Drug repositioning based on *co*-expressed *g*ene-set *e*nrichment *a*nalysis (cogena)

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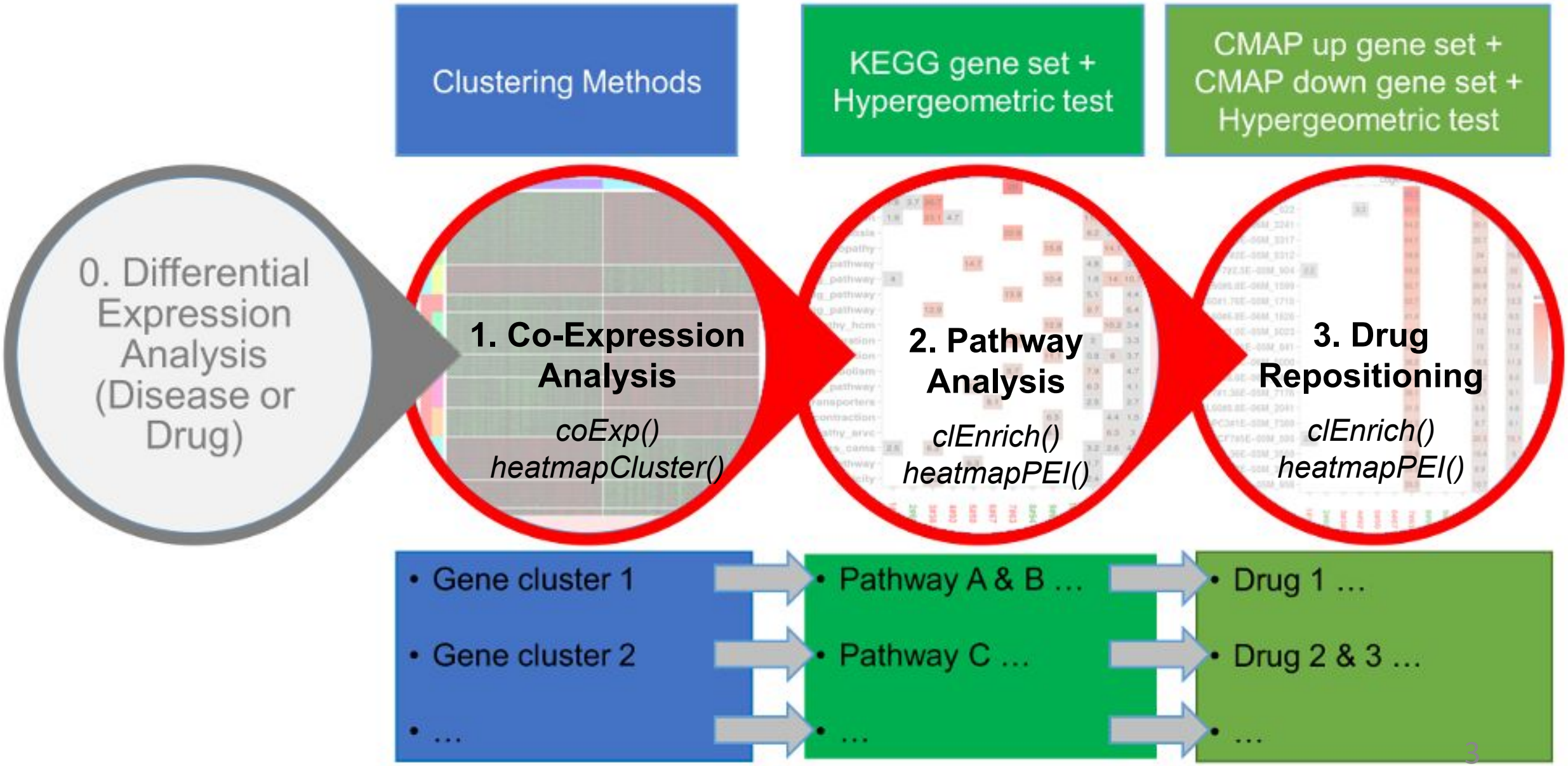
Cogena: a framework for *co*-expressed *g*ene-set *e*nrichment *a*nalysis

- Co-expressed genes may be very biologically relevant
  - Co-expressed genes are more highly connected in pathways
  - May be mechanistically important in disease
  - May represent more robust drug targets

