

Generation of mechanistic hypotheses linking signalling and metabolism in cancer with COSMOS

Aurelien Dugourd - Saezlab



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Introduction



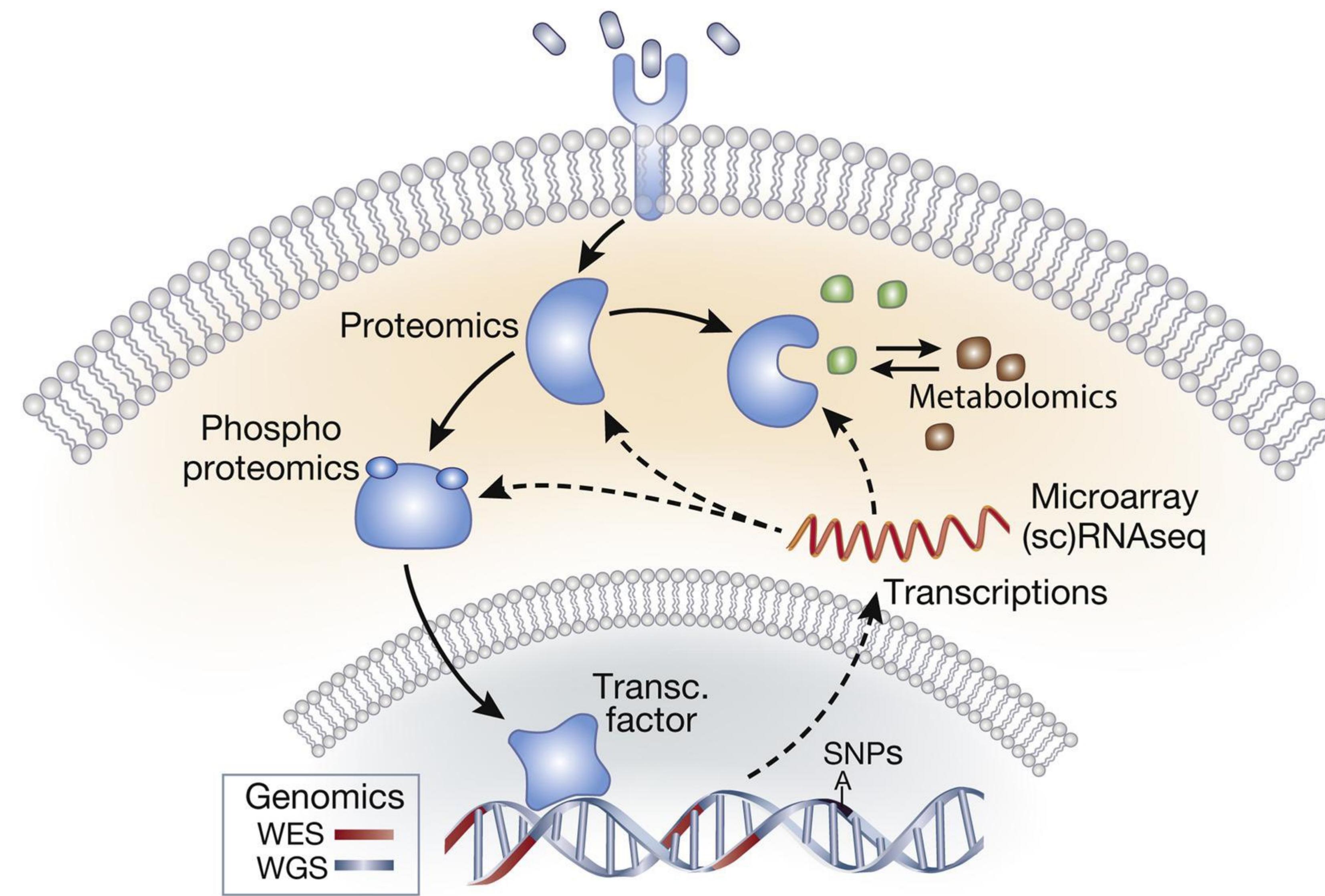
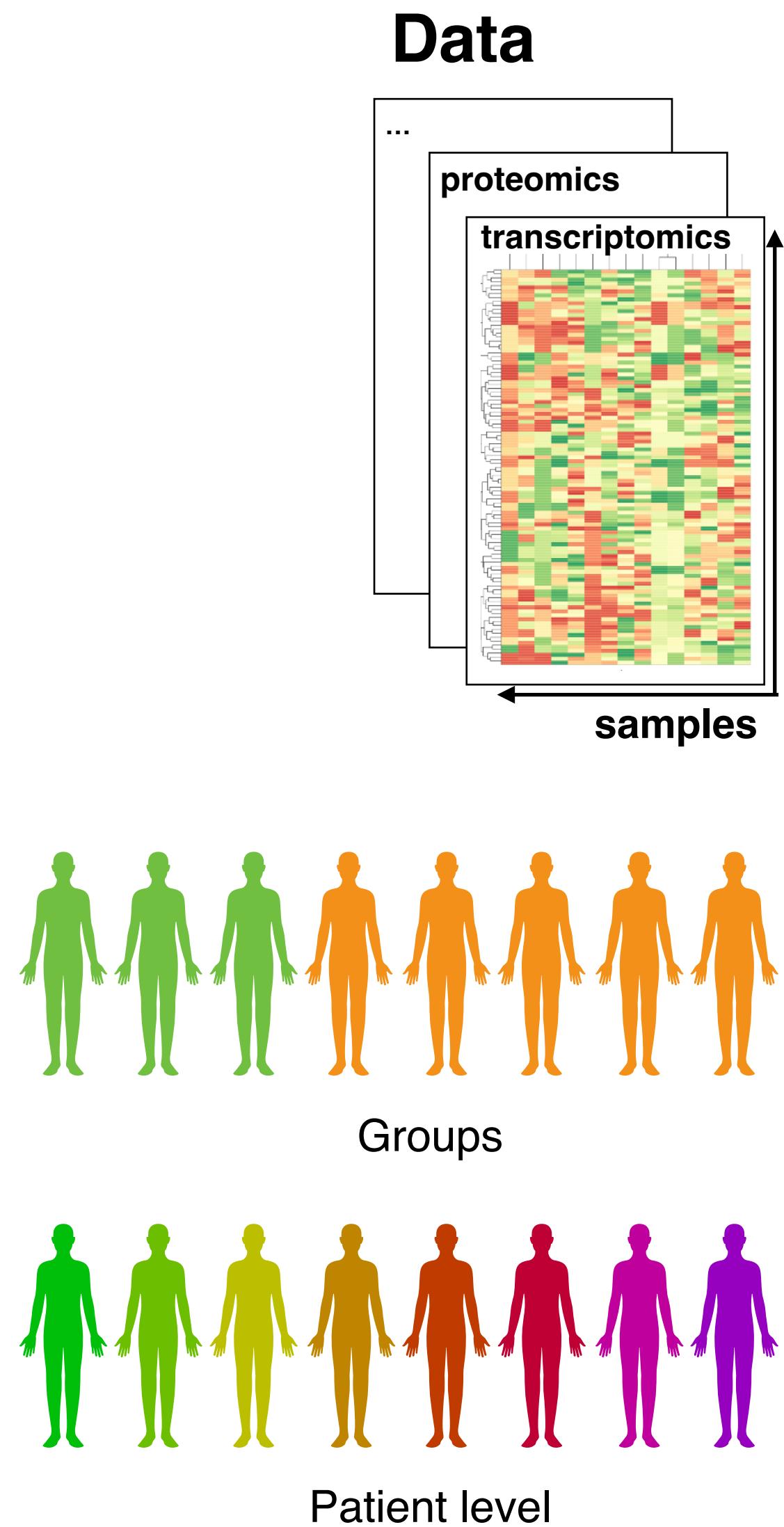
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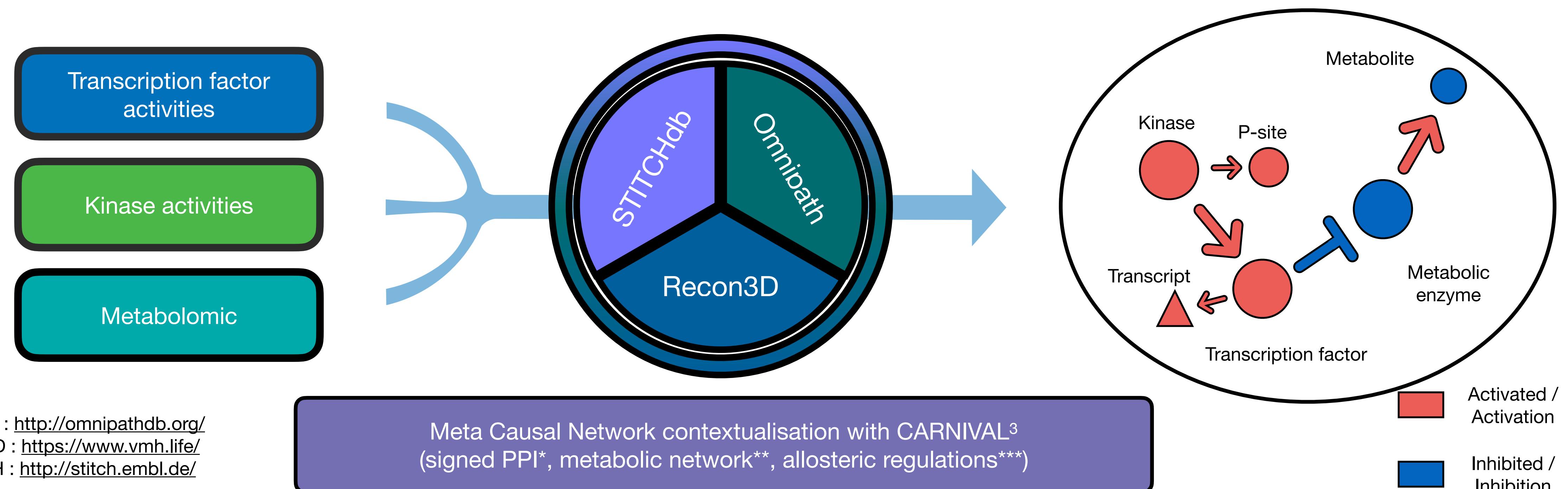


