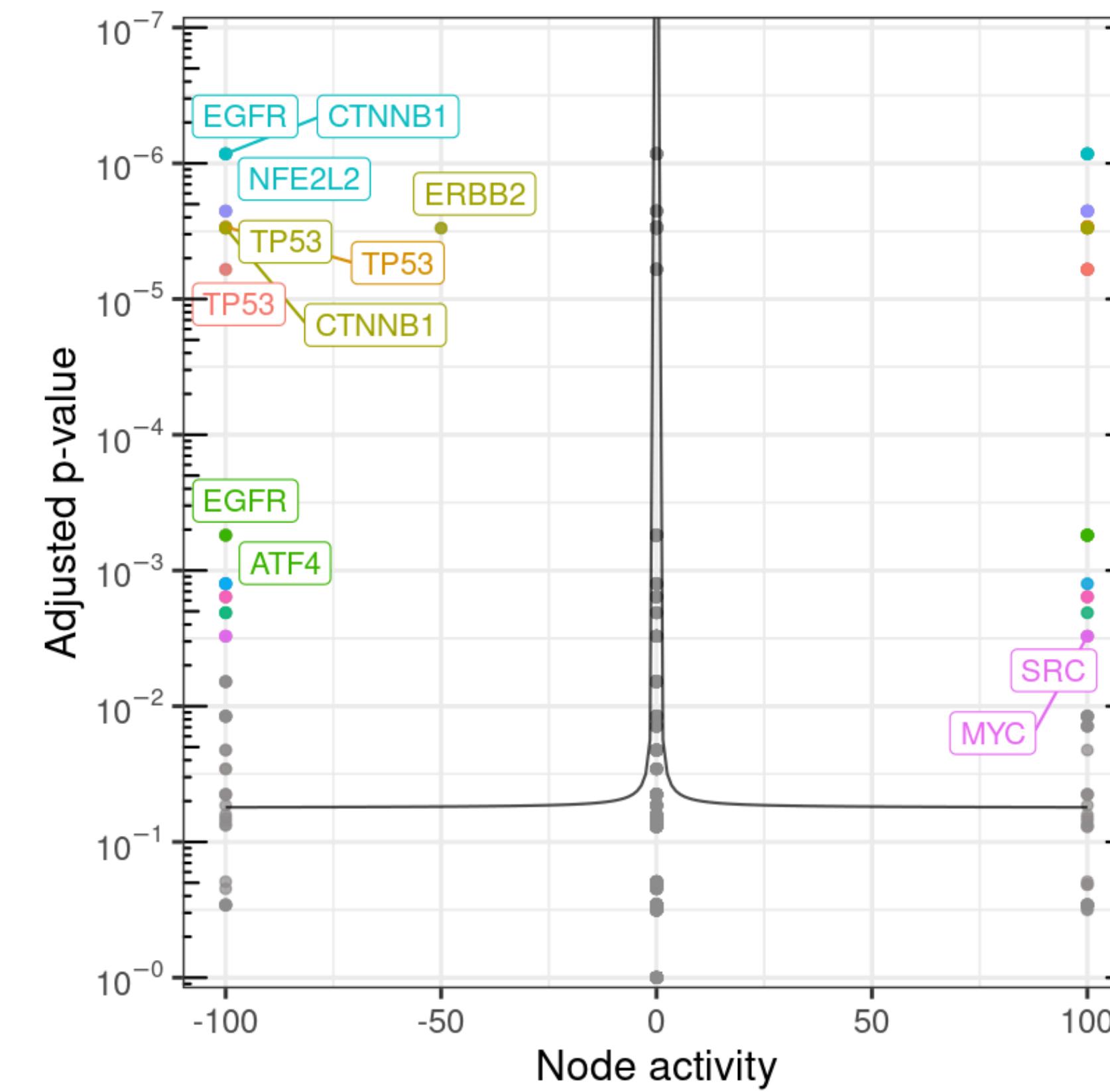
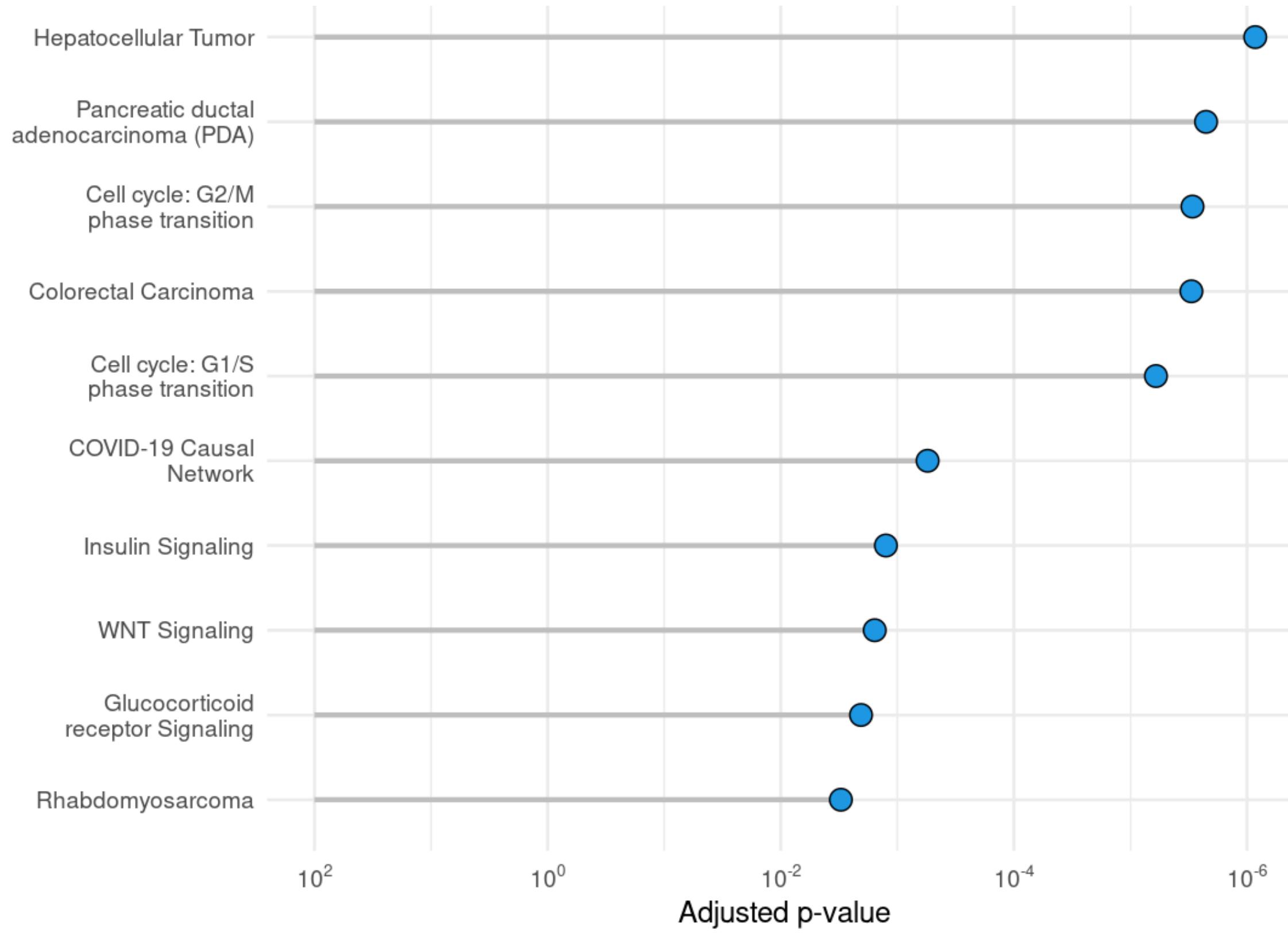


What can CARNIVAL tell us?





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