Co-expressed gene-set enrichment analysis for drug repositioning with examples of psoriasis and periodontal diseases

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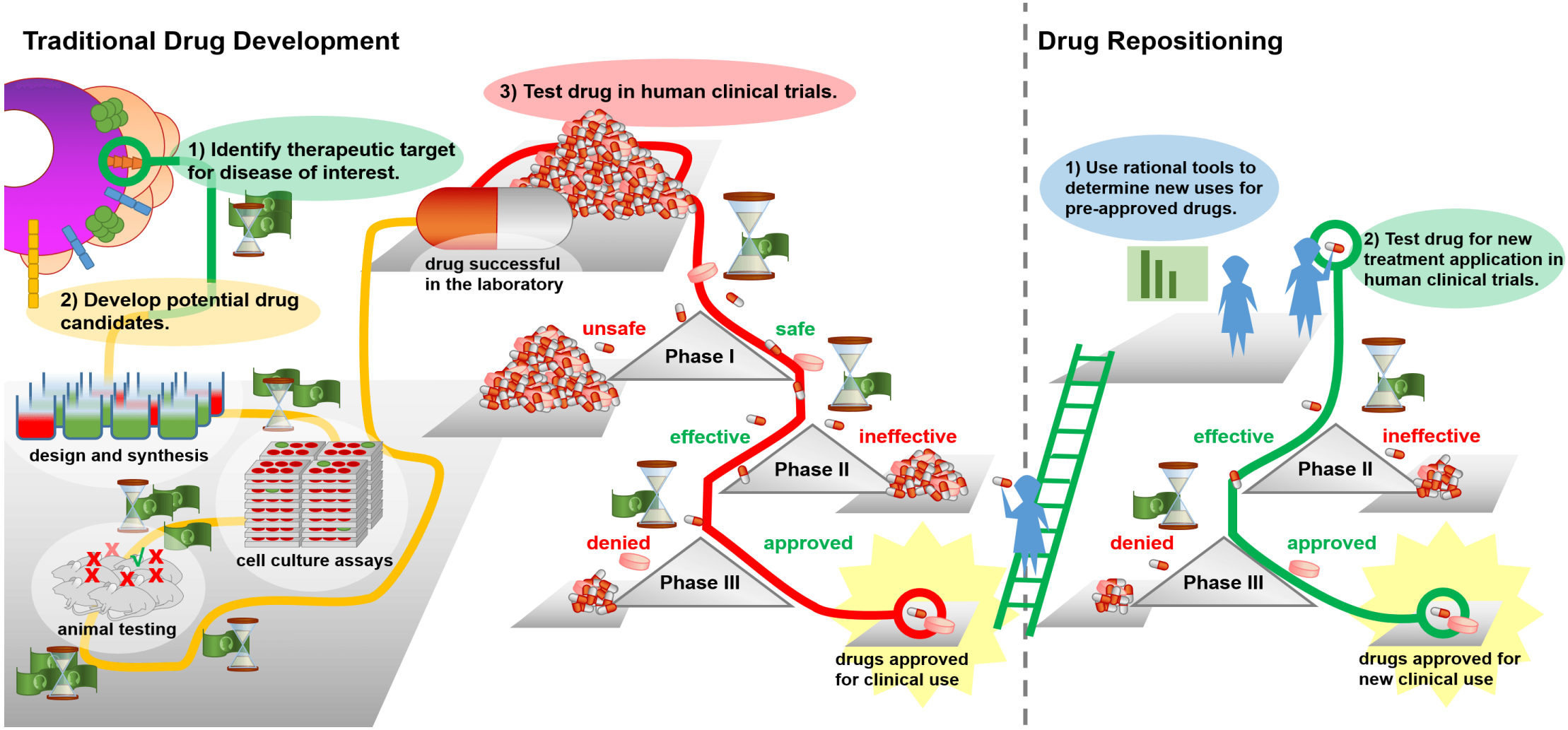
Drug repositioning: discovering new indications for approved drugs

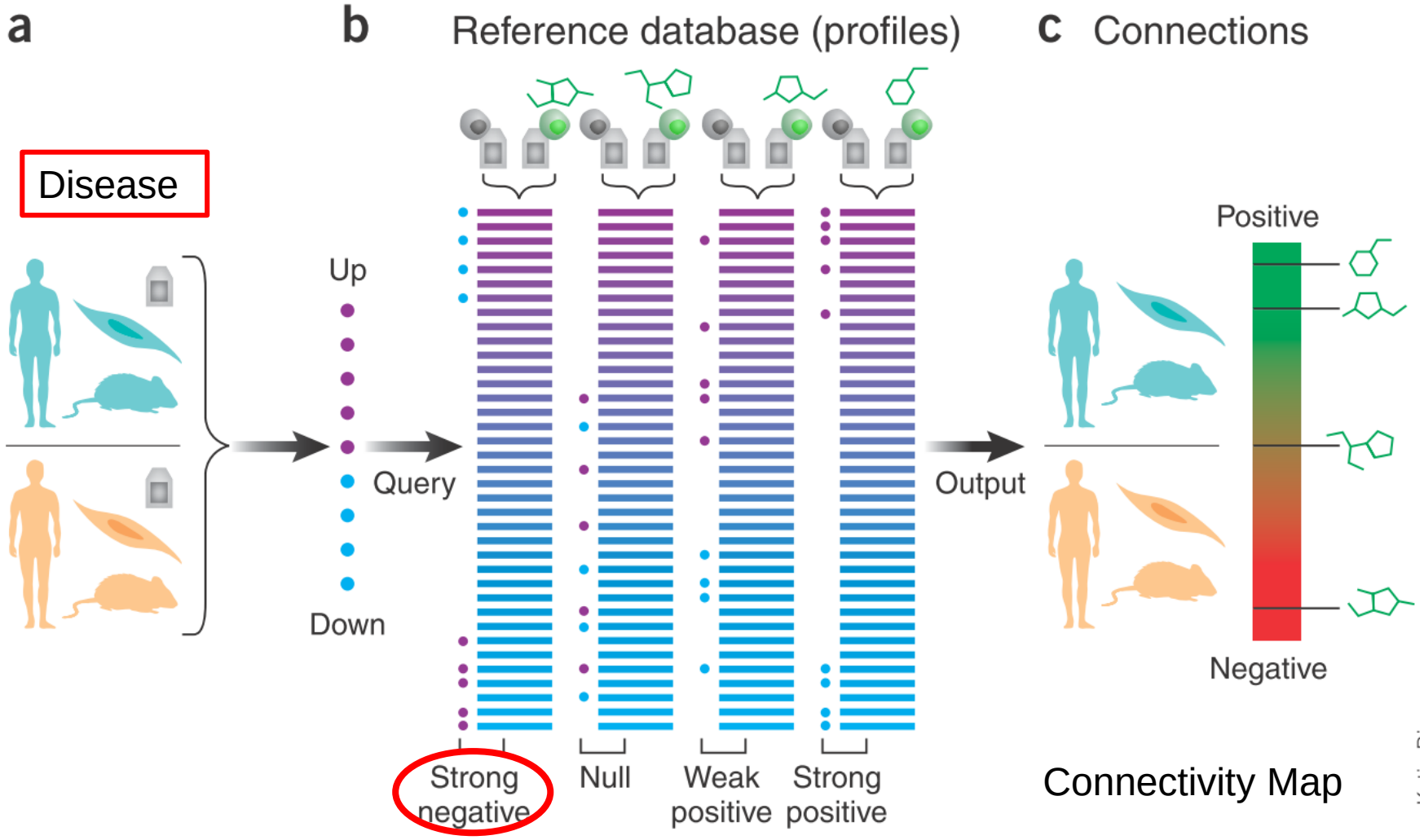


- **Advantages of Drug repositioning:** Less steps, shorten period, more effective cost and lower risk!