Different omics technologies to measure molecular processes





COSMOS: Multi-omic integration pipeline



Systematic generation of testable hypothesis to connect signalling and metabolism with the NCI60 datasets



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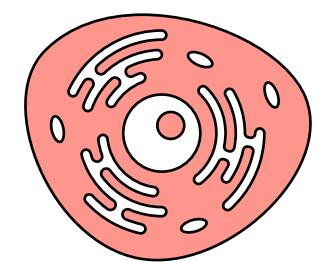
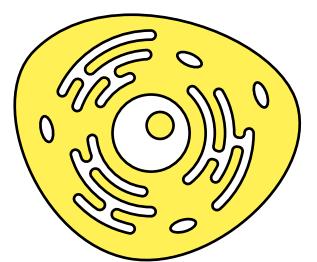
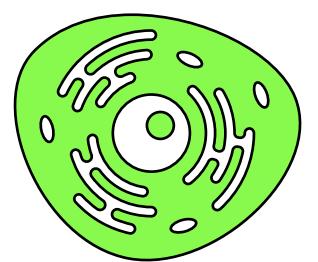
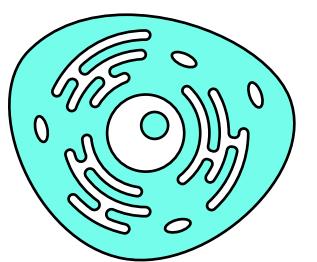
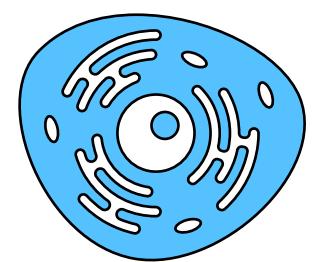
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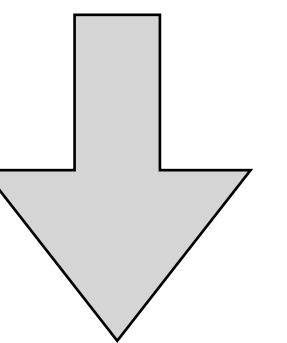
DTP Developmental Therapeutics Program

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Services Available Directly From DTP	<p>Discovery & Development Services</p> <p>Last Updated: 08/11/20</p> <h3>NCI-60 Human Tumor Cell Lines Screen</h3> <h4>Introduction</h4> <p>The NCI-60 Human Tumor Cell Lines Screen has served the global cancer research community for >20 years. The screen was implemented in fully operational form in 1990 and utilizes 60 different human tumor cell lines to identify and characterize novel compounds with growth inhibition or killing of tumor cell lines. It is designed to screen up to 3,000 small molecules (synthetic or purified natural products) per year for potential anticancer activity. The operation of this screen utilizes 60 different human tumor cell lines, representing leukemia, melanoma and cancers of the lung, colon, brain, ovary, breast, prostate, and kidney cancers.</p> <p>This screen is unique in that the complexity of a 60 cell line dose response produced by a given compound results in a biological response pattern which can be utilized in pattern recognition algorithms (COMPARE). Using these algorithms, it is possible to assign a putative mechanism of action to a test compound, or to determine that the response pattern is unique and not similar to that of any of the standard prototype compounds included in the NCI database. In addition, following characterization of various cellular molecular targets in the 60 cell lines, it may be possible to select compounds most likely to interact with a specific molecular target.</p> <p>This screen also allows prioritization of selected agents for further evaluation by NCI in collaboration with the submitter. The screening service is offered at no cost to submitters, other than shipping costs, although requests are reviewed and only those conforming to defined guidelines are selected for screening. There is a limit of 10 structure submission requests per 30 day period.</p> <ul style="list-style-type: none">• Compound submission for NCI-60 screening• Data Retrieval and Testing Decisions• List of NCI-60 human tumor cell lines• Screening methodology (One-dose and Five-dose Assay)• Sample handling and Preparation• Database of Screening Results• Molecular characterization of NCI-60• Publications						
Services Available Through NExT	Stepping Stones	DTP Branches and Offices	Office of the Associate Director	Preclinical Therapeutics Grants Branch	Molecular Pharmacology Branch	Biological Testing Branch	Toxicology and Pharmacology Branch
Drug Synthesis and Chemistry Branch	Natural Products Branch	Biological Resources Branch	Pharmaceutical Resources Branch	Information Technology Branch	ImmunoOncology Branch		