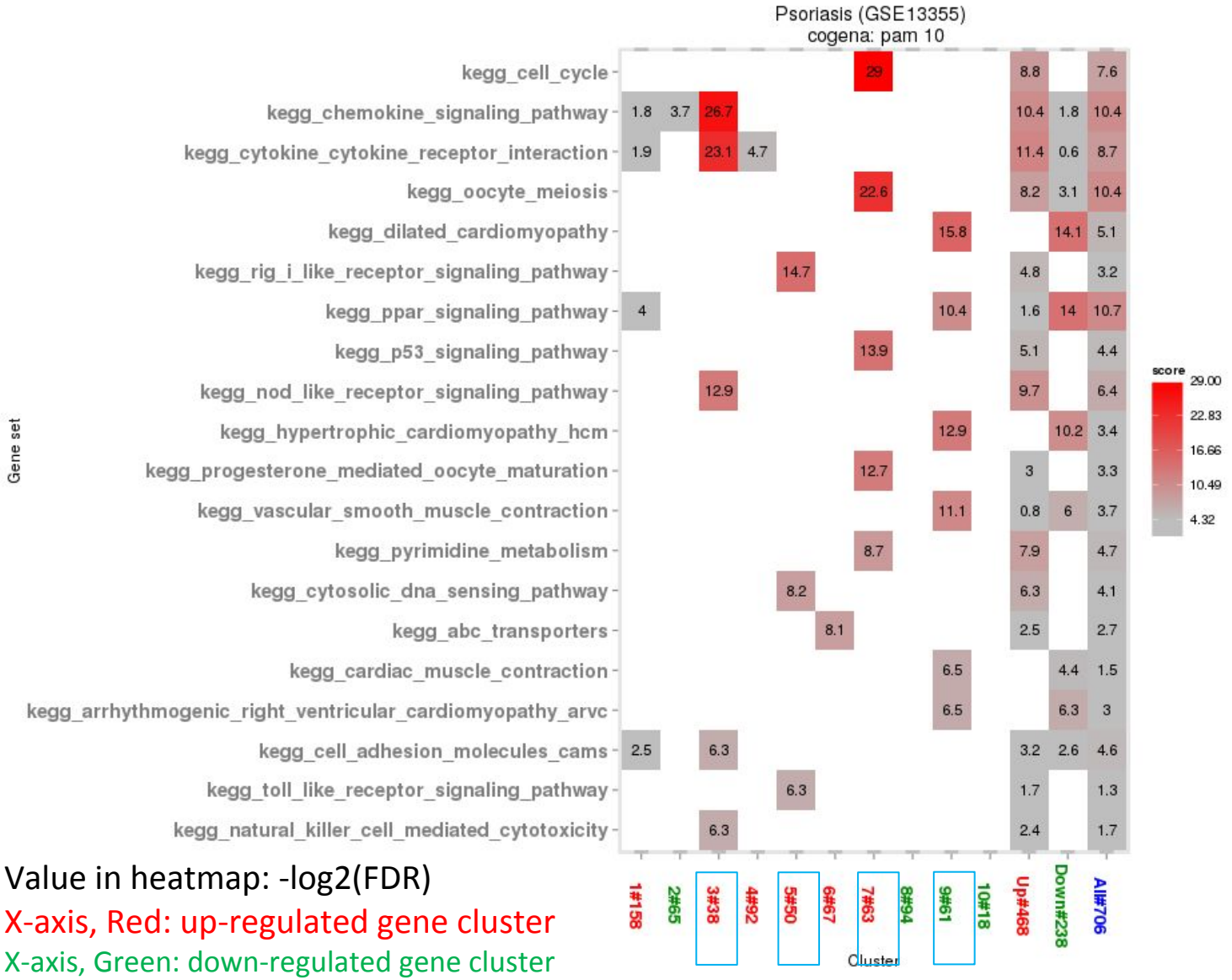
- Pathway analysis and drug repositioning analysis on co-expressed genes can be more informative than transcriptome wide analysis

- cogena can be applied to drug repositioning and mode of action discovery, illustrated by a psoriasis exemplar.
  - Code available at http://zhilongjia.github.io/psoriasis/

Drug repositioning pipeline based on cogena



Pathway analysis for *psoriasis* based on cogena



Value in heatmap: -log2(FDR)

