解放軍总医院
CHINESE PLA GENERAL HOSPITAL

Transcriptome-based drug repositioning for COVID-19

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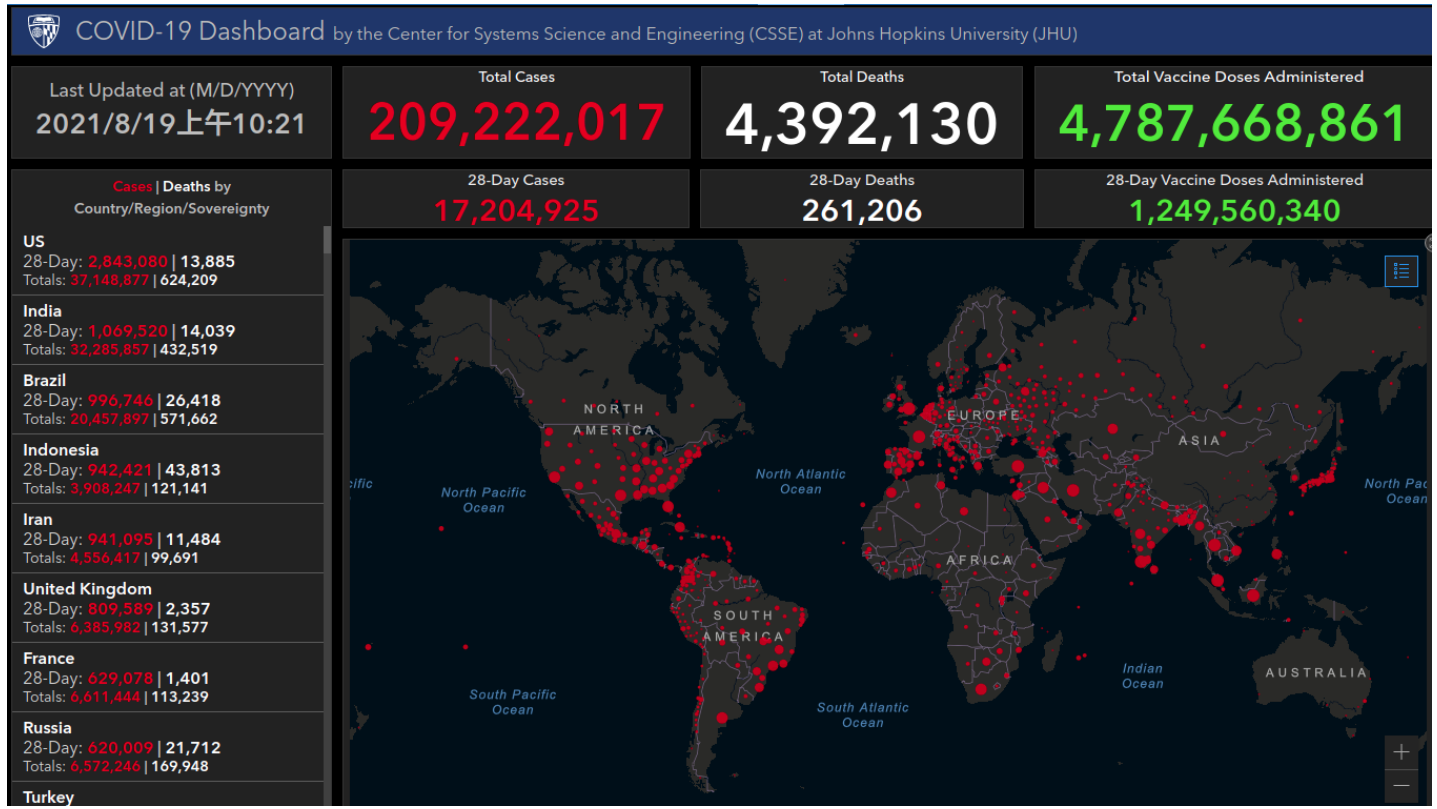
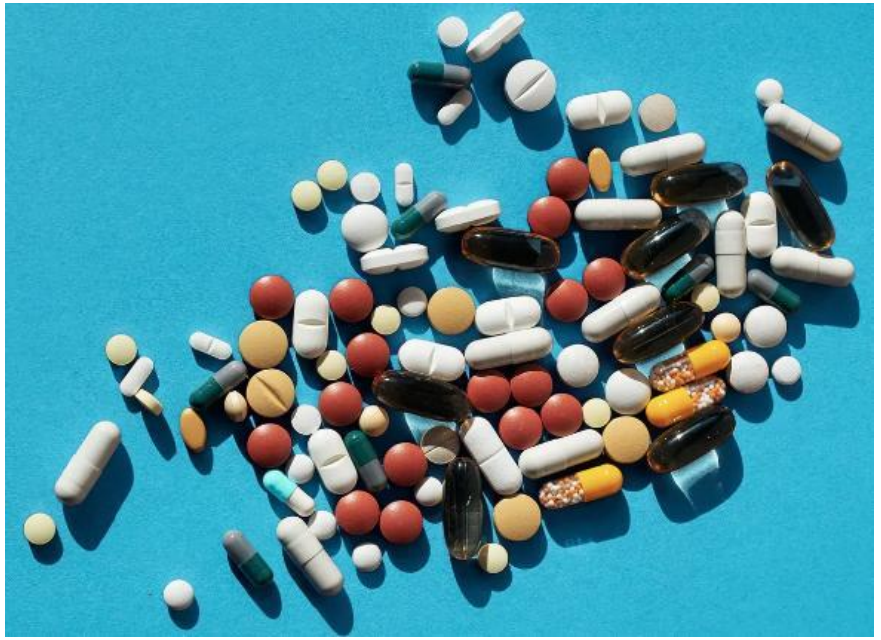
Coronavirus (COVID-19) Pandemic