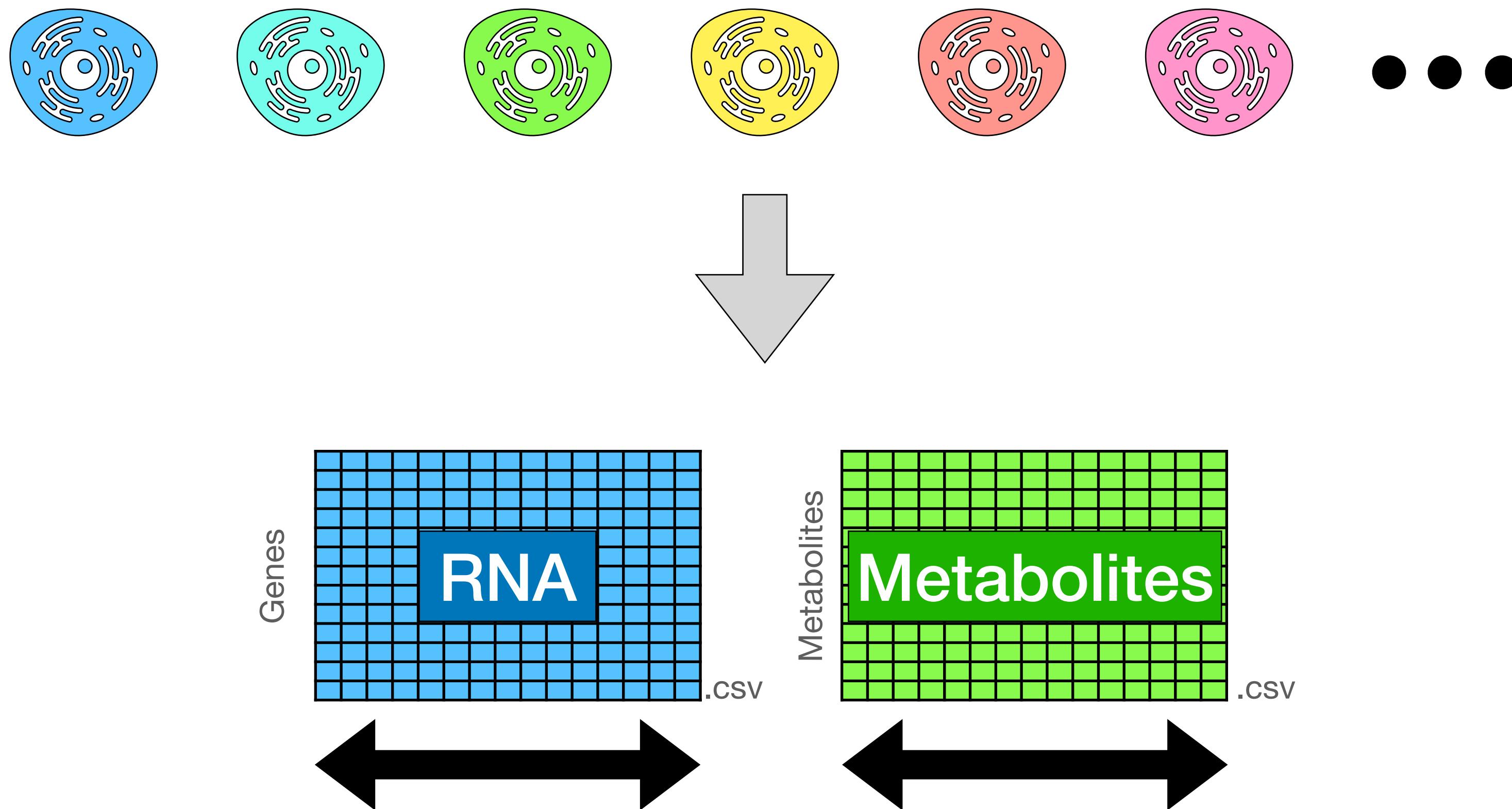
NCI60 cancer cell lines



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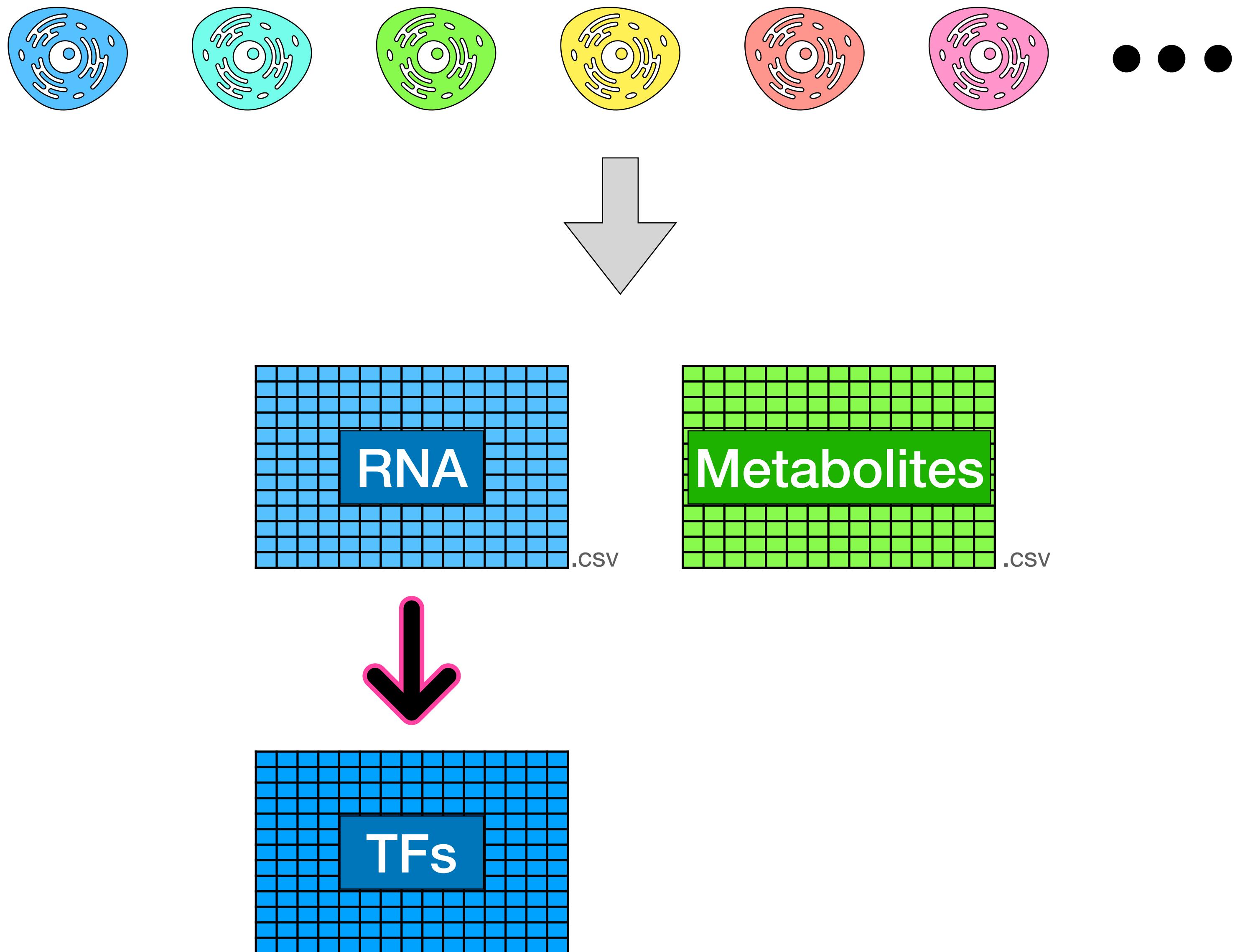


NCI60 cancer cell lines

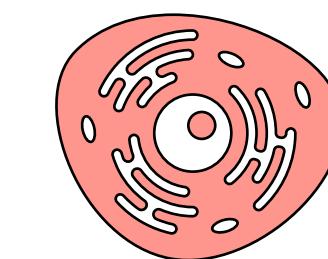
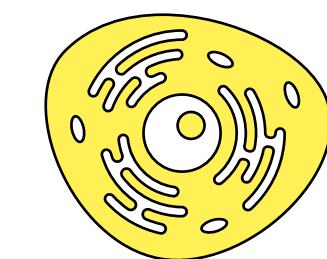
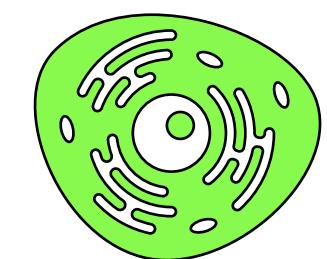
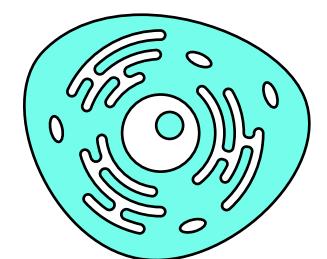
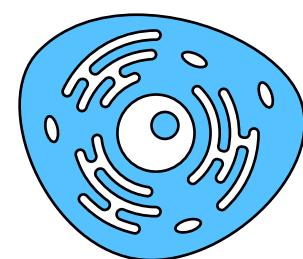


Values are z-transformed across cell lines - each value represent how high or low a gene/metab is in a cell line compared to the other cell lines

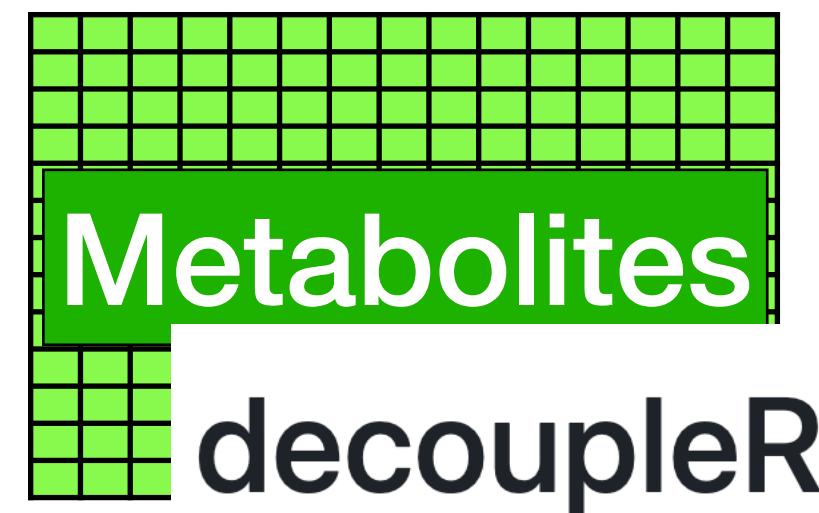
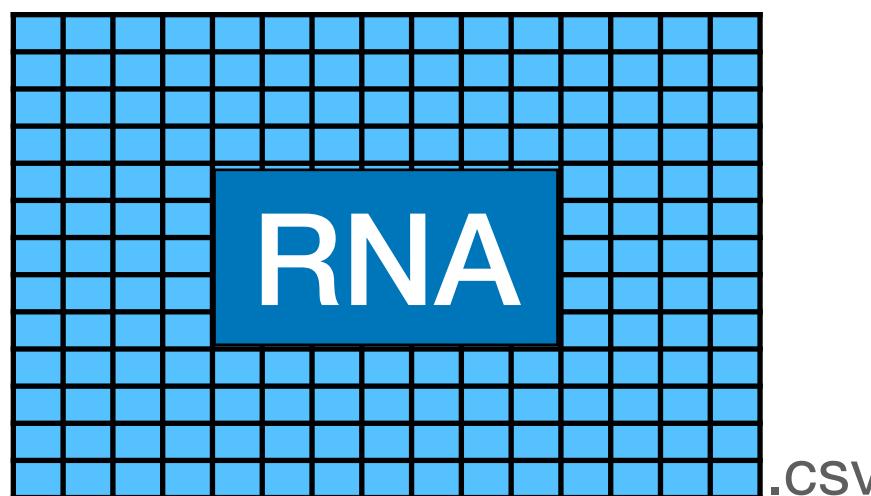
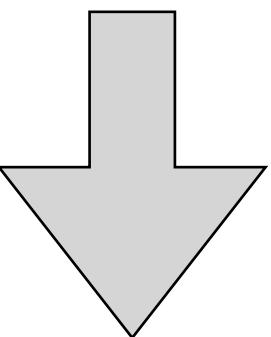
NCI60 cancer cell lines