Ref: http://sitn.hms.harvard.edu/flash/2016/re-engineering-cures-big-data-age-precision-medicine-computational-drug-repositioning/

Basic hypothesis of transcriptome-based drug repositioning

If a drug can recovery the changed genes caused by a disease, the drug probably can treat the disease.



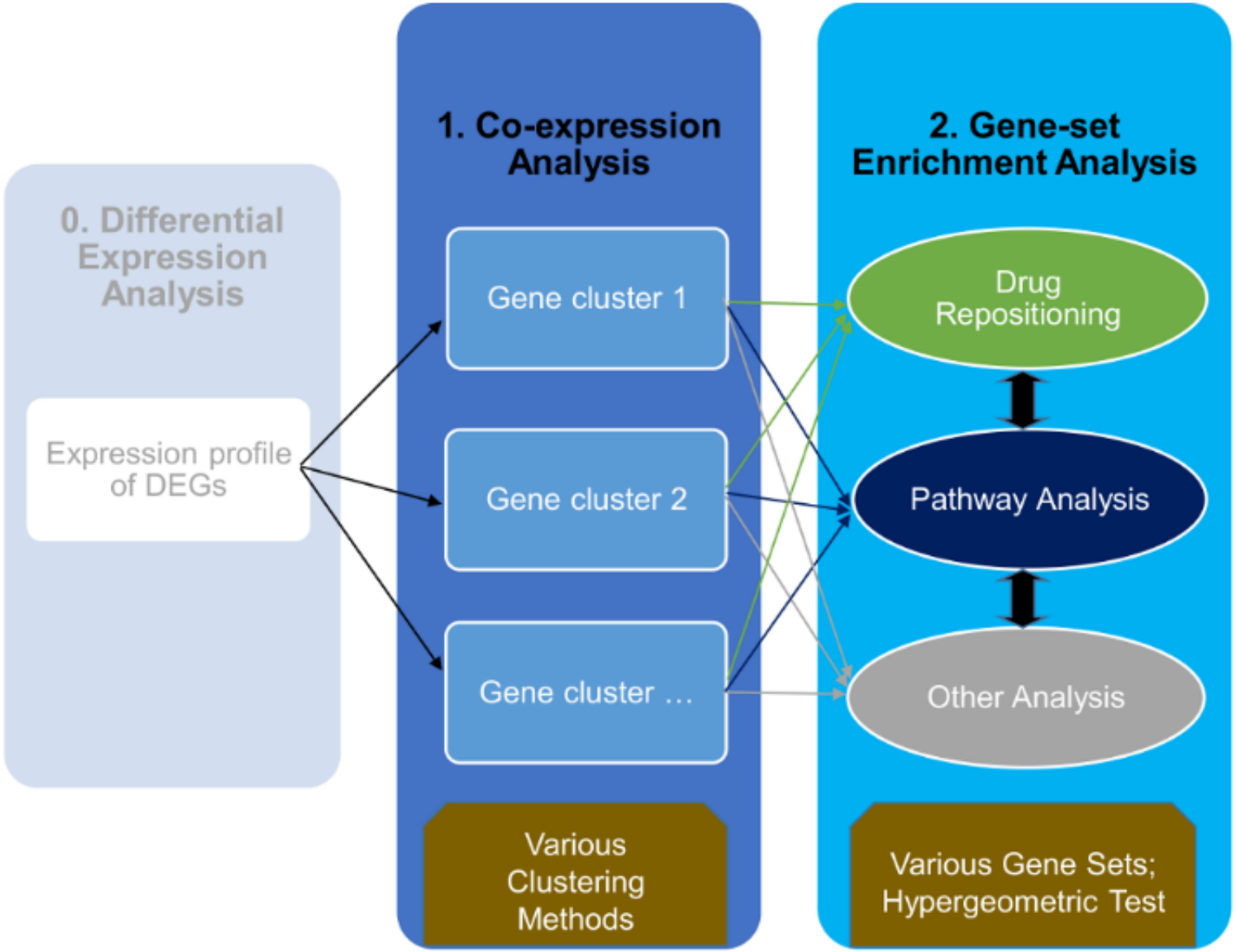
Lamb, Justin, et al. "The Connectivity Map: using gene-expression signatures to connect small molecules, genes, and disease." science 313.5795 (2006): 1929-1935.

Michnick, Stephen W. "The connectivity map." *Nature chemical biology* 2.12 (2006): 663-664.

Issues

- No versatile Co-expression analysis tool
  - In general, co-expressed genes functions collaboratively
  - They are probably involved in similar or same pathway or Gene Ontology
- No clue to the Drug Mode of Action (MoA) in the CMap-based drug repositioning pipeline
  - Pathway and GO are a clue to drug MoA

Cogena: Co-expressed gene-set enrichment analysis

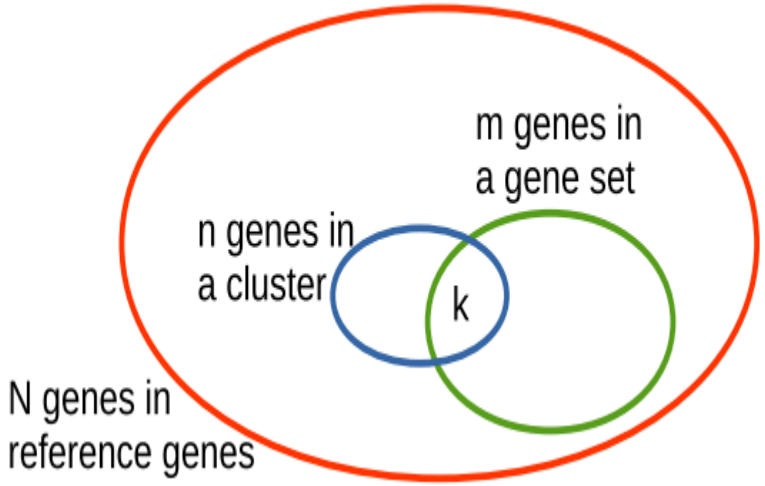


Gene sets:

MSigDB Molecular Signatures Database

CONNECTIVITY MAP

Hypergeometric test：

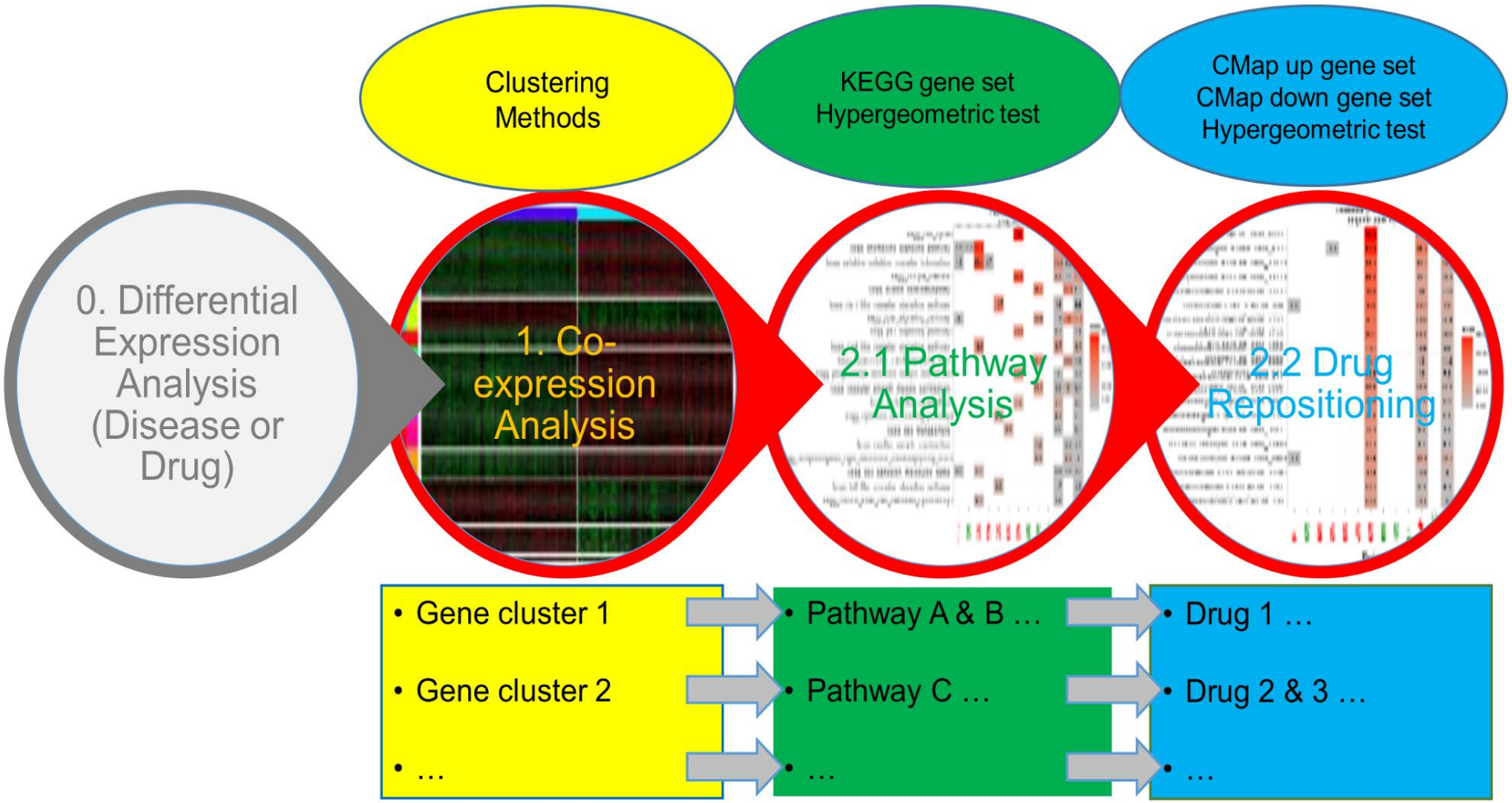


$$P\{x \geq k\} = \sum_{x=k}^{\infty} \binom{m}{x} \binom{N-m}{n-x} / \binom{N}{n}$$

$$ES = -\log_2(\mathrm{FDR})$$

Cogena for drug repositioning

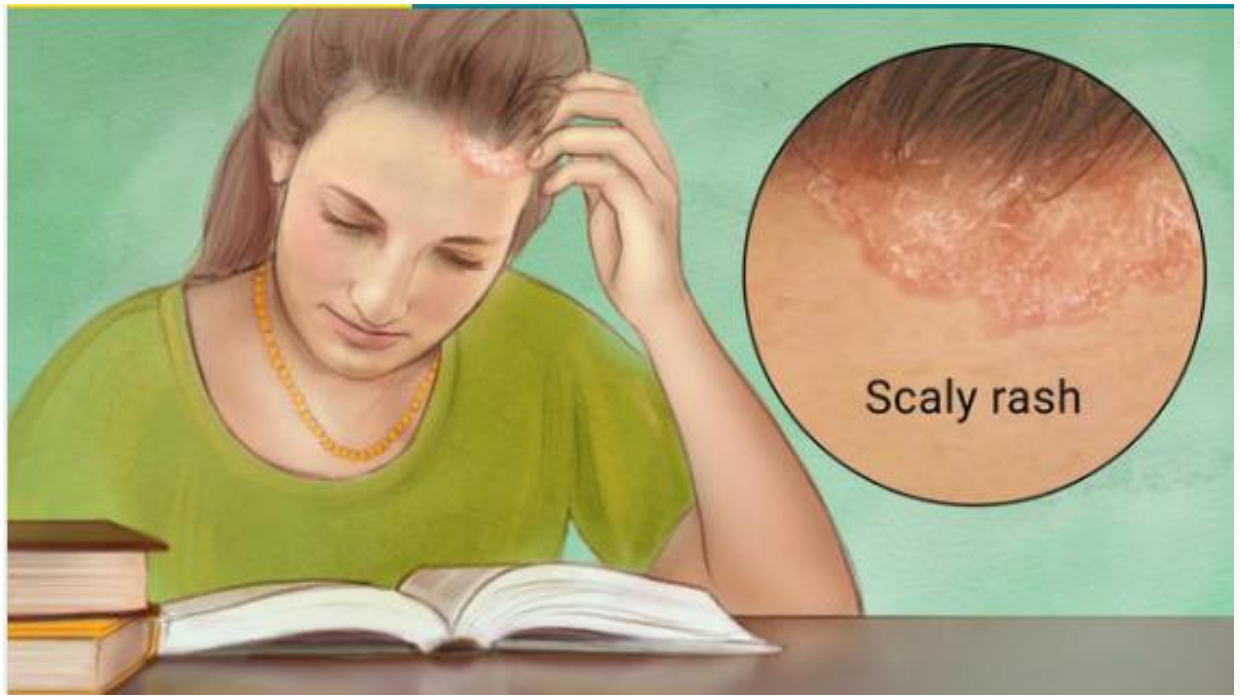
Targeting co-expressed genes could be more precise than all the DEGs.

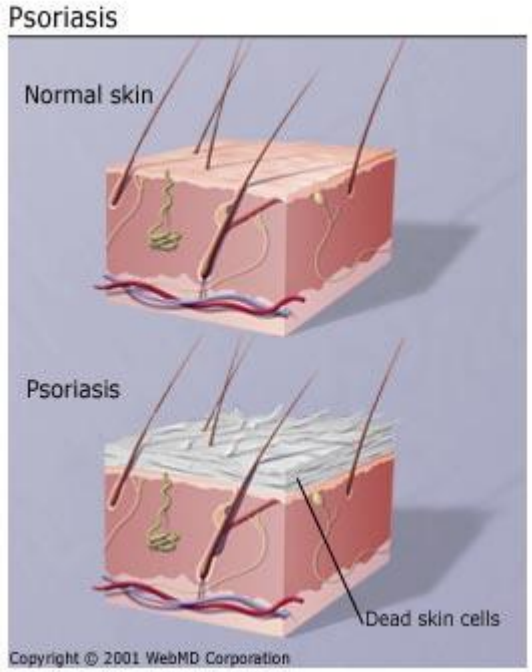


- Combination Pathway and Drug repositioning provides a clue to the MoA of Drug.