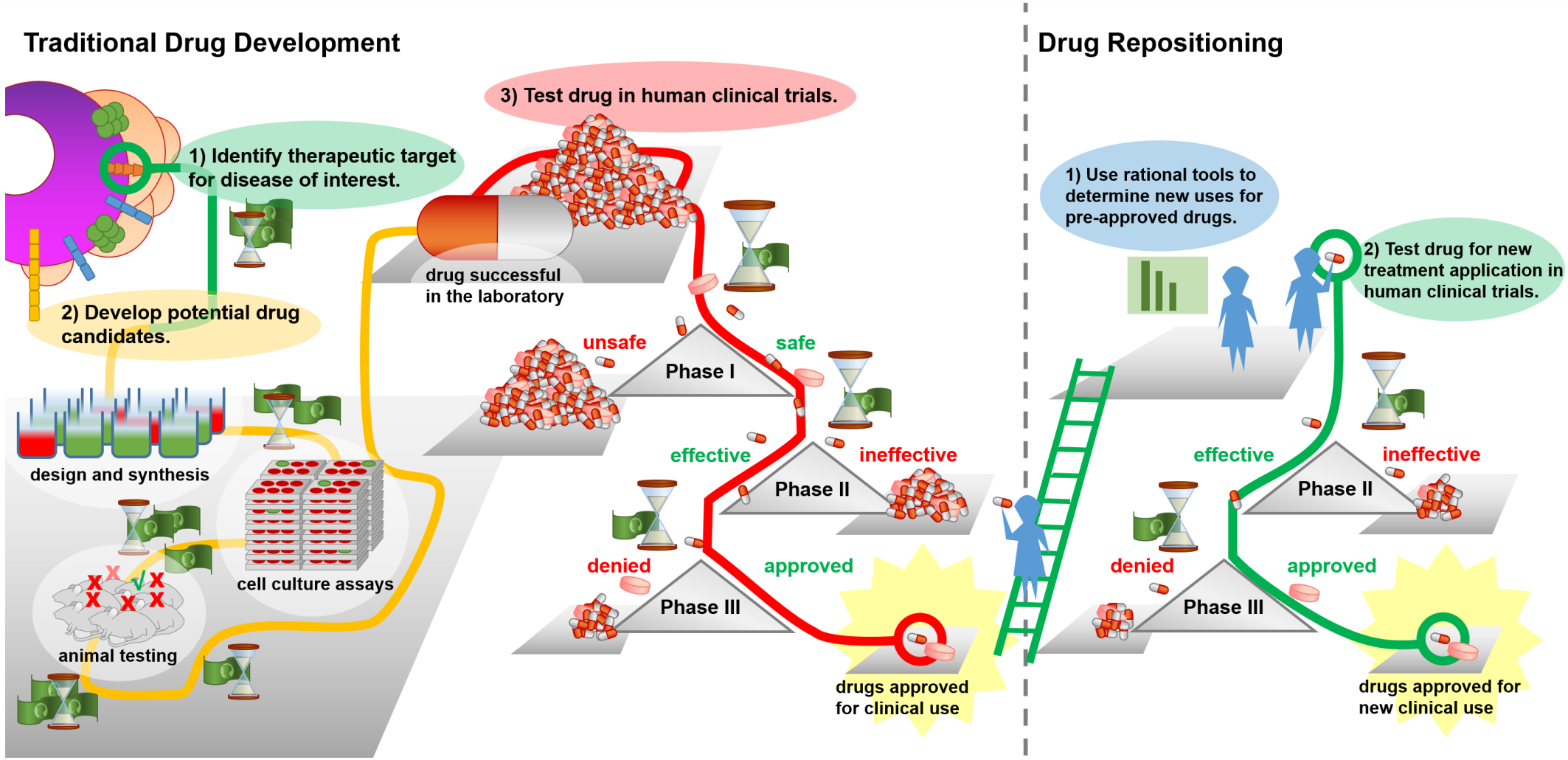


209M cases (19 Aug 2021)

No effective drugs for COVID-19

https://coronavirus.jhu.edu/map.html
https://www.wired.com/story/covid-19-drug-research-is-a-big-huge-mess/

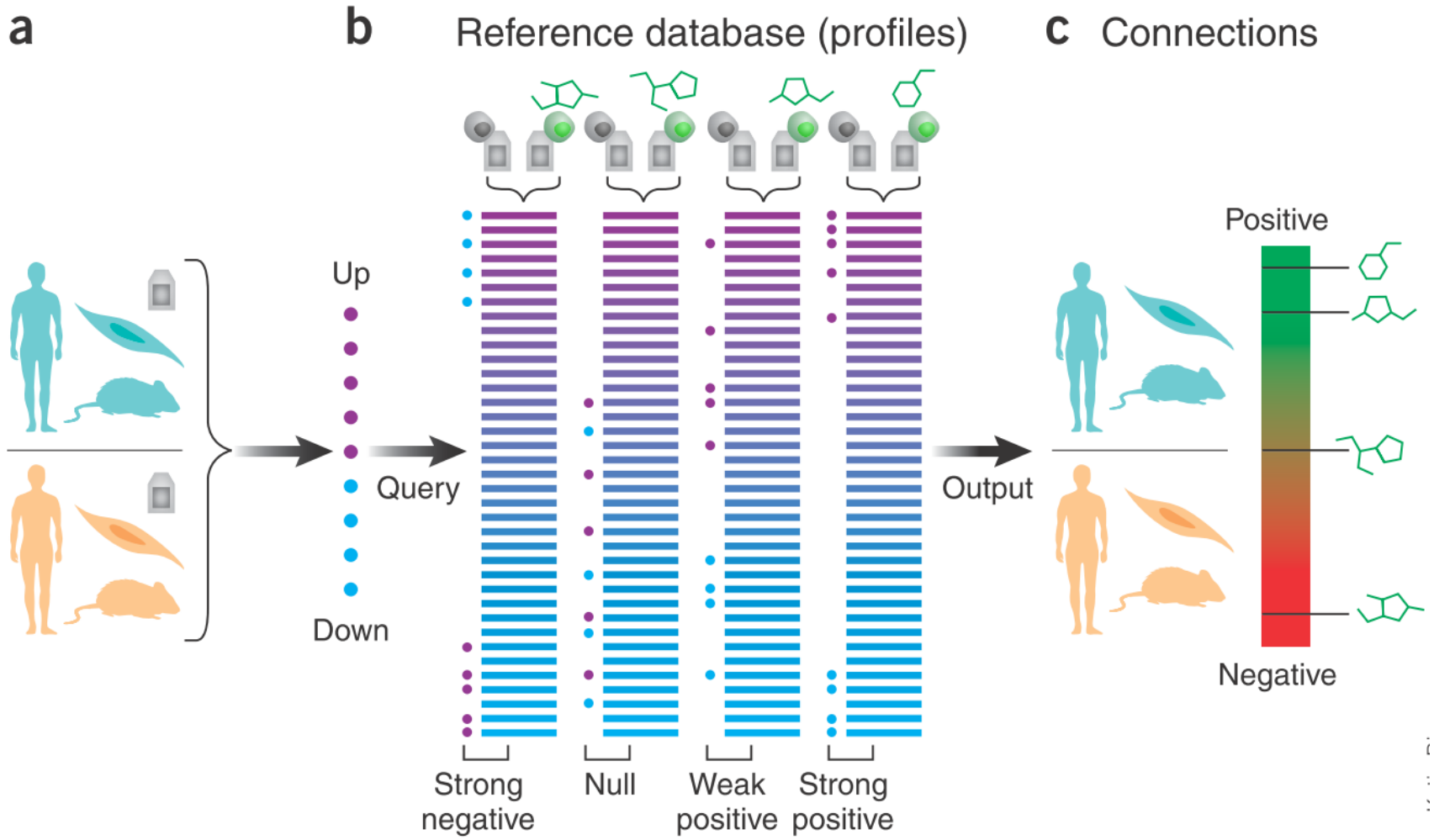
Drug repositioning: identifying new indications for old drugs



Drug repositioning, is a powerful tool for drug development, esp. for COVID-19.