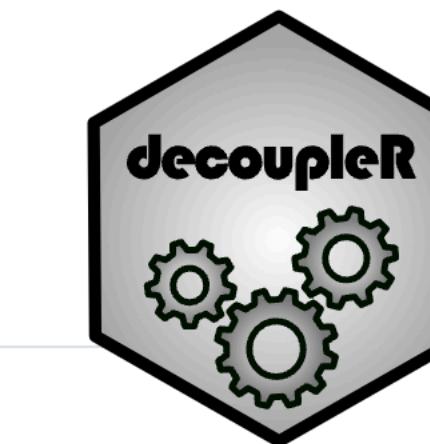
NCI60 cancer cell lines



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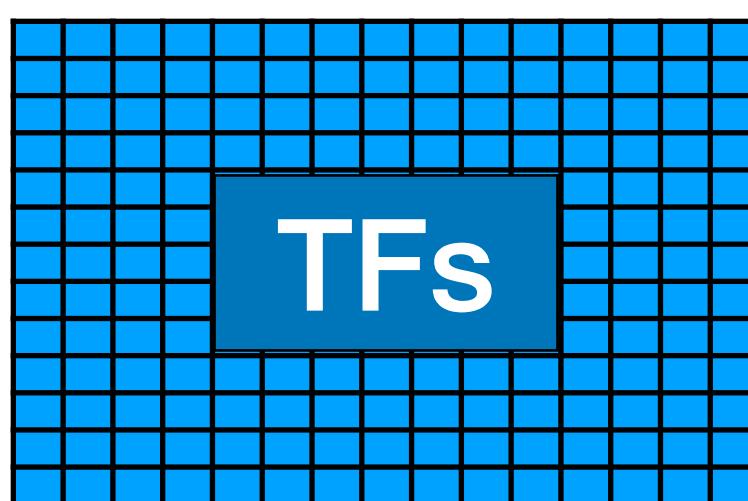


<https://github.com/saezlab/decoupleR>

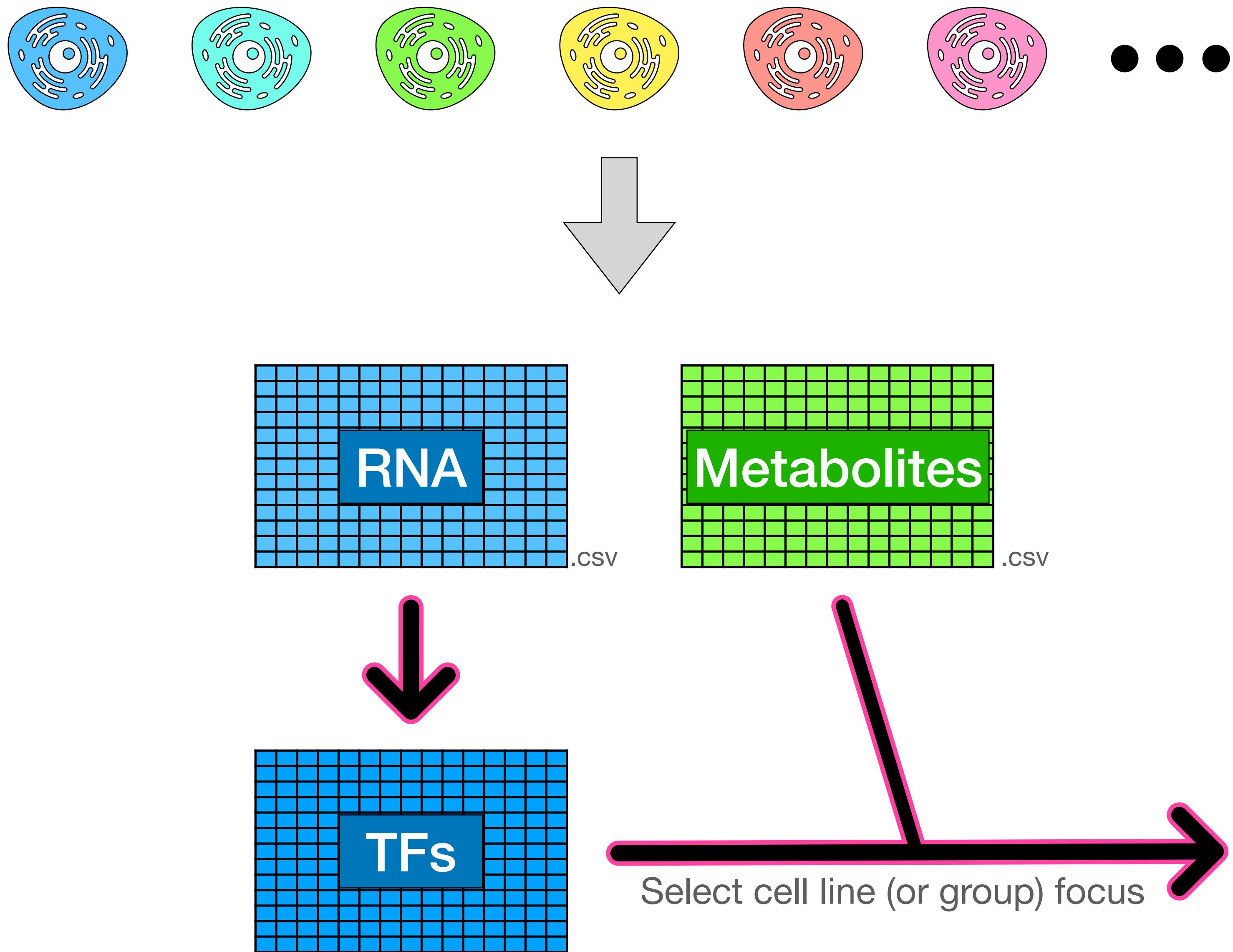


Overview

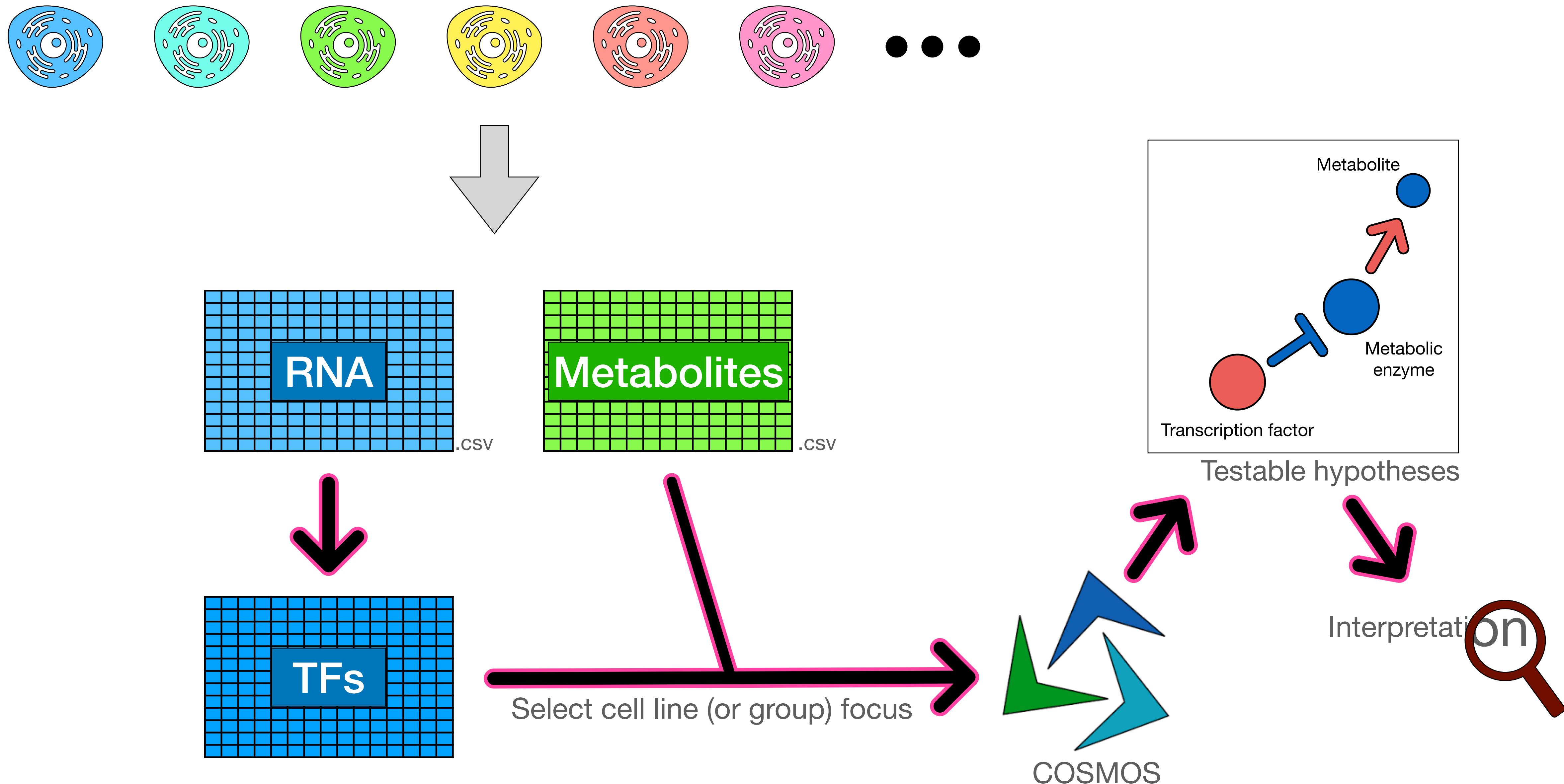
There are many methods that allow us to extract biological activities from omics data. `decoupleR` is a Bioconductor package containing different statistical methods to extract biological signatures from prior knowledge within a unified framework. Additionally, it incorporates methods that take into account the sign and weight of network interactions. `decoupleR` can be used with any omic, as long as its features can be linked to a biological process based on prior knowledge. For example, in transcriptomics gene sets regulated by a transcription factor, or in phospho-proteomics phosphosites that are targeted by a kinase.



