BioVisionAlexandria 2014
April 7-9, 2014
Bibliotheca Alexandrina, Alexandria, Egypt

Functional genomics of cancer stem cell and repurposed drug discovery

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Systems Biology (I)

- "Systems biology is an interdisciplinary field of study that focuses on complex interactions within biological systems, especially, how it is controlled and regulated"

- "Systems biology is about putting together rather than taking apart, integration rather than reduction, and makes heavy use of mathematical and computational models

Systems Biology (II)

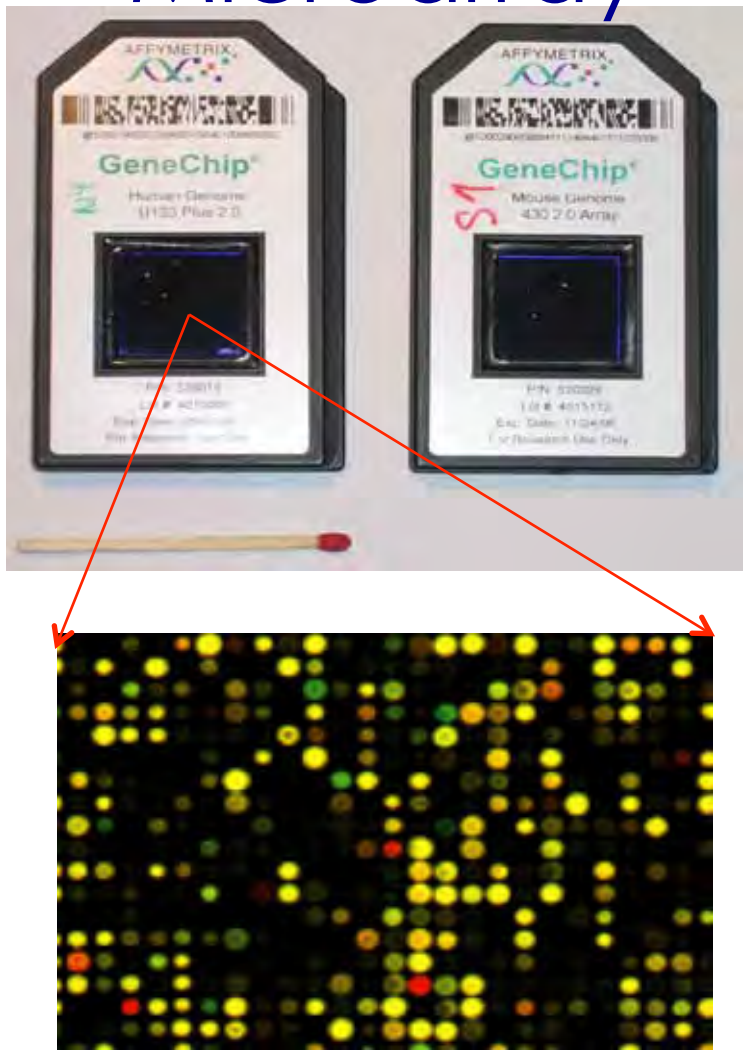
- Advances in high-through methods, especially sequencing techniques, and powerful computers have made the practice of systems biology possible

- Subject closely related subjects: genomics, proteomics, transcriptomics, metabolomics, epigenomics, …