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

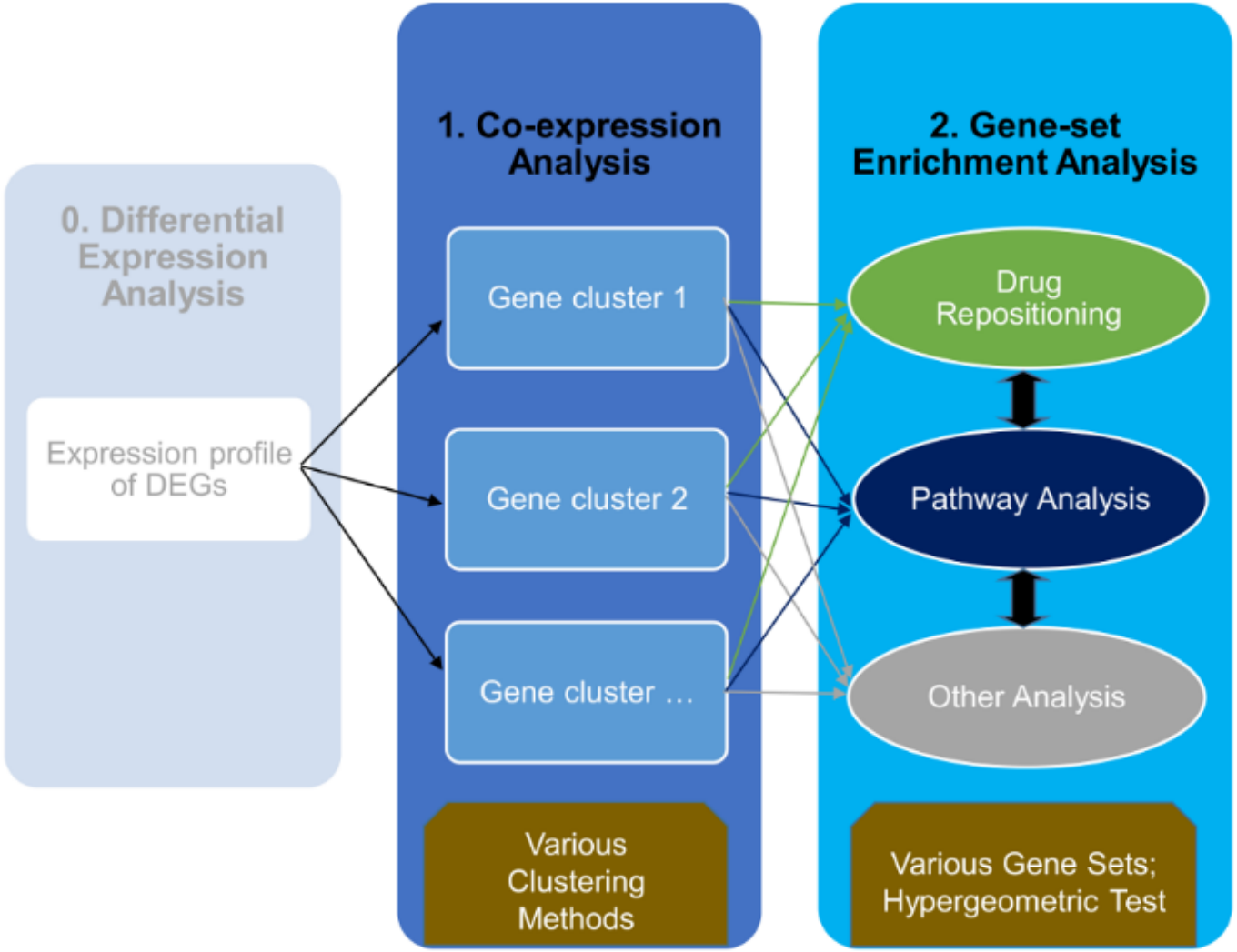
Rationale of Transcriptome-based Drug repositioning



Lamb, Justin, et al. "The Connectivity Map: using gene-expression signatures to connect small molecules, genes, and disease." science313.5795 (2006): 1929-1935.
Michnick, Stephen W. "The connectivity map." *Nature chemical biology* 2.12 (2006): 663-664.

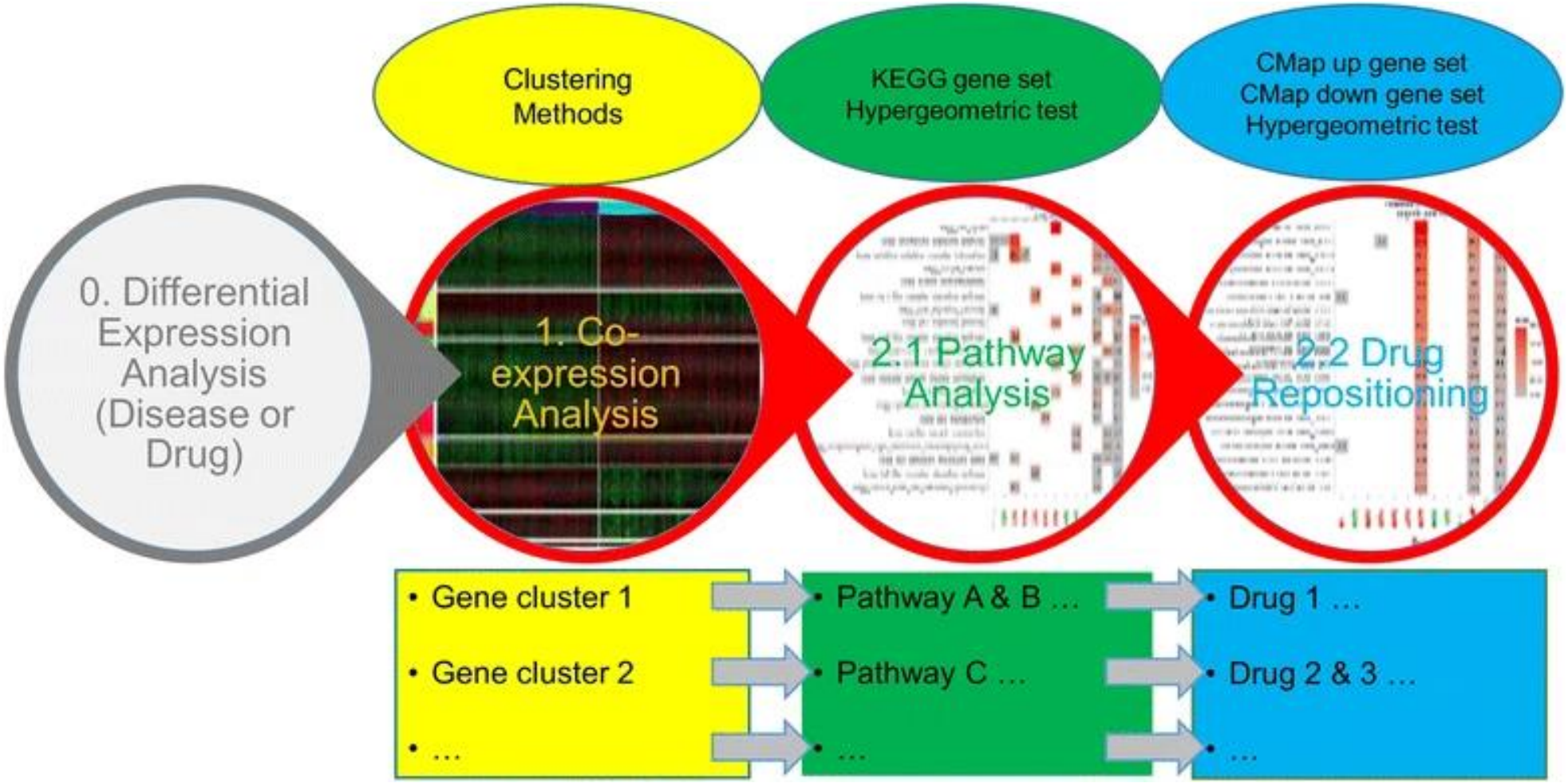
cogena: co-expressed gene-set enrichment analysis