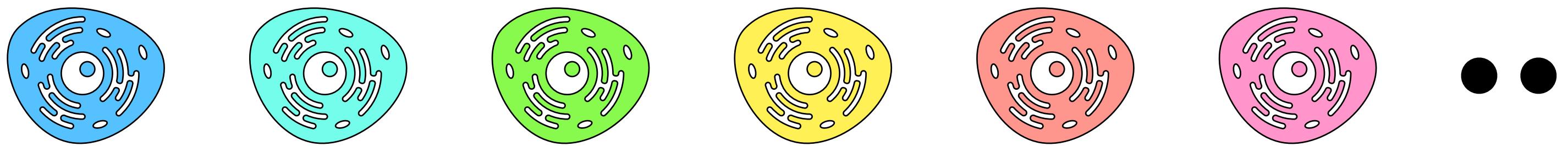
NCI60 cancer cell lines



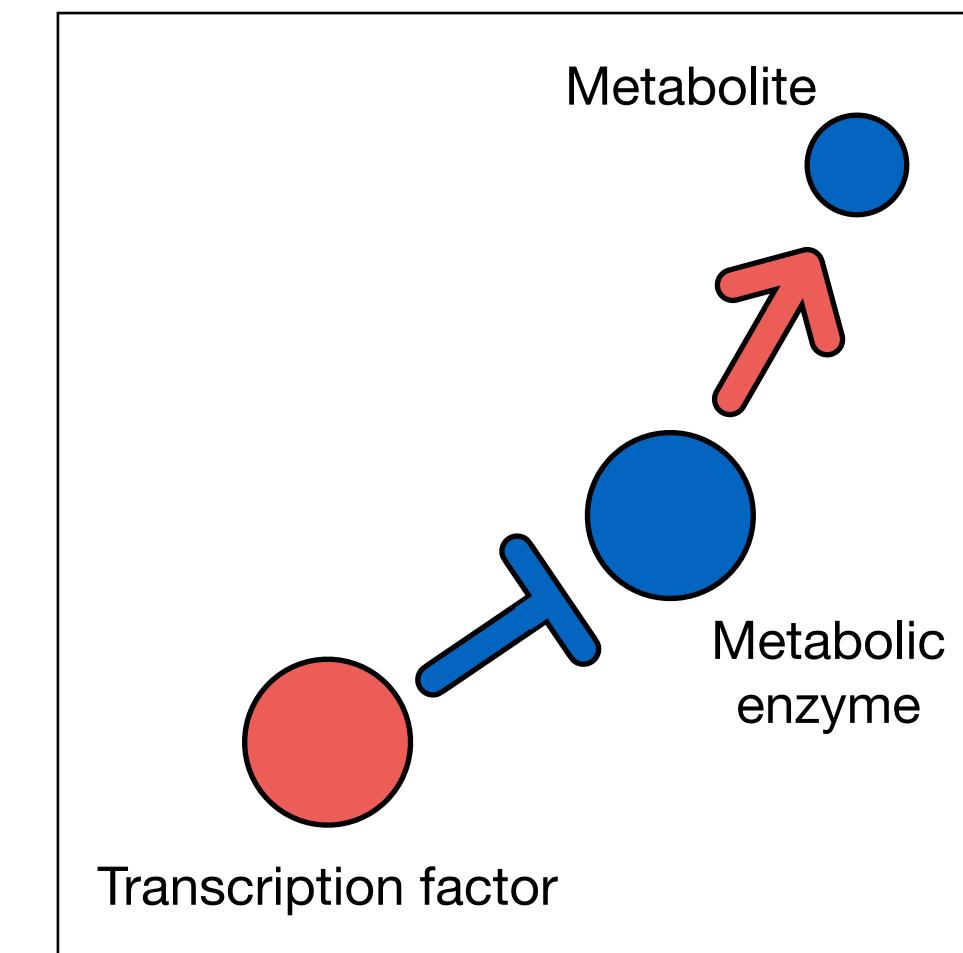
NCI60 cancer cell lines



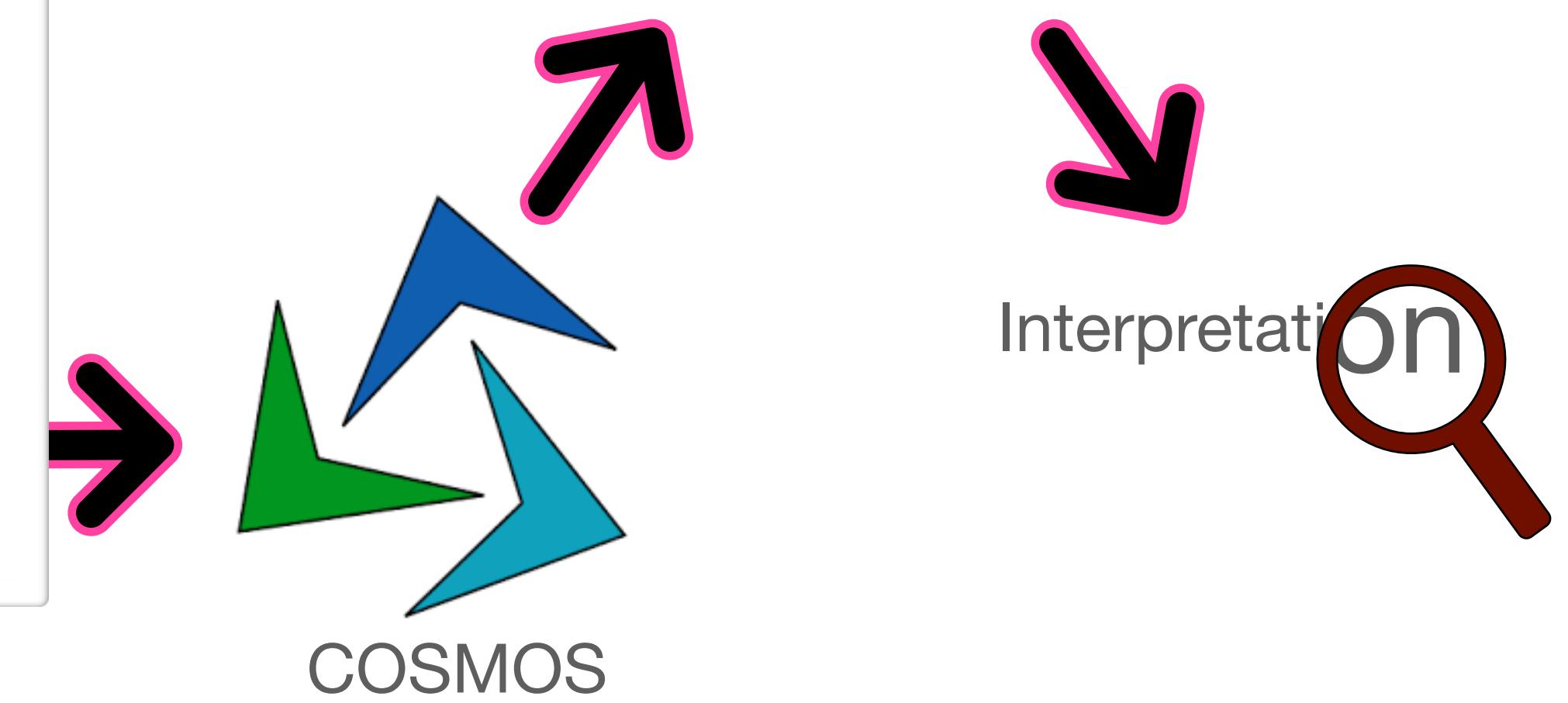
NCI60 cancer cell lines



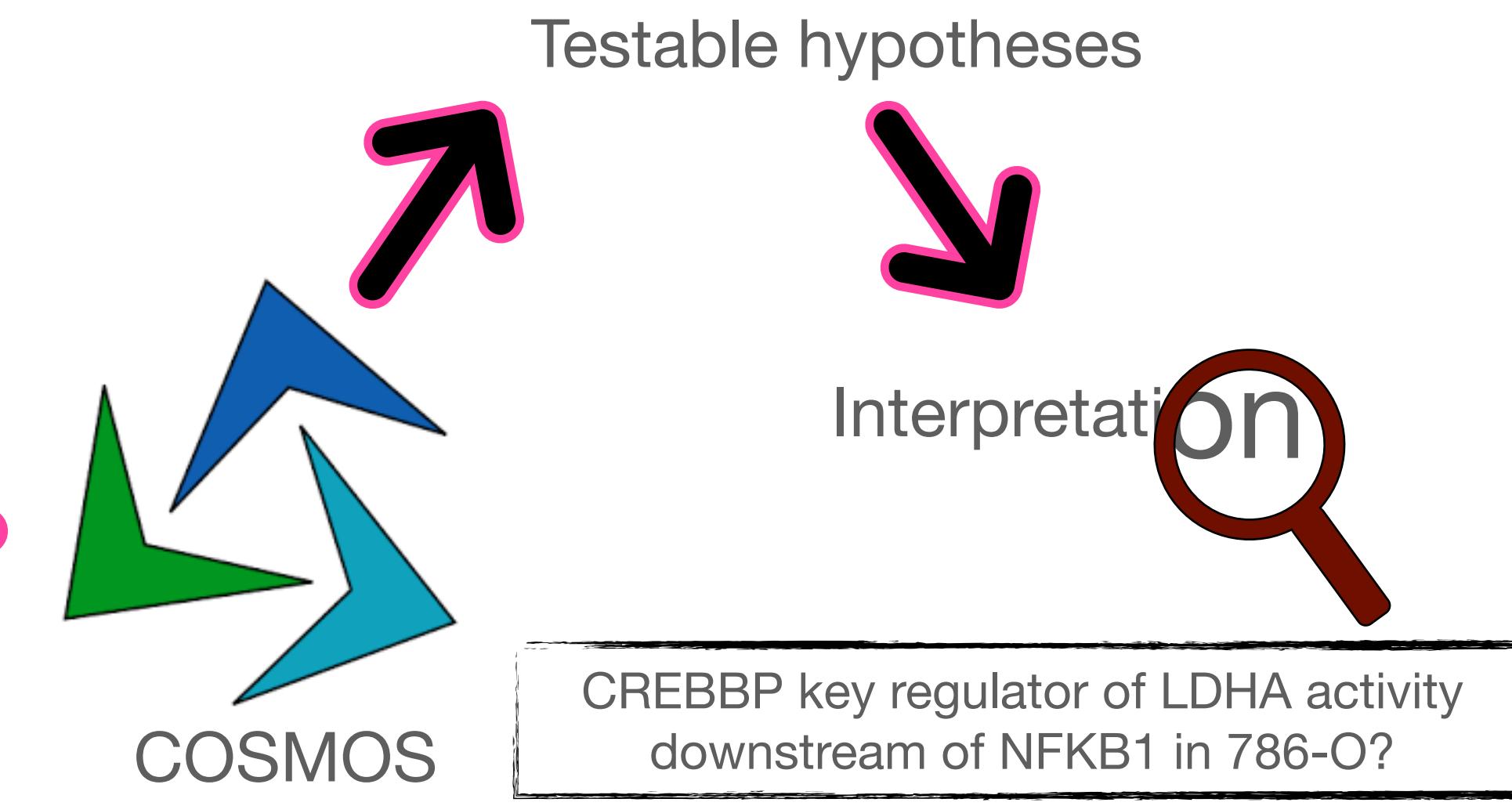
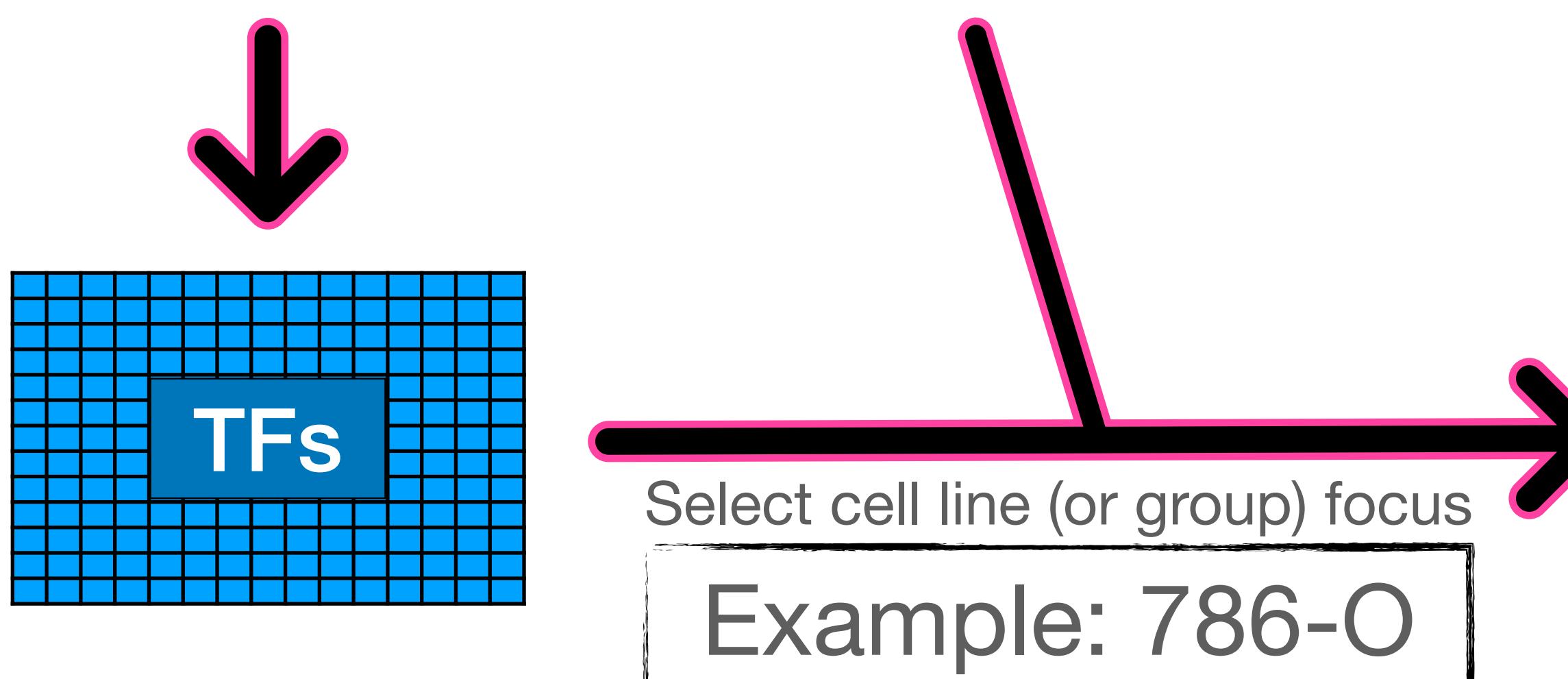
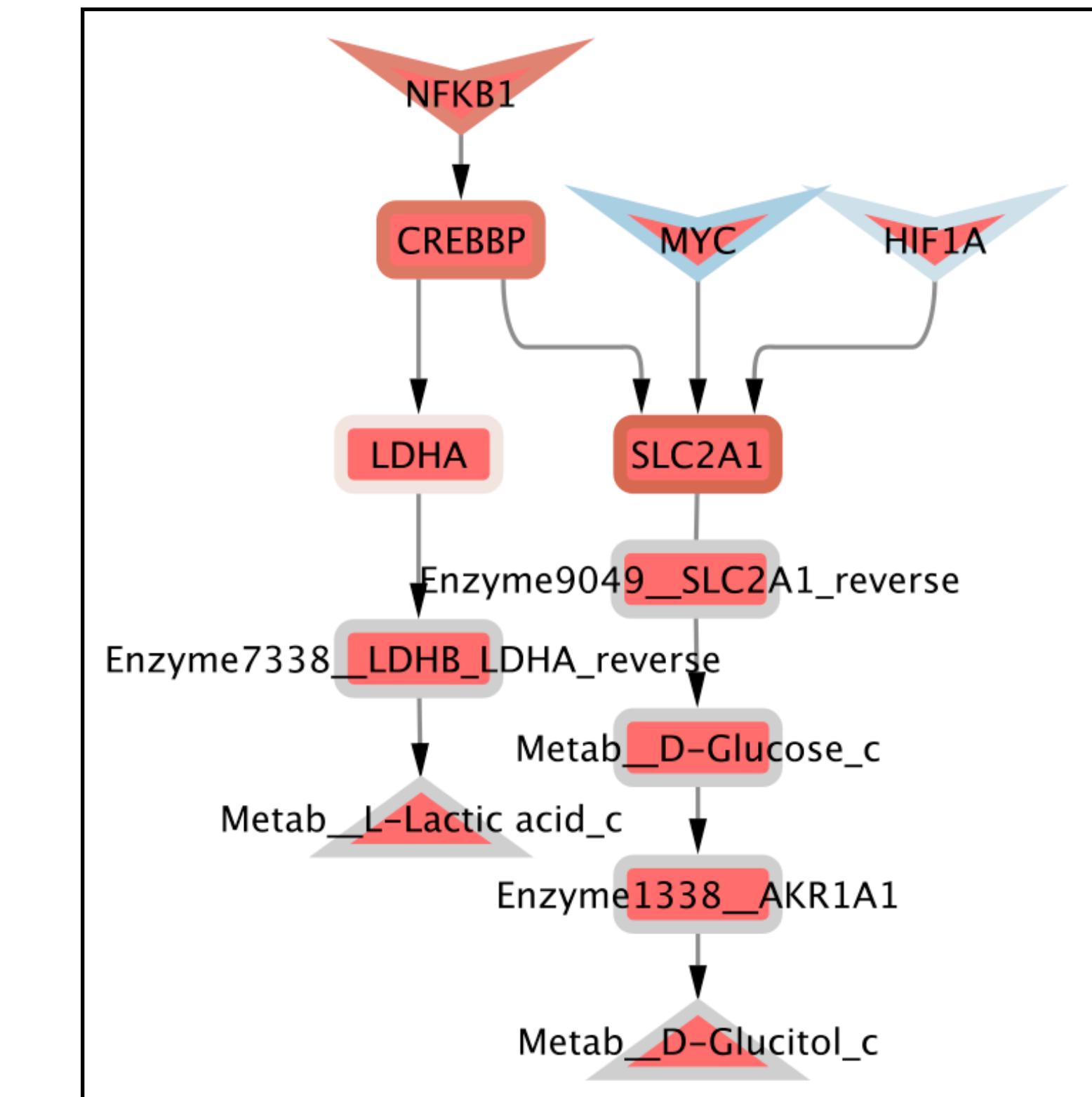
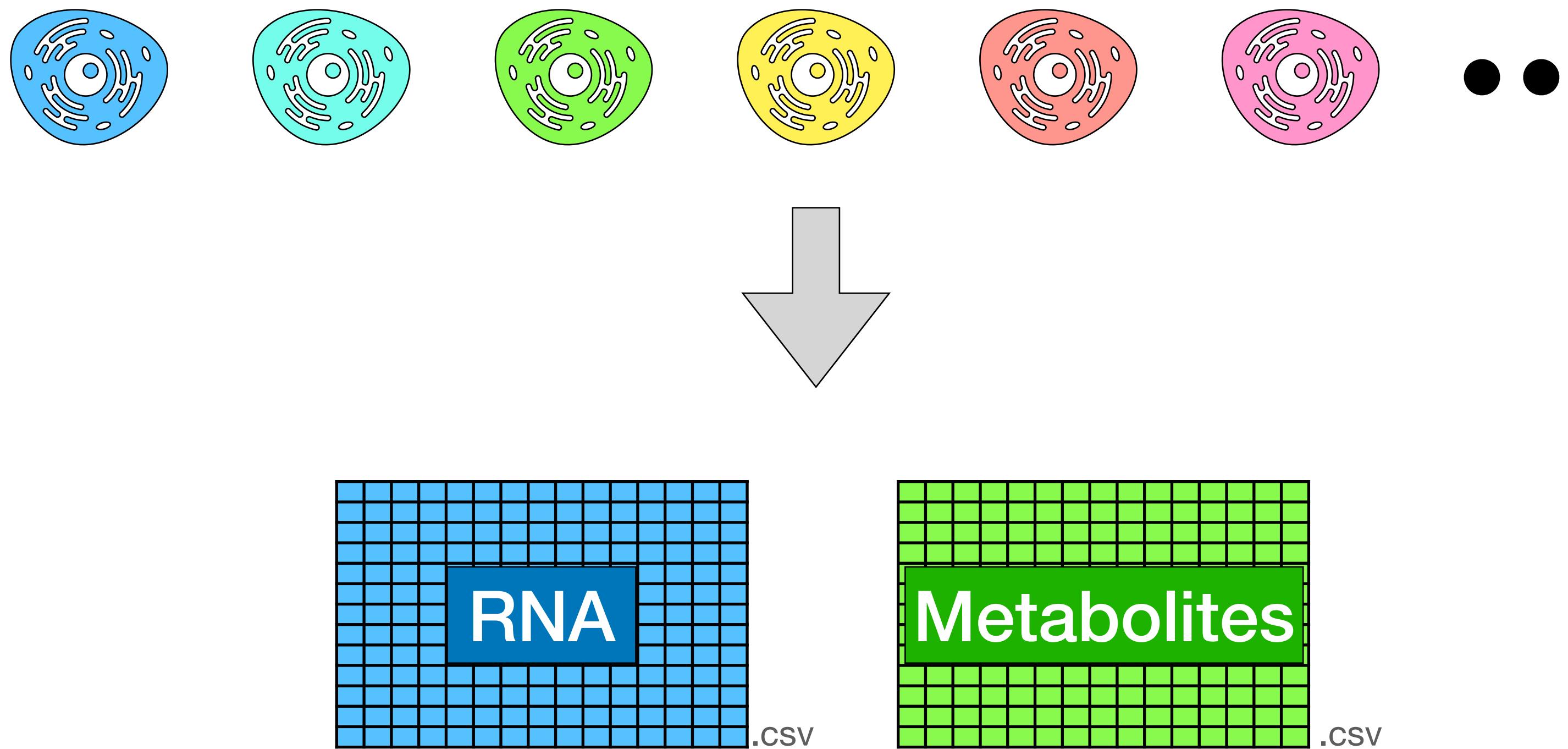
```
1 library(cosmosR)
2 library(readr)
3 library(dplyr)
4
5 data("meta_network")
6 load("data/cosmos/cosmos_inputs.RData")
7
8 names(cosmos_inputs)
9
10 cell_line <- "786-0"
11
12 sig_input <- cosmos_inputs[[cell_line]]$TF_scores
13 metab_input <- cosmos_inputs[[cell_line]]$metabolomic
14 RNA_input <- cosmos_inputs[[cell_line]]$RNA
```