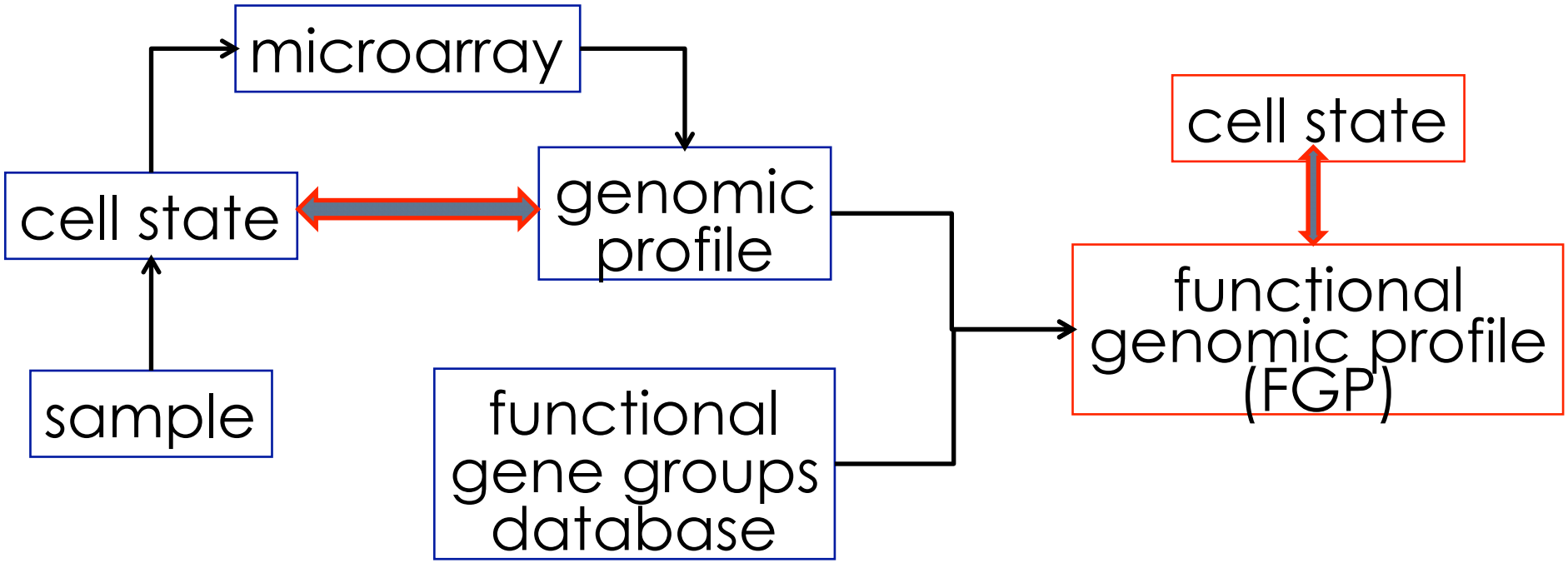
Gene expression data – metadata on cell activity

- Cell functions are carried out by proteins
- Proteins are "made" by genes that are expressed
- Expressed genes appear as mRNAs in the cell
- Quantitative measures of mRNA densities in the cell samples are indirect measures of cell activity
- These can be done by microarrays experiments (lately, by "next-generation sequencing" facilities)