- Genes which are both differentially expressed and co-regulated in a biological state, are more likely to be drivers of the underlying biology
- Co-expression is a critical layer of information to include in pathway analysis.



Jia Z, Liu Y, Guan N, Bo X, Luo Z, Barnes MR. Cogena, a novel tool for co-expressed gene-set enrichment analysis, applied to drug repositioning and drug mode of action discovery. BMC Genomics. 2016 May 27;17:414.

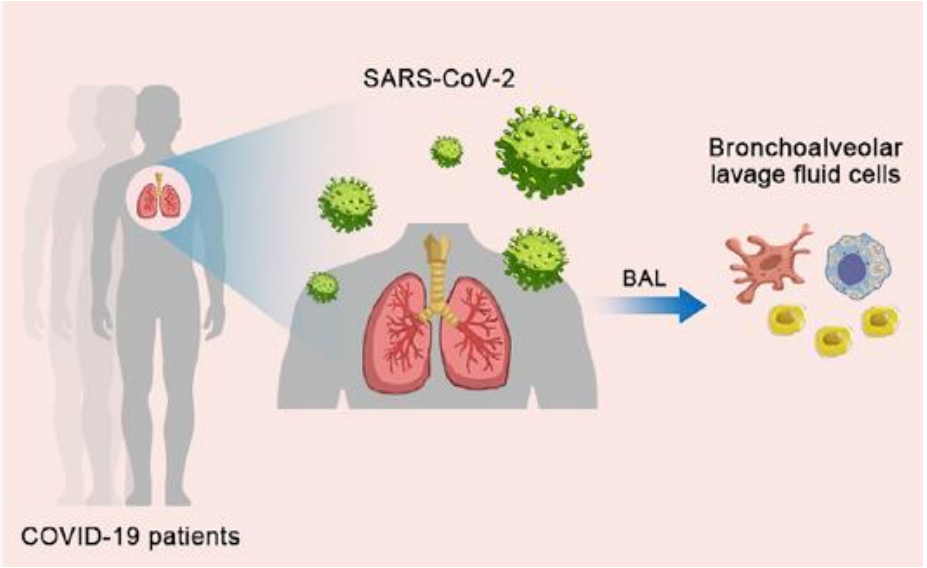
cogena for drug repositioning and drug mode of action discovery



Recombine the blocks of cogena to repurpose drugs and illuminate the MoA of drug via genes and pathway.