Cogena-based drug repositioning for psoriasis

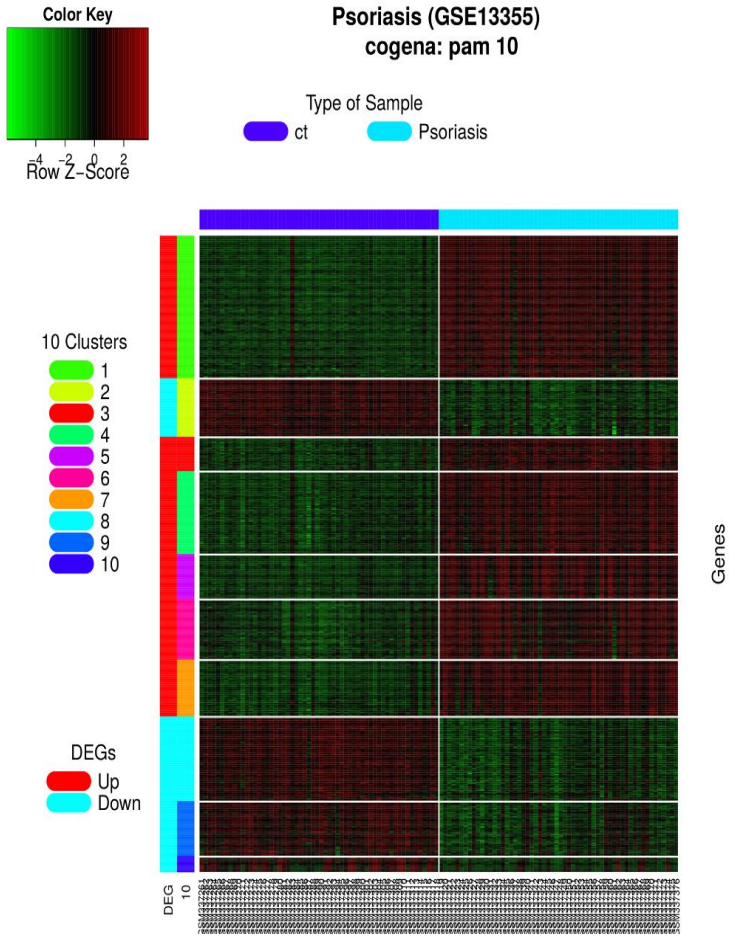
- Psoriasis is a long-lasting autoimmune disease characterized by patches of abnormal skin.
- 2%-3% of people throughout the world.
- Treatments for moderate to severe psoriasis include Methotrexate and Biologics.