X-axis, Red: up-regulated gene cluster

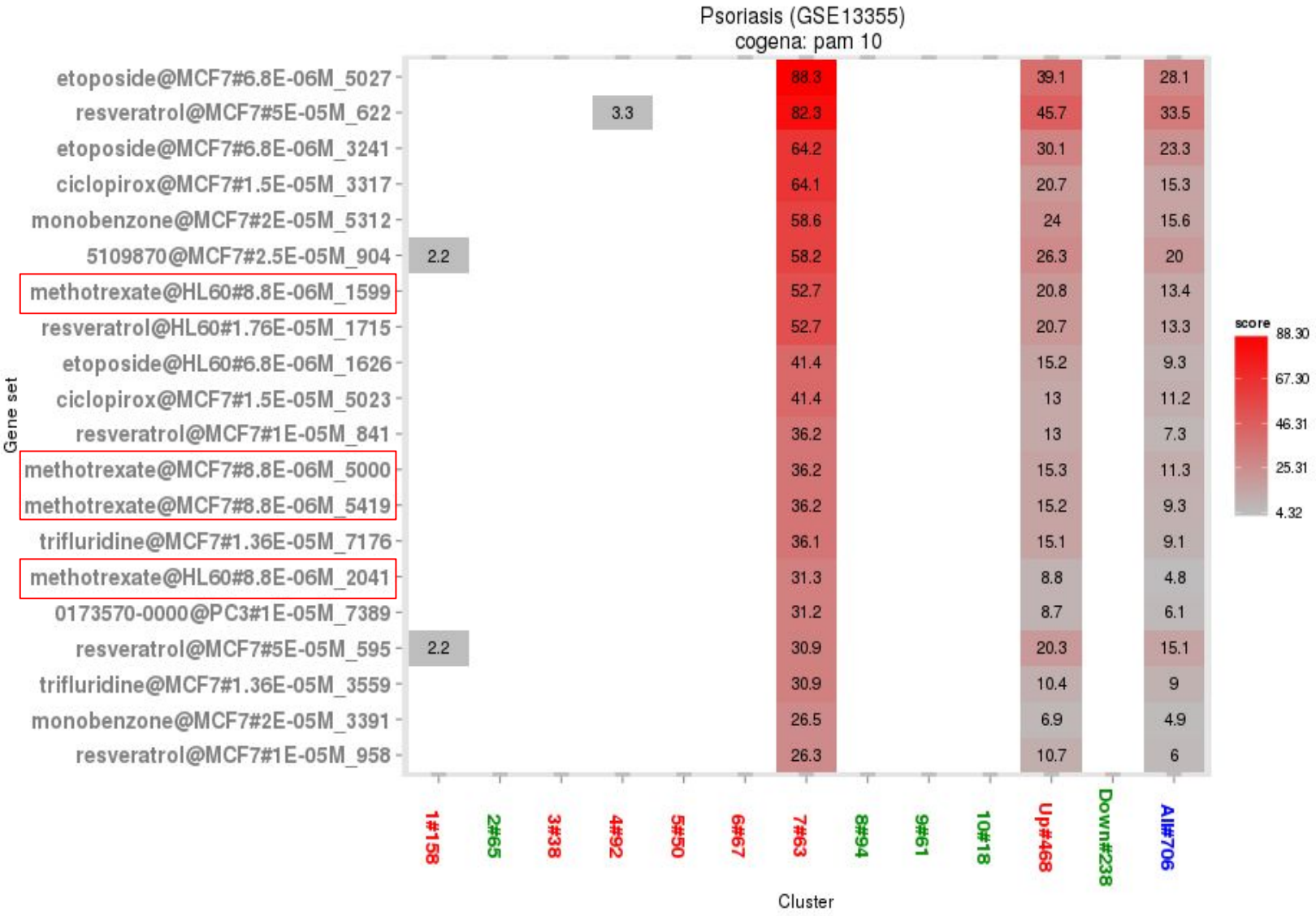
X-axis, Green: down-regulated gene cluster

```r
# Parameters for funtion clEnrich
annoGMT <- "c2.cp.kegg.v5.0.symbols.gmt.xz" # kegg pathway gene set
annofile <- system.file("extdata", annoGMT, package="cogena")
sampleLabel <- GSE13355label$state
names(sampleLabel) <- rownames(GSE13355label)

#############################################################################
# cogena analysis (Pathway analysis)
cogena_result <- clEnrich(genecl_result, annofile=annofile, sampleLabel=sampleLabel)

# Summary the results obtained by cogena
summary(cogena_result)
```

- Immune-related pathways in cluster 3 and 5.
- Cell cycle and p53 signalling pathways in cluster 7.
- PPAR signalling pathways in cluster 9.

Drug repositioning for psoriasis based on cluster 7 (cell cycle & P53 pathway)

```
# Drug repositioning based on CmapDn100 gene set
cmapDn100_cogena_result <- clEnrich_one(genecl_result, "pam", "10",
        annofile=system.file("extdata", "CmapDn100.gmt.xz", package="cogena"),
        sampleLabel=sampleLabel)
```



Methotrexate (ranked 7th) is a first-line drug for psoriasis and an inhibitor of the enzyme folic acid reductase, which leads to the inhibition of DNA synthesis and cellular replication.

Ciclosporin (ranked 9th), an FDA-approved drug for psoriasis, is a powerful immunosupressant. (Enriched in Cluster 5, including RIG-i like receptor signaling pathway; Data not shown)

Conclusions

- In a Psoriasis example, cogena retrieves disease relevant mechanisms and drugs
- Cogena is a powerful Bioconductor package for drug repositioning and drug mode of action discovery
- Cogena is available from Bioconductor or https://github.com/zhilongjia/cogena
- Reproduciable research: http://zhilongjia.github.io/psoriasis/