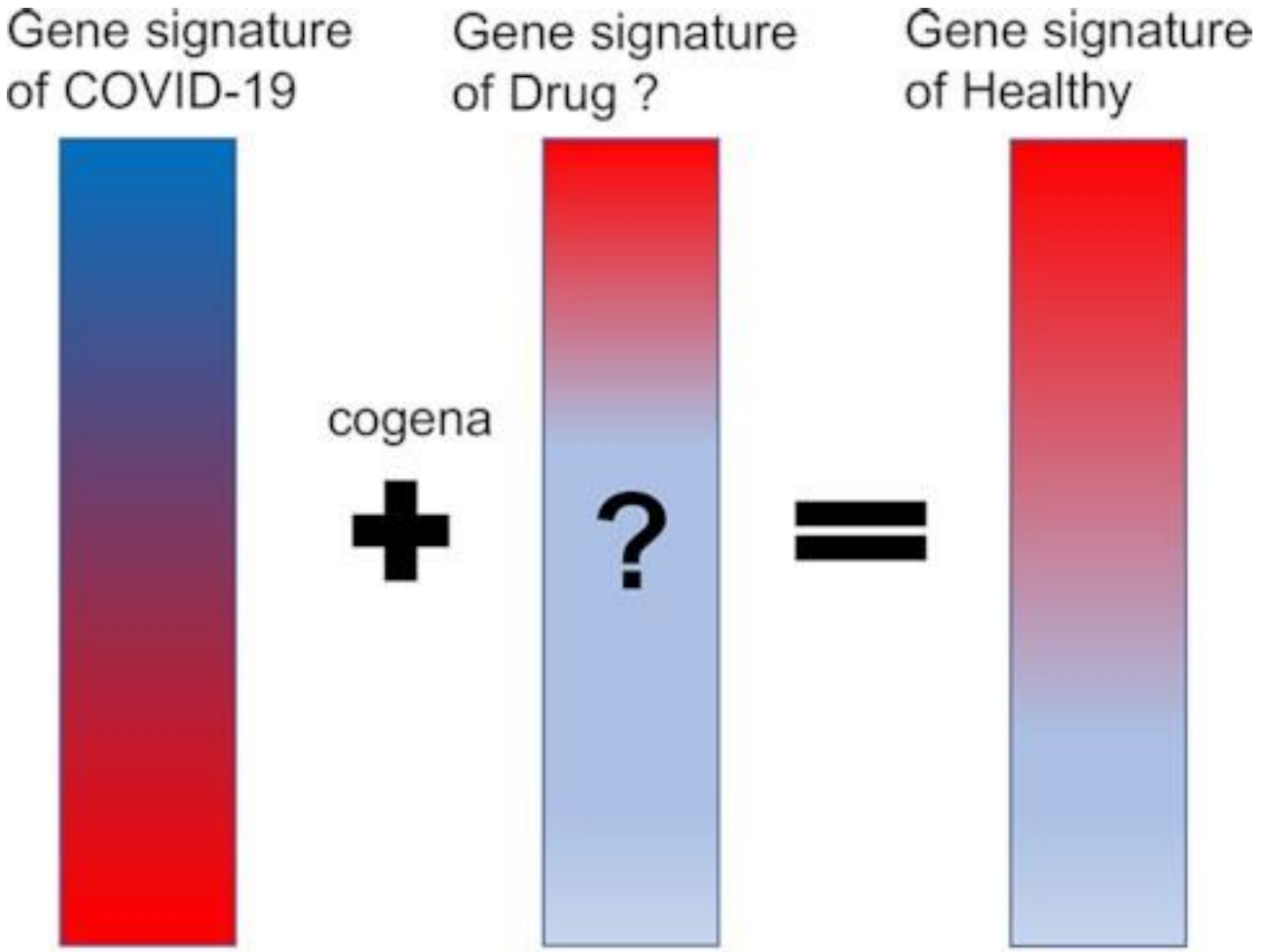
Data of COVID-19

- Size:
  - 8 severe COVID-19 patients
  - 20 healthy controls
- Sample type: bronchoalveolar lavage fluid (BALF)
- Metatranscriptome (hosts and microbes)



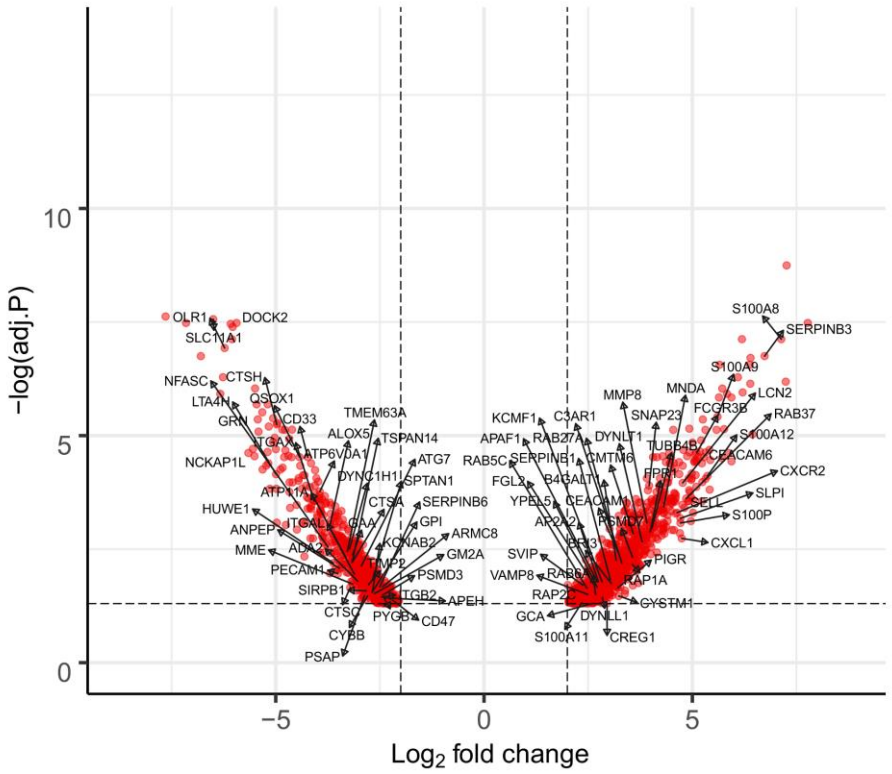
Zhou Z, Ren L, Zhang L, Zhong J, Xiao Y, Jia Z, Guo L, Yang J, Wang C, Jiang S, Yang D, Zhang G, Li H, Chen F, Xu Y, Chen M, Gao Z, Yang J, Dong J, Liu B, Zhang X, Wang W, He K, Jin Q, Li M, Wang J. Heightened Innate Immune Responses in the Respiratory Tract of COVID-19 Patients. Cell Host Microbe. 2020 Jun 10;27(6):883-890.e2.

Idea



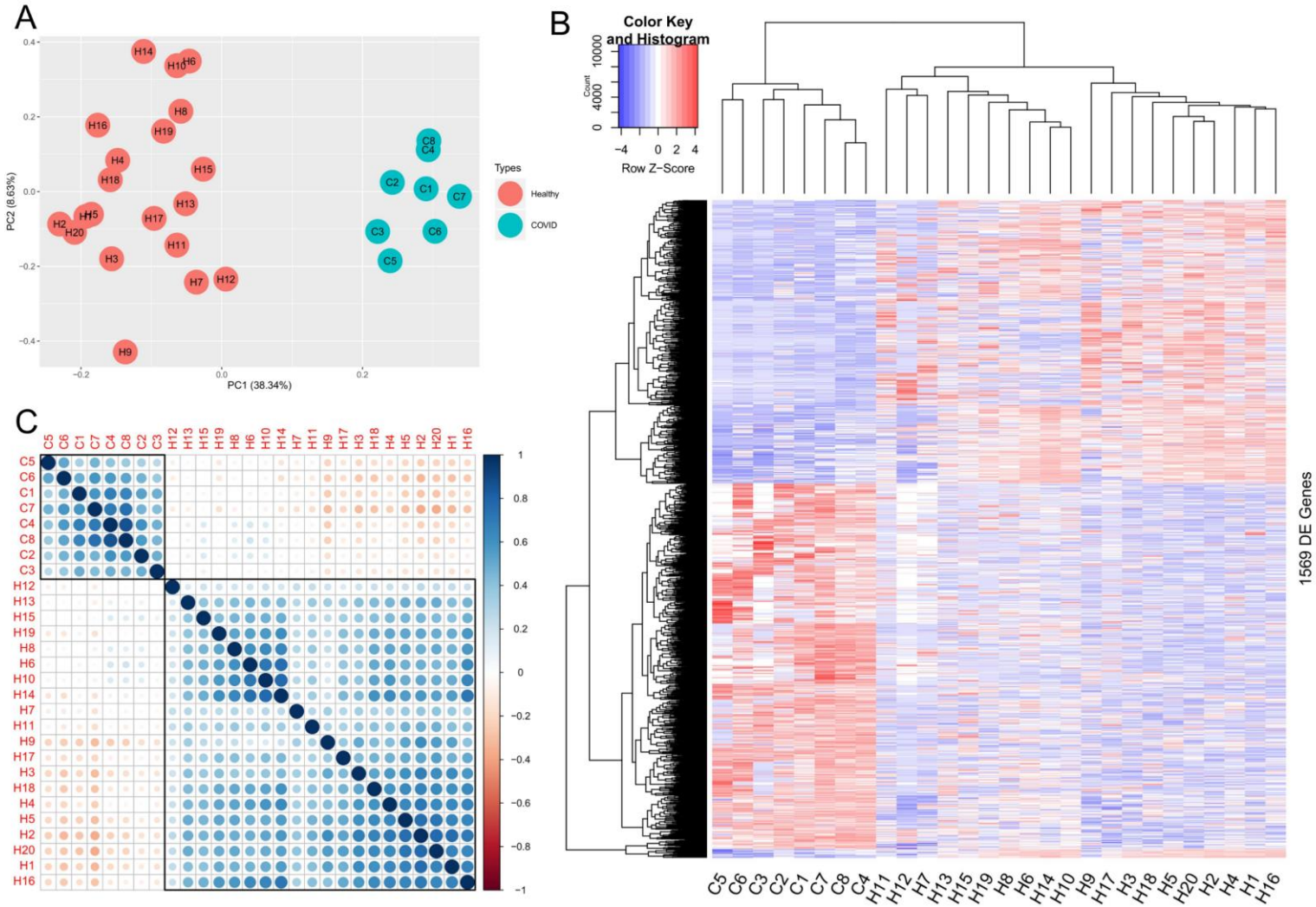
Jia Z, Song X, Shi J, Wang W, He K. Transcriptome-based drug repositioning for coronavirus disease 2019 (COVID-19). Pathog Dis. 2020 Jun 1;78(4):ftaa036. doi: 10.1093/femspd/ftaa036.