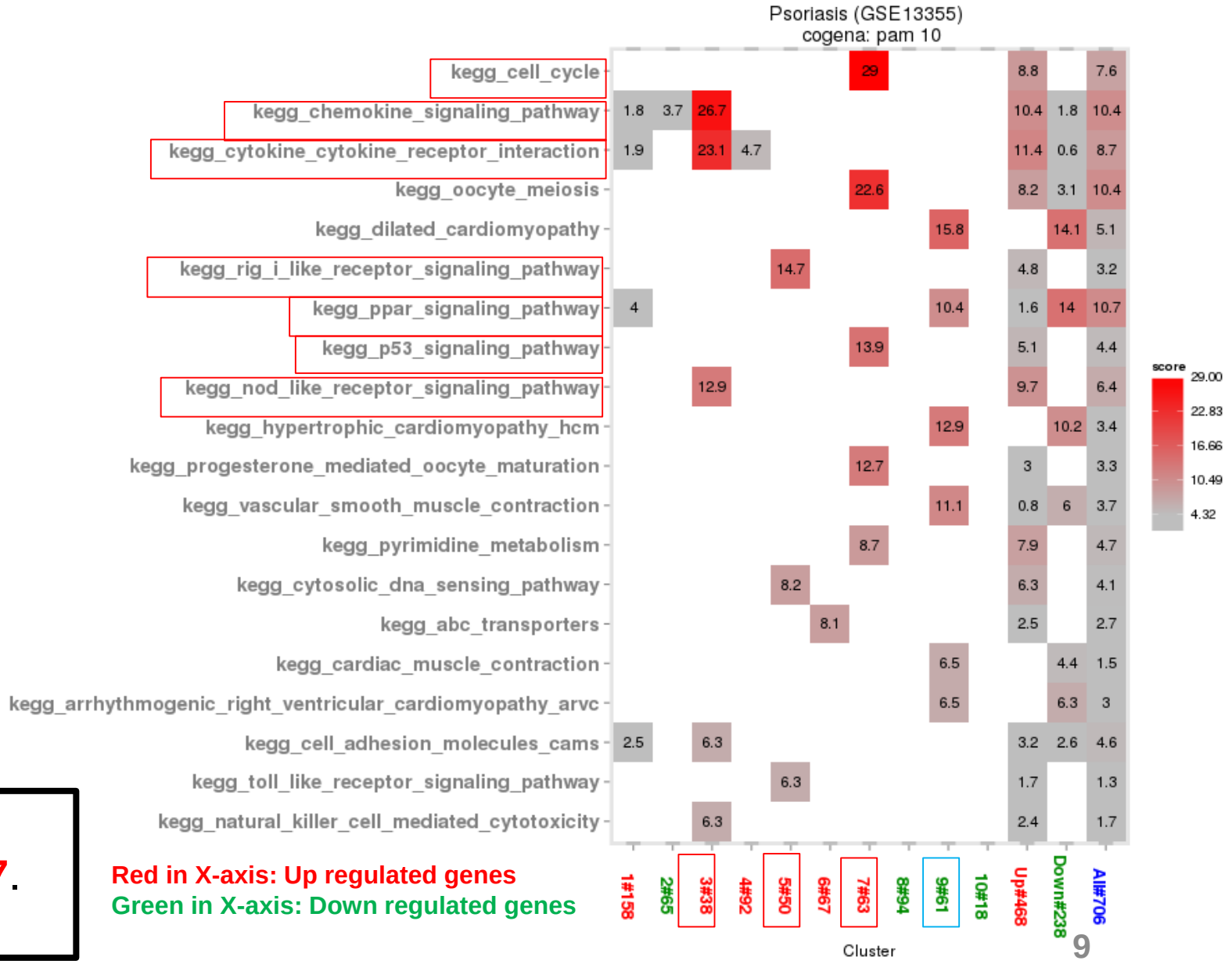




https://en.wikipedia.org/wiki/Psoriasis

Cogena-based drug repositioning for psoriasis

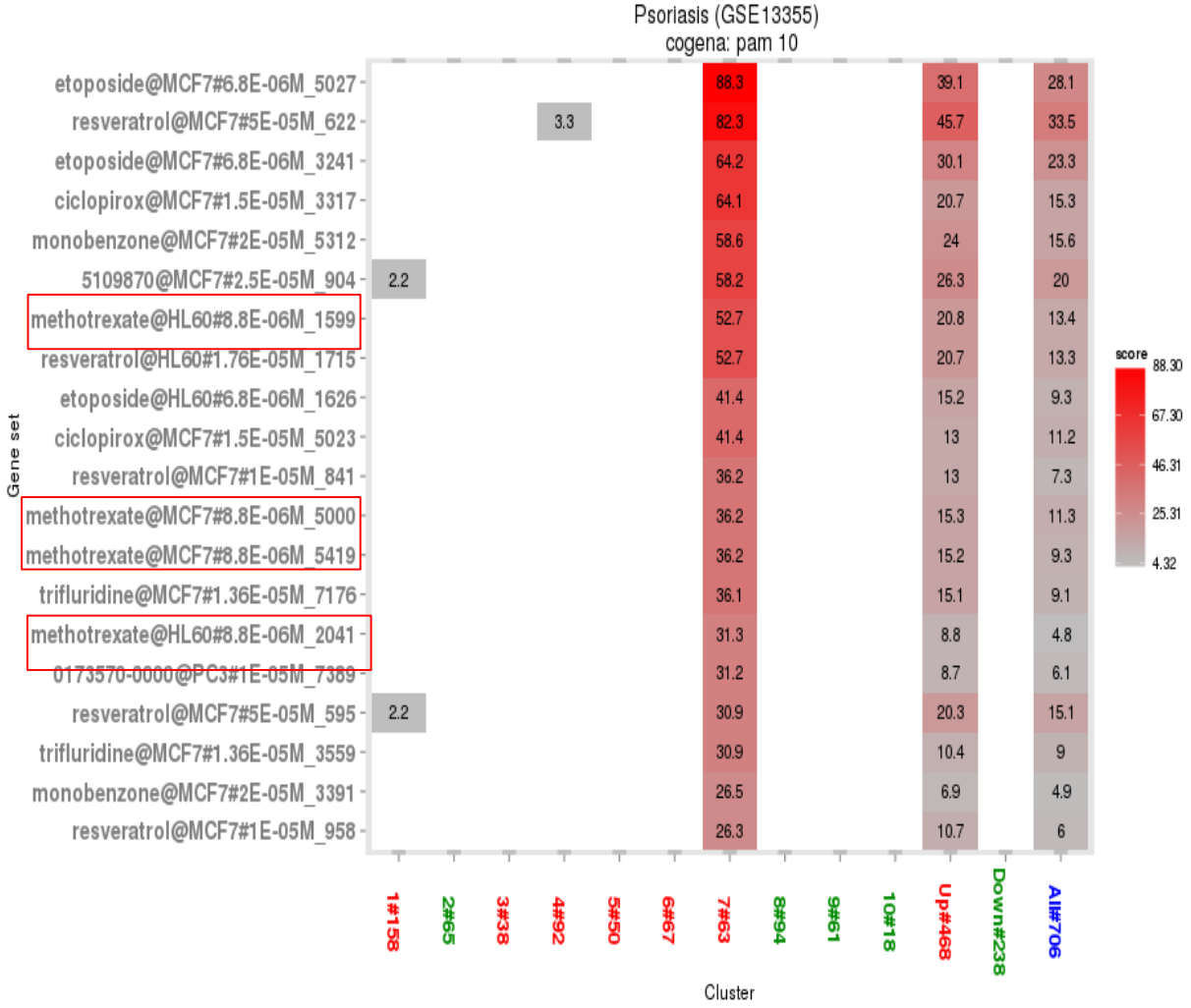


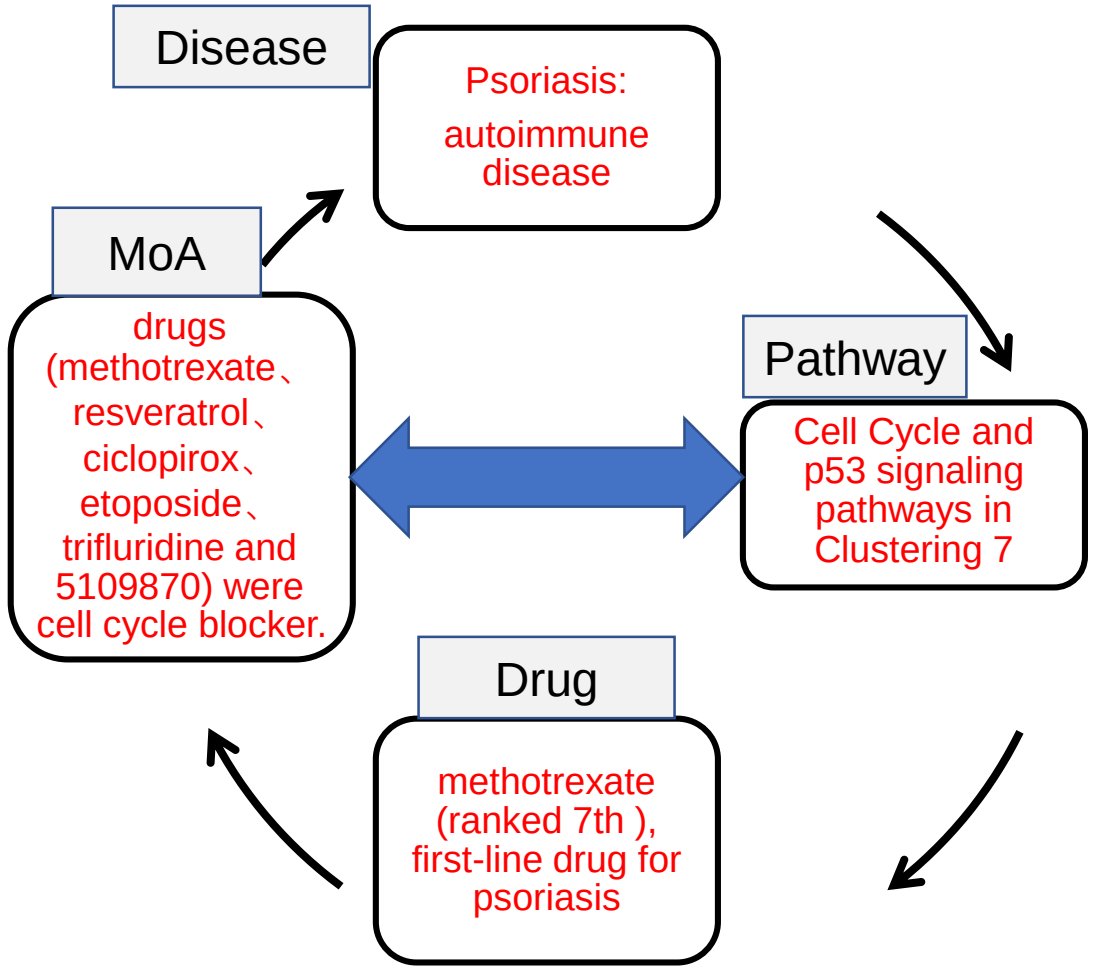


Immune-related pathways in C**3**, C**5**.
Cell Cycle/p53 signaling pathways in C**7**.
PPAR signaling pathway in C**9**.

Red in X-axis: Up regulated genes
Green in X-axis: Down regulated genes

Cogena-based drug repositioning for psoriasis



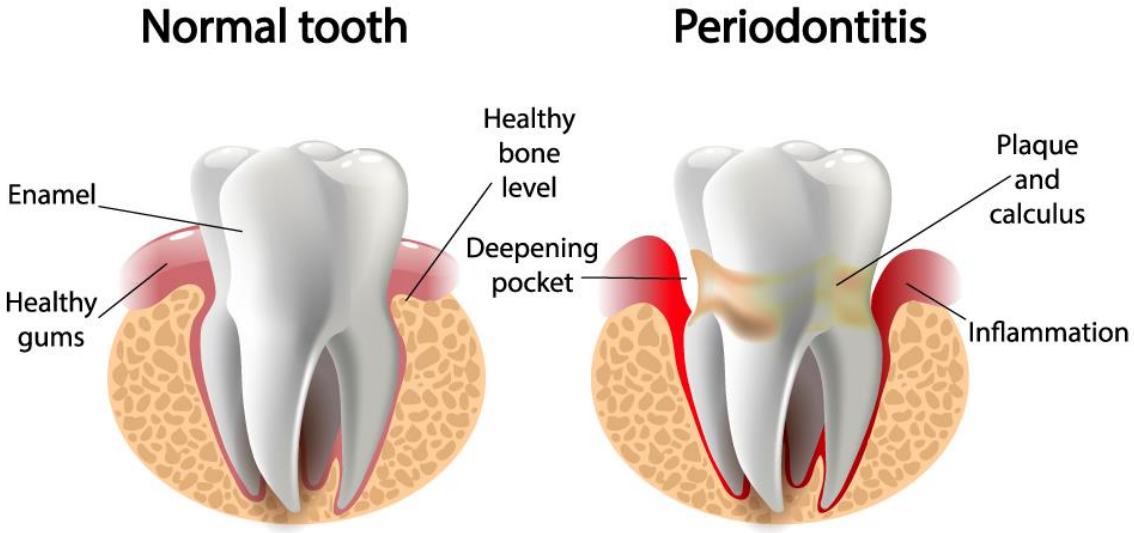


Most drugs in cluster 7 are cell cycle blockers and probably could be promising candidate drugs for psoriasis and even more generally autoimmune diseases.

Jia, Zhilong, et al. "Cogena, a novel tool for co-expressed gene-set enrichment analysis, applied to drug repositioning and drug mode of action discovery." BMC genomics 17.1 (2016): 414.