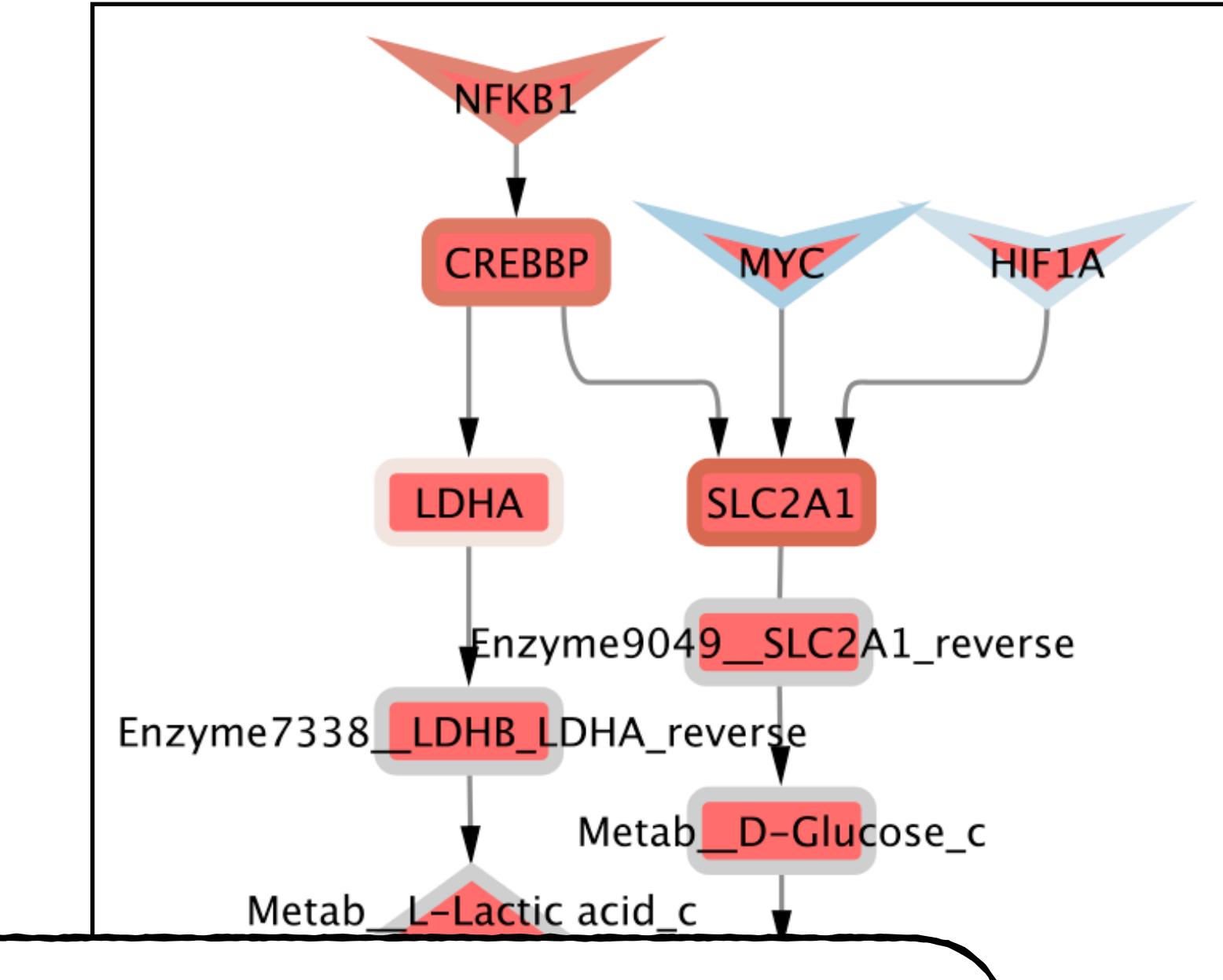
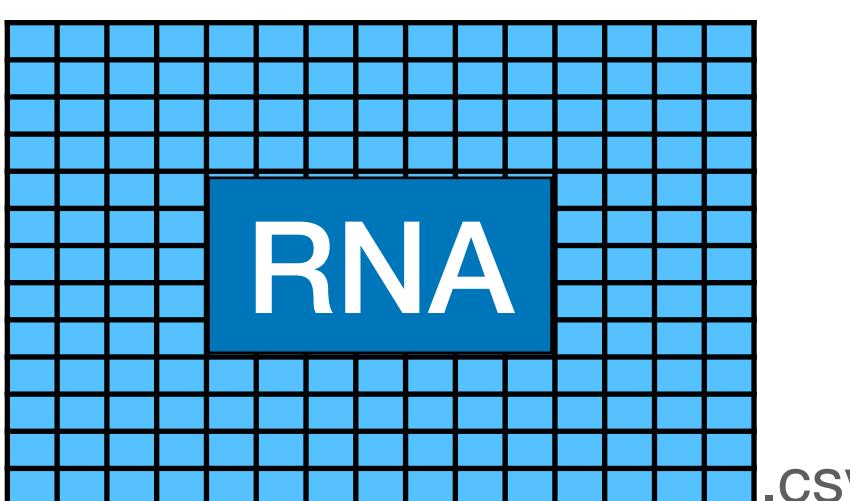
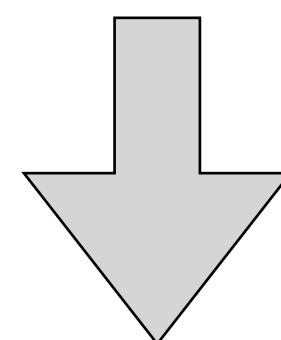
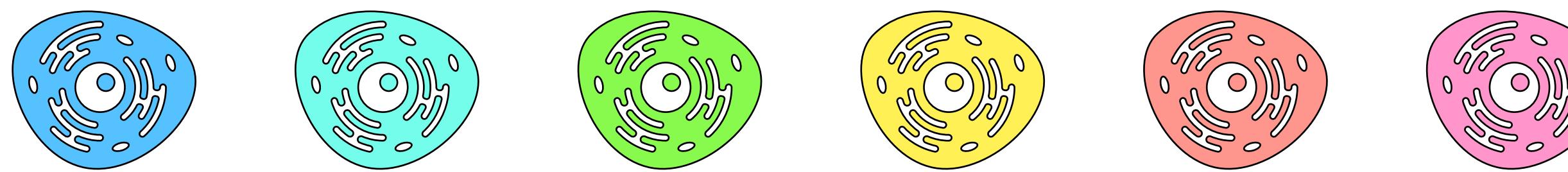
Testable hypotheses