DEGs clearly distinguish the COVID and healthy groups



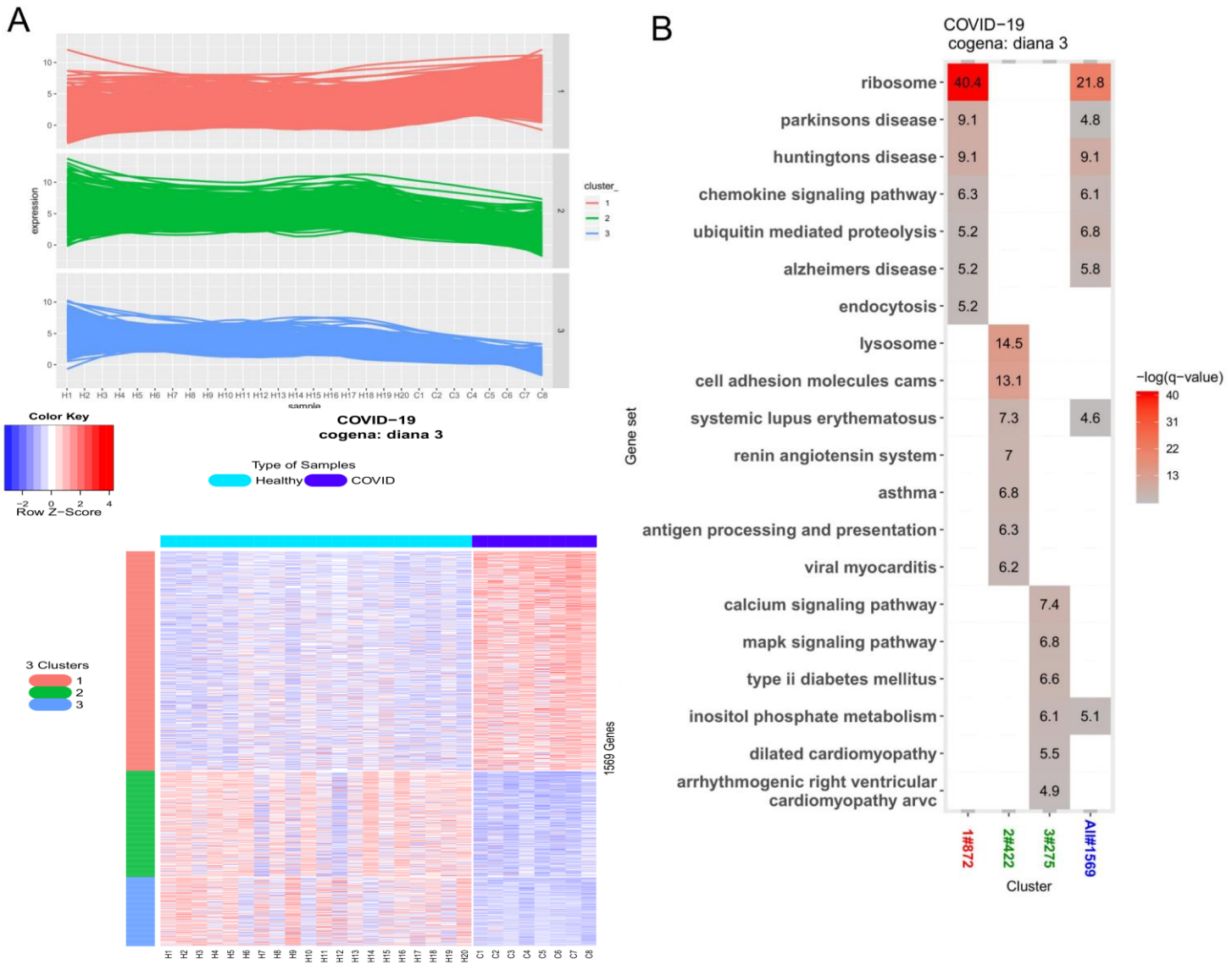
1569 differentially expressed genes

- 872 upregulated genes
- 697 downregulated genes



The two groups could be clearly separated with all the DEGs

Functional analysis of coexpressed genes



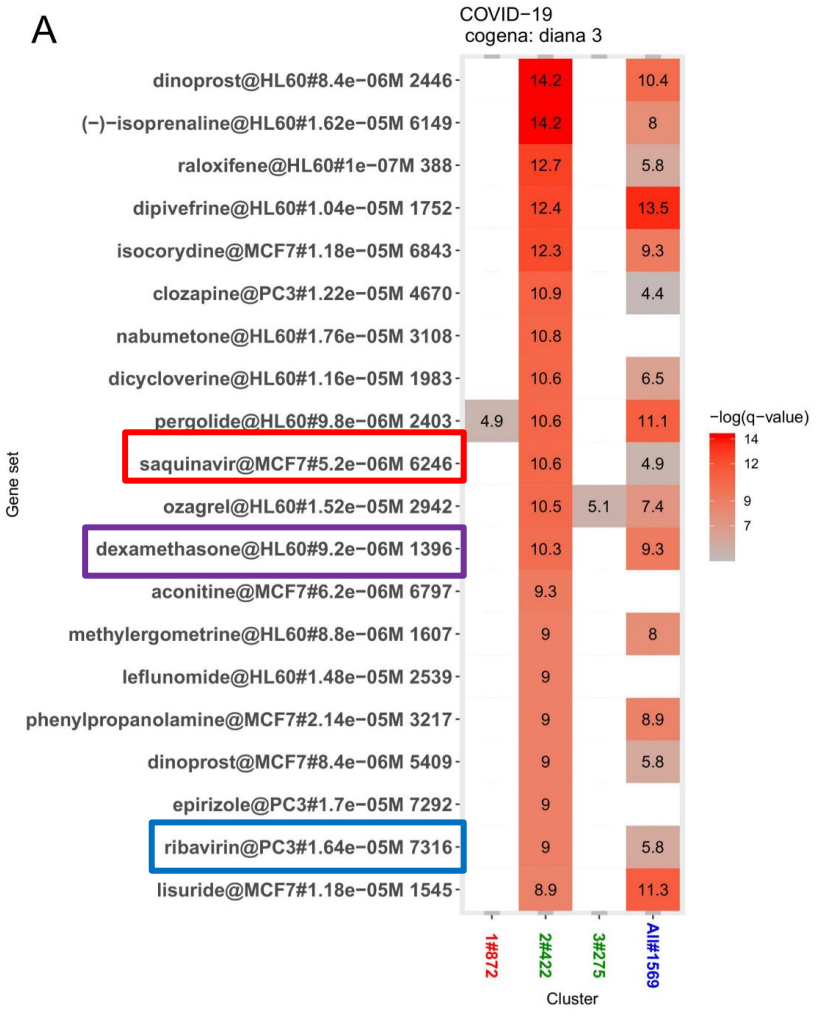
- C1: Ribosome, chemokine signaling and **endocytosis** pathways. Generally, endocytosis plays a role in viral entrance into the early endosomes in cells.
- C2: **Lysosome**, renin-angiotensin system and asthma pathways. Lysosomes are involved in destroying invading viruses, and the downregulation of lysosome-associated gene expression suggests dysregulation of the innate immune system.
- C3: Calcium and MAPK signaling pathways.

Computational drug repositioning for COVID-19 pneumonia

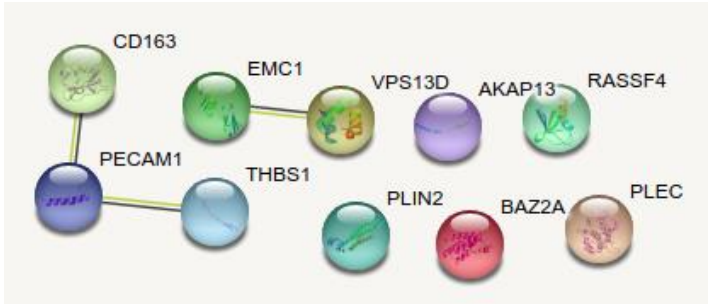
- **Saquinavir**, a protease inhibitor ranked 10th, is used to help control HIV infection. Also identified by several docking methods.