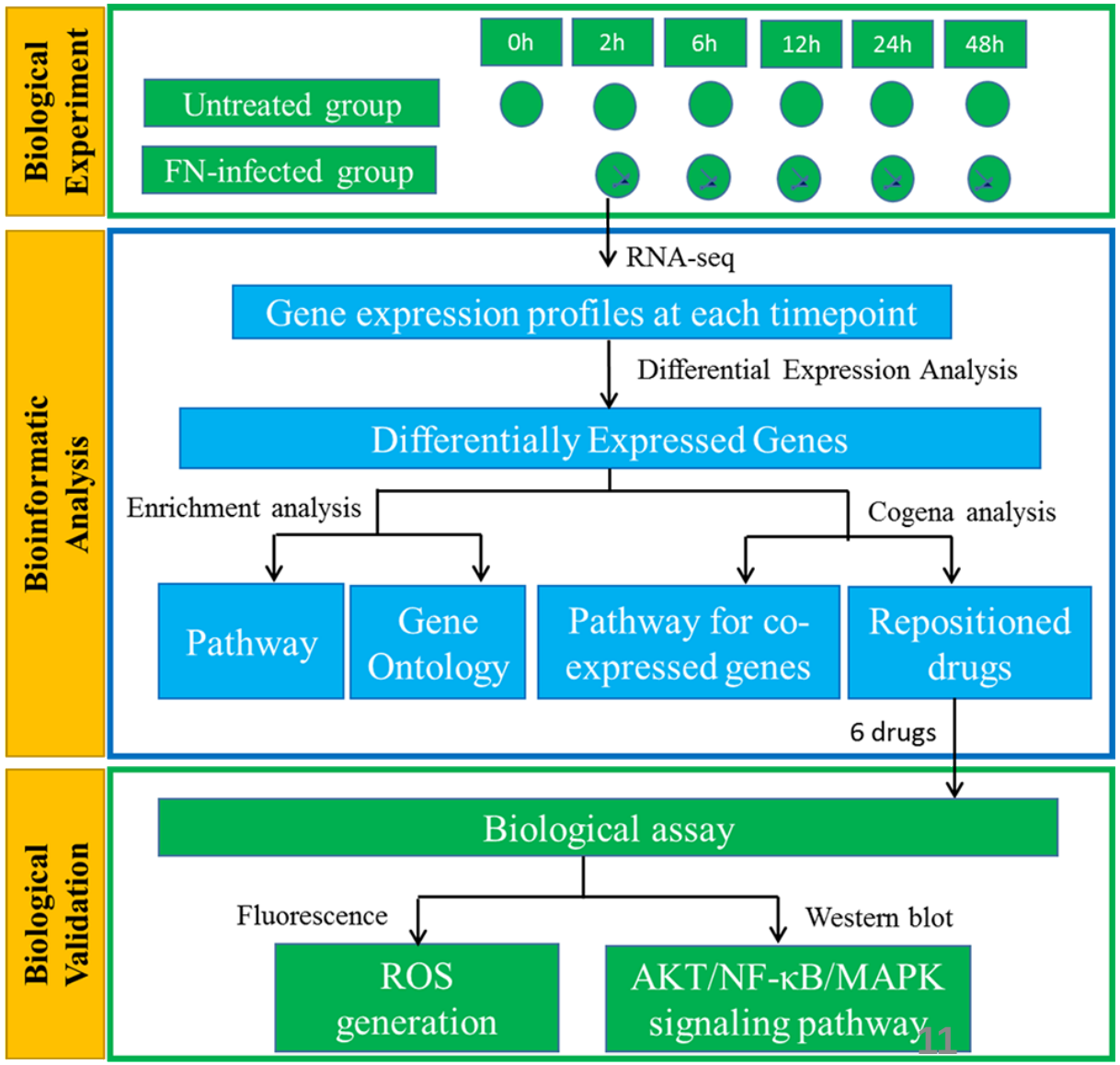
Cogena-based drug repositioning for periodontal diseases

- Periodontal disease is caused by the interaction of dental plaque biofilm and the host immune system.
- *Fusobacterium nucleatum* (*FN*) is a high-frequency pathogen in periodontal disease.
- Gingival fibroblasts (GF) are the most abundant cell types in periodontal connective tissues