NCI60 cancer cell lines

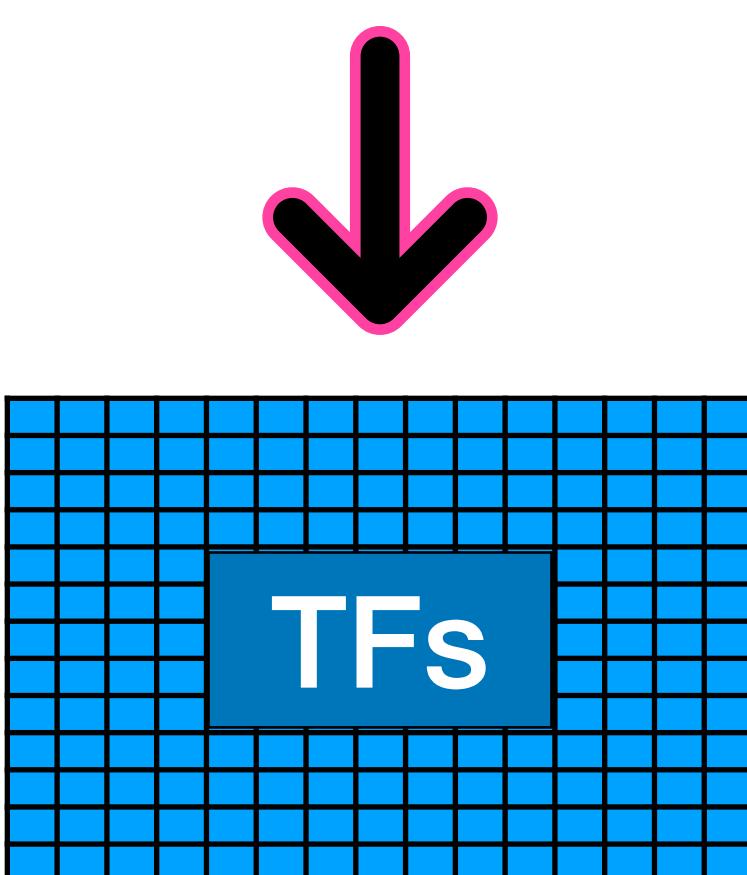


NCI60 cancer cell lines



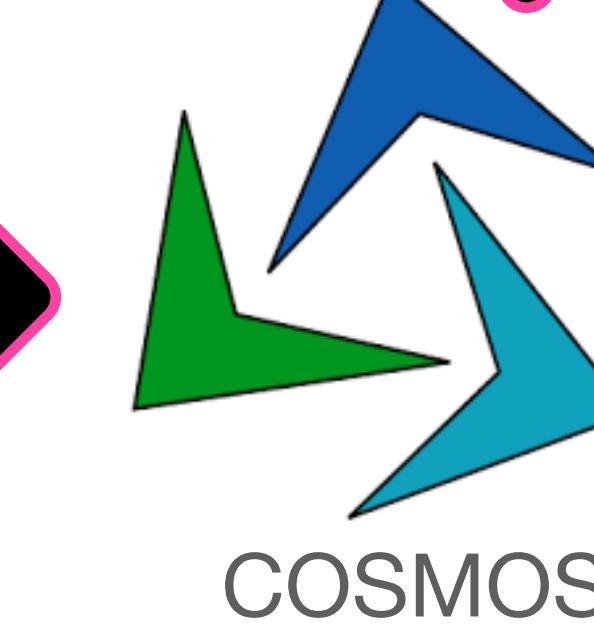
Test different cell lines, network depth, sig->metab / metab->sig

Testable hypotheses



Select cell line (or group) focus

Example: 786-O



CREBBP key regulator of LDHA activity downstream of NFKB1 in 786-O?

Formatted data and example script available in GitHub

saezlab / NCI60_cosmos Public

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main 1 branch 0 tags Go to file Add file Code About

adugourd	Update README.md	cdc8ac6	yesterday	5 commits
data	first commit			yesterday
results	first commit			yesterday
scripts	first commit			yesterday
support	first commit			yesterday
.gitignore	first commit			yesterday
EBI practical.key	first commit			yesterday
LICENSE	Create LICENSE			yesterday
NCI60.Rproj	first commit			yesterday
README.md	Update README.md			yesterday

Readme GPL-3.0 License 0 stars 3 watching 0 forks

Formatting NCI60 data into cosmos ready inputs and generation of testable hypothesis connecting cell-line specific TF and metabolic deregulations.

Releases No releases published Create a new release

Packages No packages published Publish your first package

Languages R 100.0%

README.md

NCI60_cosmos

Formatting NCI60 data into cosmos ready inputs and generation of testable hypothesis connecting cell-line specific TF and metabolic deregulations.

data/cosmso/cosmos_inputs.RData contains cosmos-ready inputs for each NCI60 cell lines.

scripts/run_cosmos.R to run cosmos analysis on a specific NCI60 cell line

! Can only be run with the new_PKN github branch of cosmosR at the present time. !

Can only be run with the new_PKN github branch of cosmosR at the present time.

Cell line specific cell lines can be run on a specific NCI60 cell line.

cosmosR can be run with the new_PKN github branch of cosmosR at the present time.

**Day 1 - Discussion, choice of cell line,
expected results...**

**Day 2 - Analysis of first chosen cell line with
COSMOS**

**Day 3 - Analysis of second chosen cell line with COSMOS -
comparison to results of first cell line**

**Day 4 - Interpretation of results and preparation of the
presentation**

Expected outcomes:

- Explore NCI60 cell line omic datasets
- Interpreting TF activities estimated from RNA seq data
- Learning to use cosmos to integrate signalling and metabolic data with prior knowledge
- Generate and interpret testable hypotheses

Softwares:

- CBC solver executable
- R 4.1>
- cosmosR R package
- (readr and dplyr R packages)