- **Dexamethasone** is a “major development” in the fight against COVID-19 in the RECOVERY trial. This finding is earlier than the trail at that time.

- **Ribavirin** can be used in combination with other antiviral medications to treat chronic hepatitis C and for SARS-CoV and MERS-CoV infections. A recommended drug in the diagnosis and treatment protocol for COVID pneumonia (trial version 5–latest) published by the National Health Commission of the P.R. of China. Also identified by several docking methods.
- Several other candidate drugs:
  - dinoprost: a smooth muscle activator
  - (-)-isoprenaline: a bronchodilator useful in obstructive lung diseases

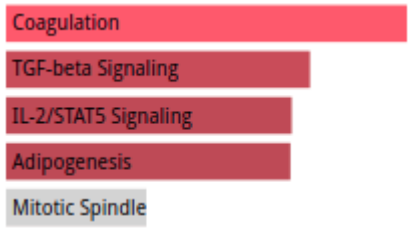


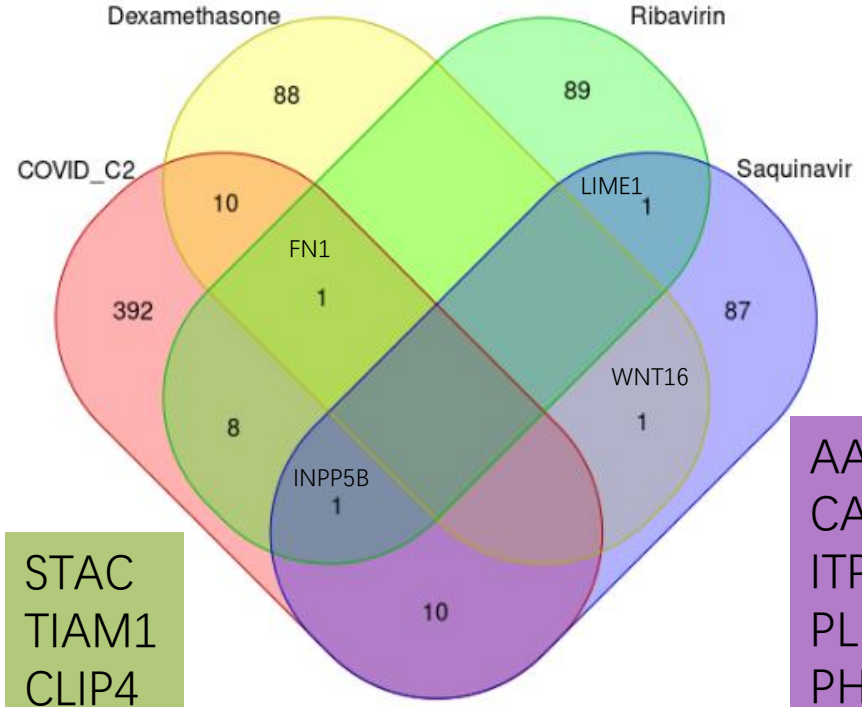
Gene and pathway levels for drugs

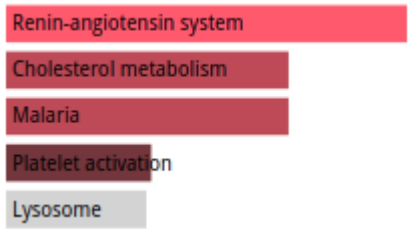


BAZ2A
RASSF4
CD163
PECAM1
PLIN2
VPS13D
EMC1
PLEC
AKAP13
THBS1

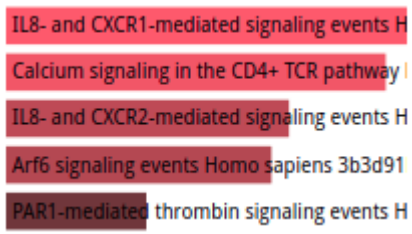
IL-2 is part of the body's **natural response** to microbial infection, and in discriminating between foreign and "self".