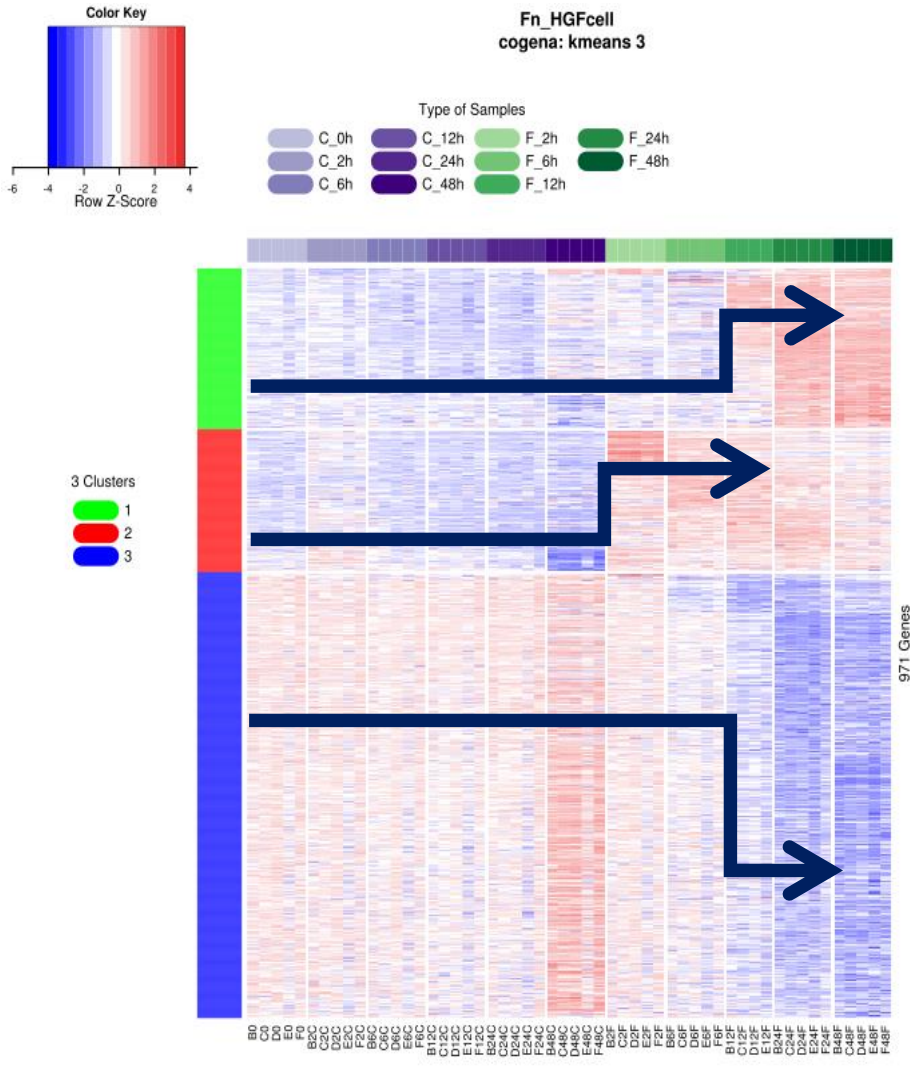


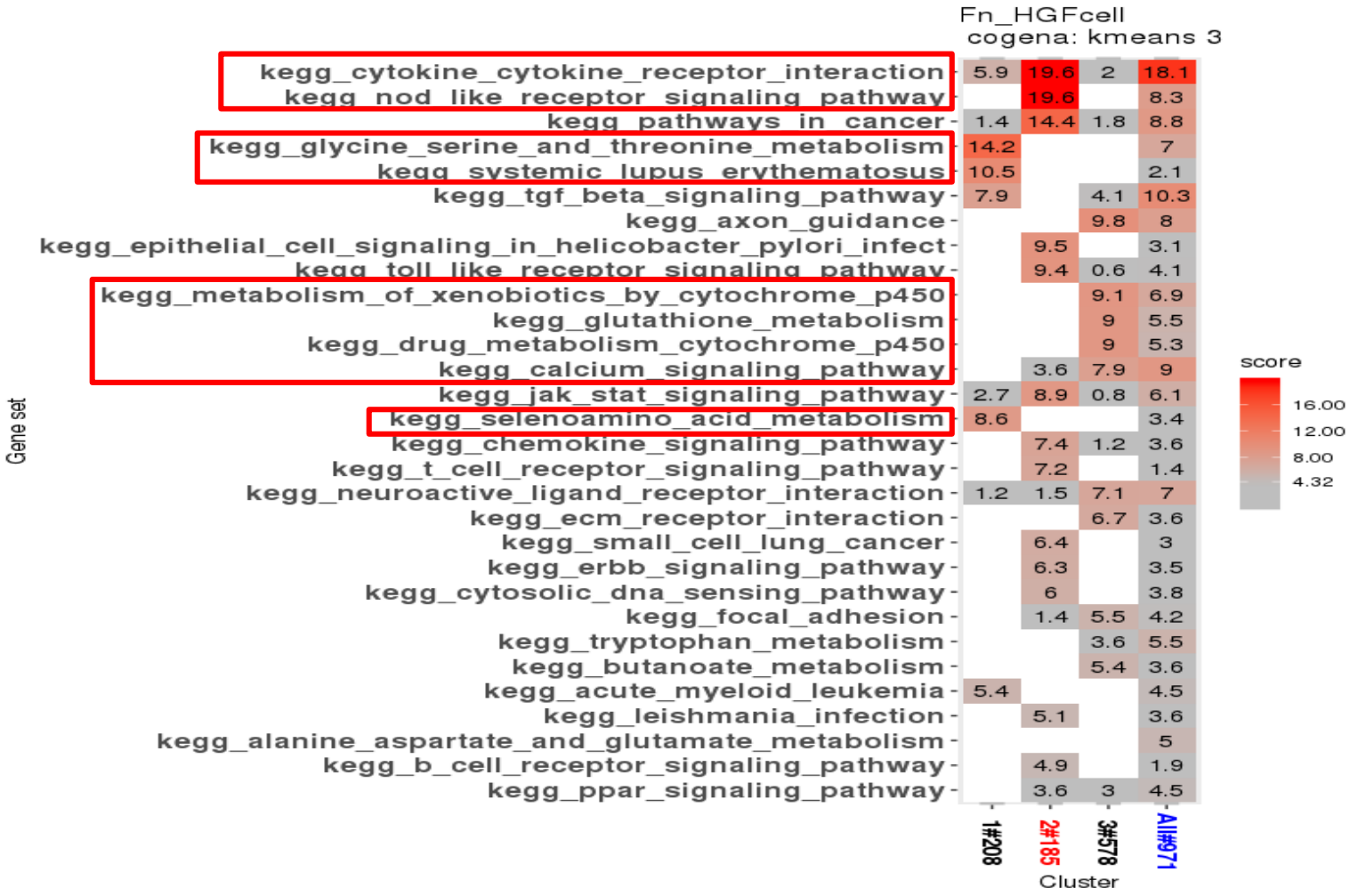
Ref (left pic): https://www.saebo.com/the-hidden-connection-between-gum-disease-and-stroke/

The entire experimental design



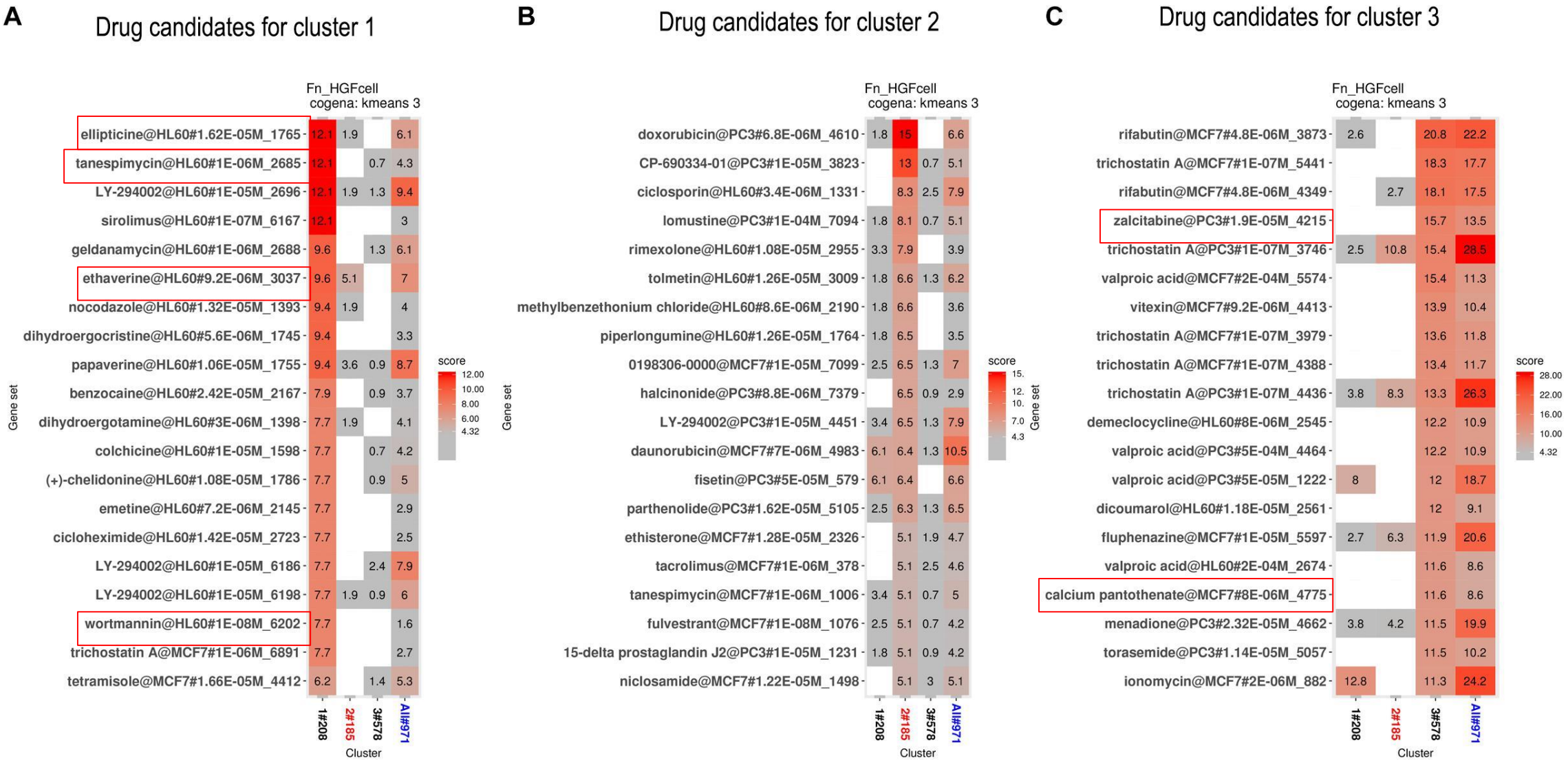
Cogena-based drug repositioning for periodontal diseases





Cluster 1: up after 12h and Cluster 3: down after 12h -- mainly enriched in metabolism-related pathways
Cluster 2: up immediately-- highly enriched in the cytokine–cytokine receptor signaling pathways.

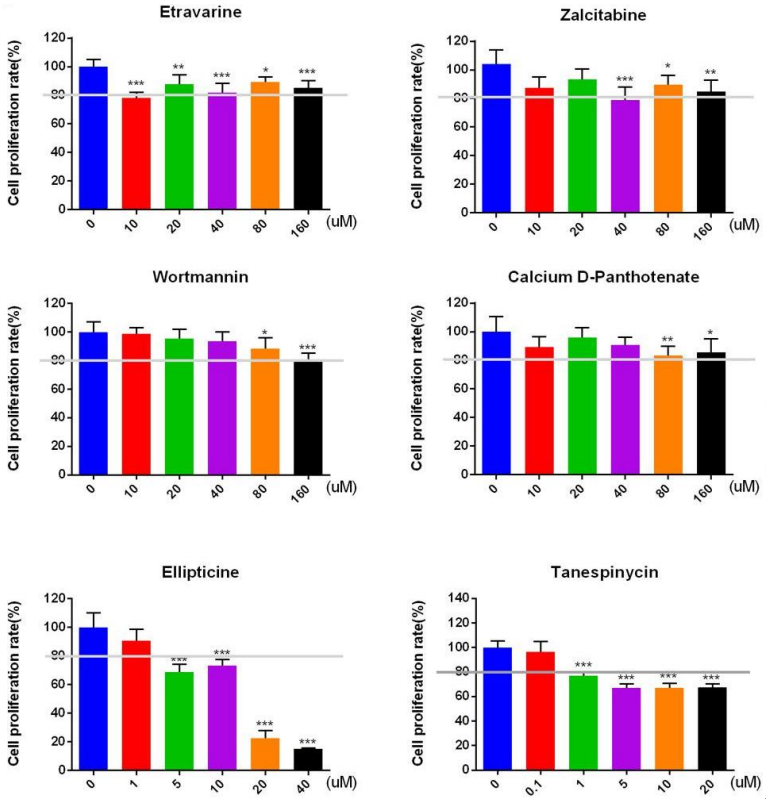
Cogena-based drug repositioning for periodontal diseases



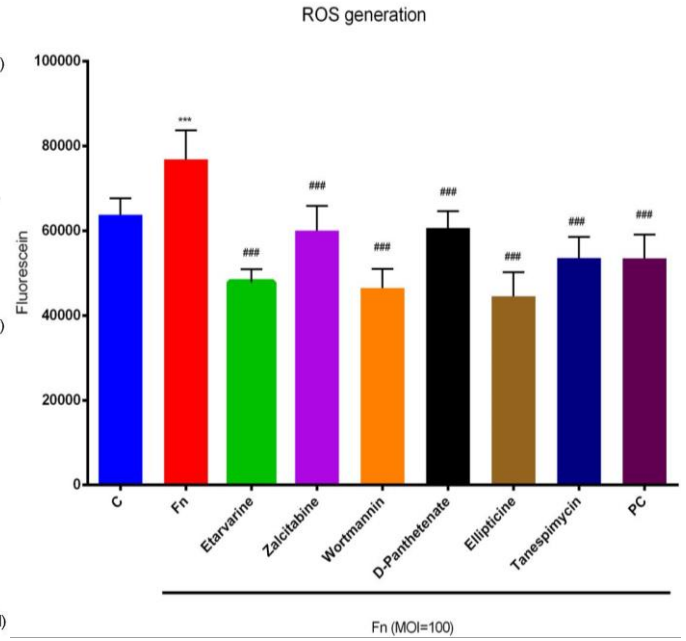
Six drugs (etravirine, zalcitabine, wortmannin, calcium D-pantothenate, ellipticine, and tanespimycin) were selected to be tested due to the scale of biological experiments and literature-based investigations.

Cogena-based drug repositioning for periodontal diseases

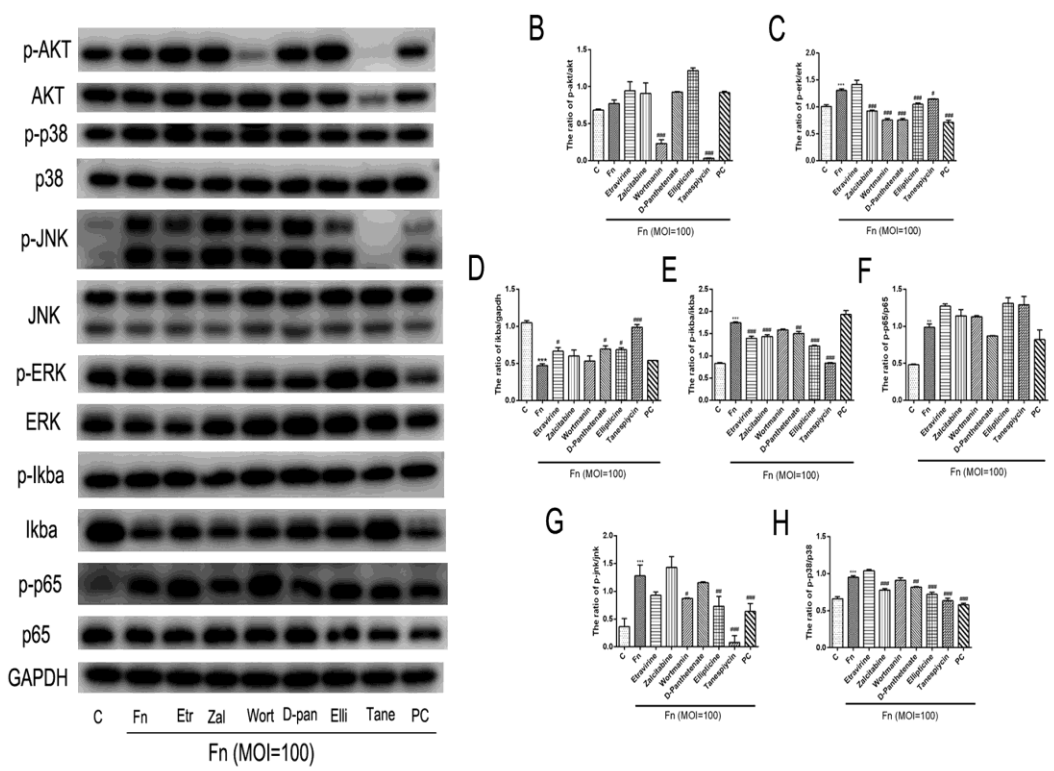
Effects of candidate drugs on GF proliferation



Effects of candidate drugs on F. nucleatum-induced ROS generation



Effects of candidate drugs on F. nucleatum-activated NF-κB, MAPK, and AKT signaling pathways in GFs



Six drugs (etravirine, zalcitabine, wortmannin, calcium D-pantothenate, ellipticine, and tanespimycin) could significantly decrease *FN*-induced ROS generation and block the PKB/AKT/MAPK signaling pathways.

Kang, Wenyan, et al. "Time-course Transcriptome Analysis for Drug Repositioning in Fusobacterium nucleatum-infected Human Gingival Fibroblasts." *Frontiers in Cell and Developmental Biology* 7 (2019): 204.

Summary

- Cogena is a tool of gene set enrichment analysis for co-expression genes.
- Cogena can be used in drug repositioning and discovering the MoA of drugs, illustrated with two disease examples.
- Cogena can be used to discovery similar drugs or treatable diseases (if the input of cogena is drug signature)

Acknowledgements

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Reproducible Research

- Cogena Bioconductor Package:
  - http://www.bioconductor.org/packages/cogena/
  - https://github.com/zhilongjia/cogena
- Psoriasis project:
  - https://github.com/zhilongjia/psoriasis
- Periodontal diseases project:
  - https://bigd.big.ac.cn/gsa/browse/CRA001739
  - https://github.com/zhilongjia/Fn_HGFcell

Thank you
Q&A

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