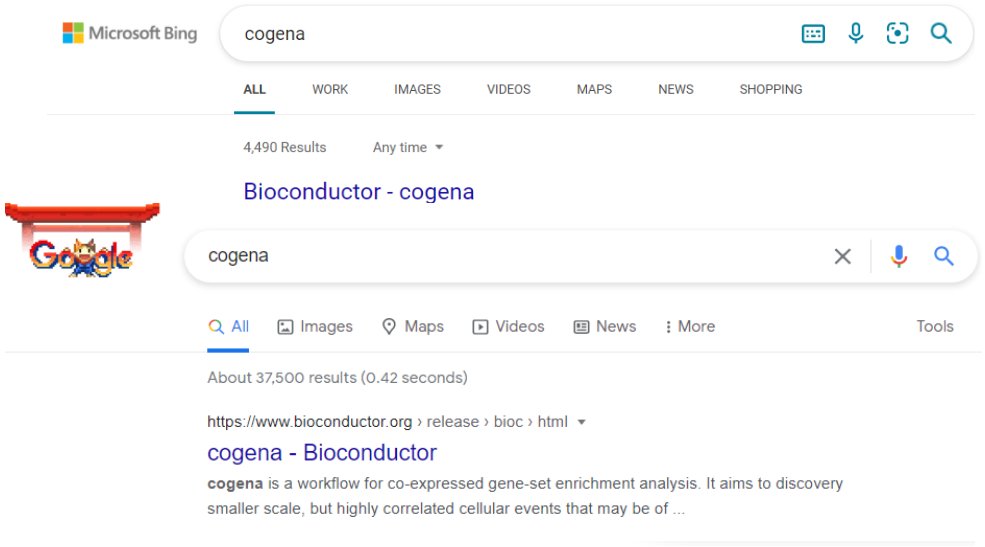
STAC
TIAM1
CLIP4
LNPEP
GM2A
STIM1
LRP1
SEL1L



AAK1
CABIN1
ITPR2
PLD3
PHKA2
ATP11A
ARRB1
ARAP1
MYOF
HLA-DQB1

Cogena and COVID-19

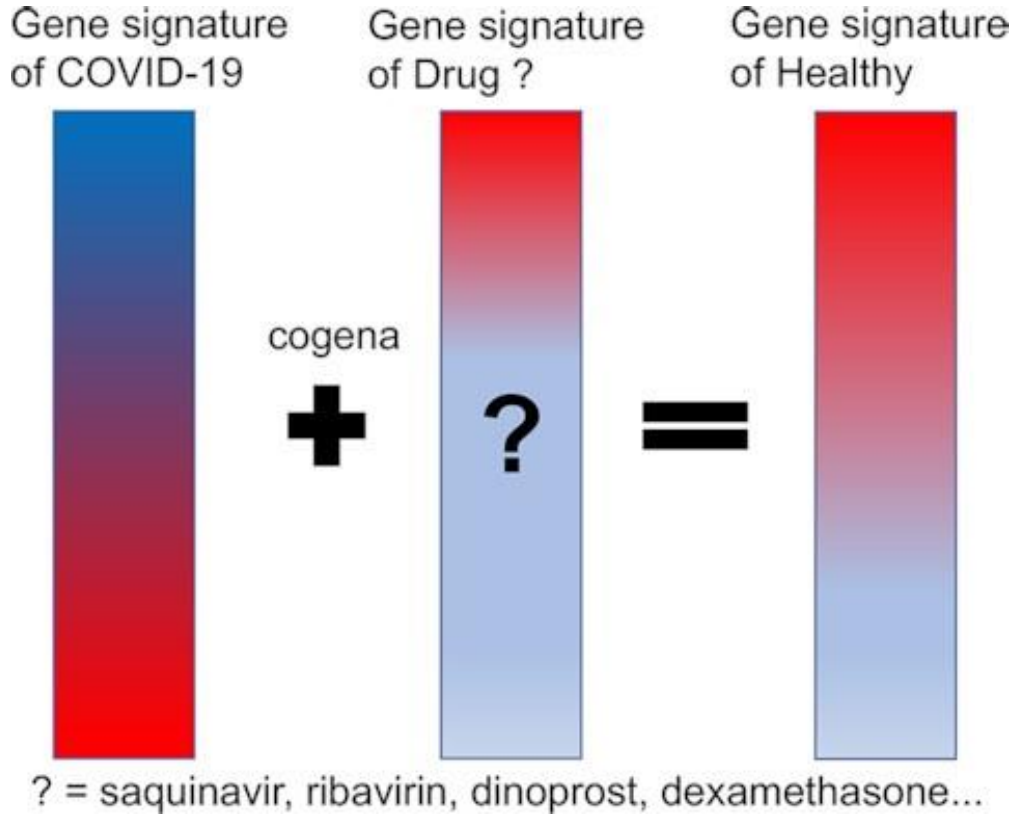
- Krishnamoorthy P, Raj AS, Roy S, Kumar NS, Kumar H. Comparative transcriptome analysis of SARS-CoV, MERS-CoV, and SARS-CoV-2 to identify potential pathways for drug repurposing. Comput Biol Med. 2021 Jan;128:104123. doi: 10.1016/j.compbiomed.2020.104123.
- Iyad Sultan, Scott Howard, Abdelghani Tbakhi et al. Drug Repositioning Suggests a Role for the Heat Shock Protein 90 Inhibitor Geldanamycin in Treating COVID-19 Infection, 22 March 2020, PREPRINT (Version 1) available at Research Square [https://doi.org/10.21203/rs.3.rs-18714/v1]



cogena: https://bioconductor.org/packages/cogena/
cogena applications:
https://github.com/zhilongjia/psoriasis
https://github.com/zhilongjia/Fn_HGFcell
Reproducible research: https://github.com/zhilongjia/COVID-19

Conclusion

- Cogena-based drug repositioning is **less computationally** intensive than docking methods.
- The transcriptome-based drug screening that identified drugs that are capable of **restoring virus-induced gene expression dysregulation**, rather than directly targeting viral or human proteins, as is the case for classical molecule docking methods. Esp. dexamethasone.



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Thank you
Q&A

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