Microarray

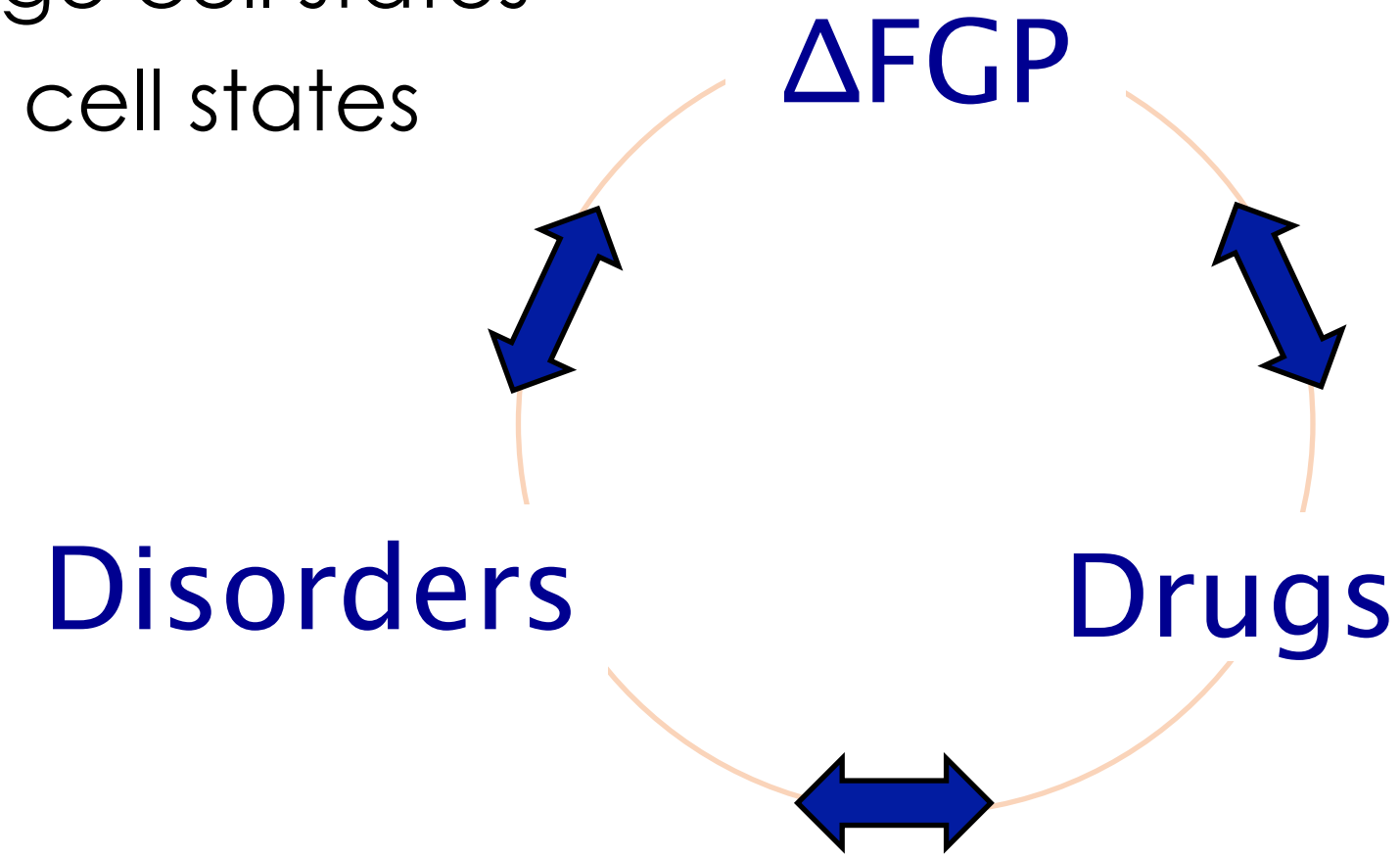


Functional genomic profile and cell state

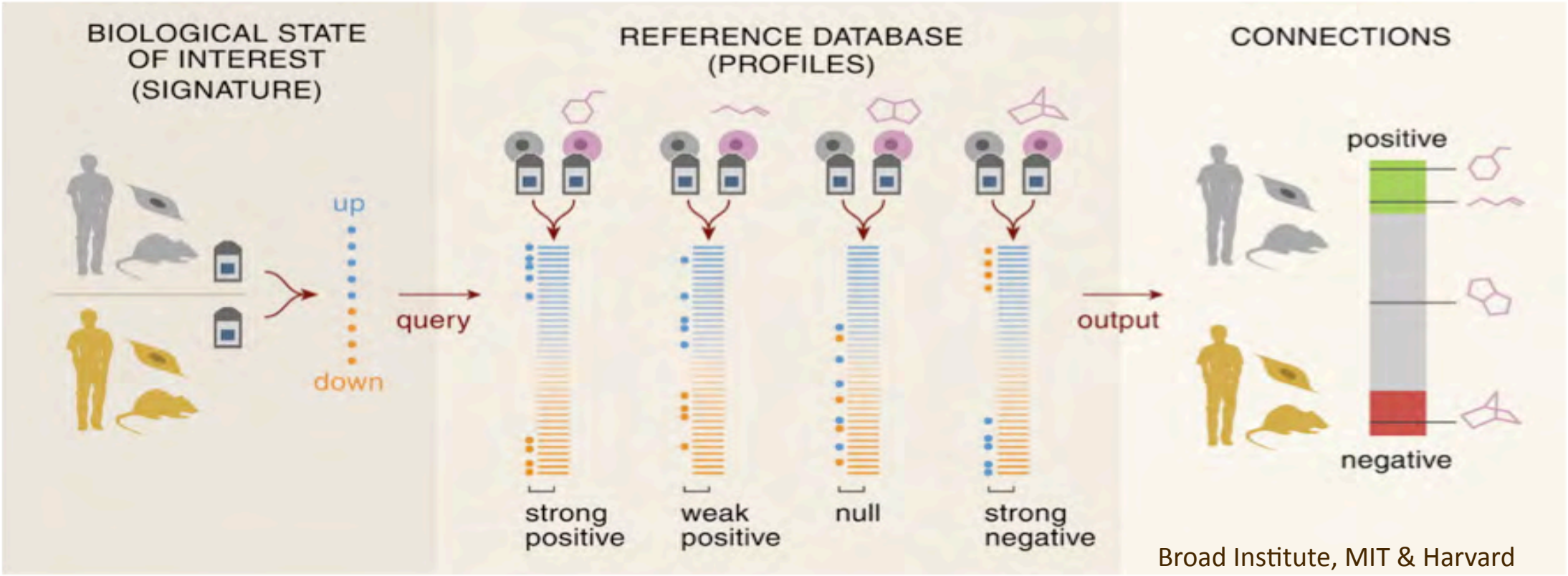


The ΔFGP-Disorder-Drug Trinity

- Changes in FGP ⇔ change in cell state
- Disorders change cell states
- Drugs change cell states



The Connectivity Map (CMap) – Database on genomic profiles of drug effects

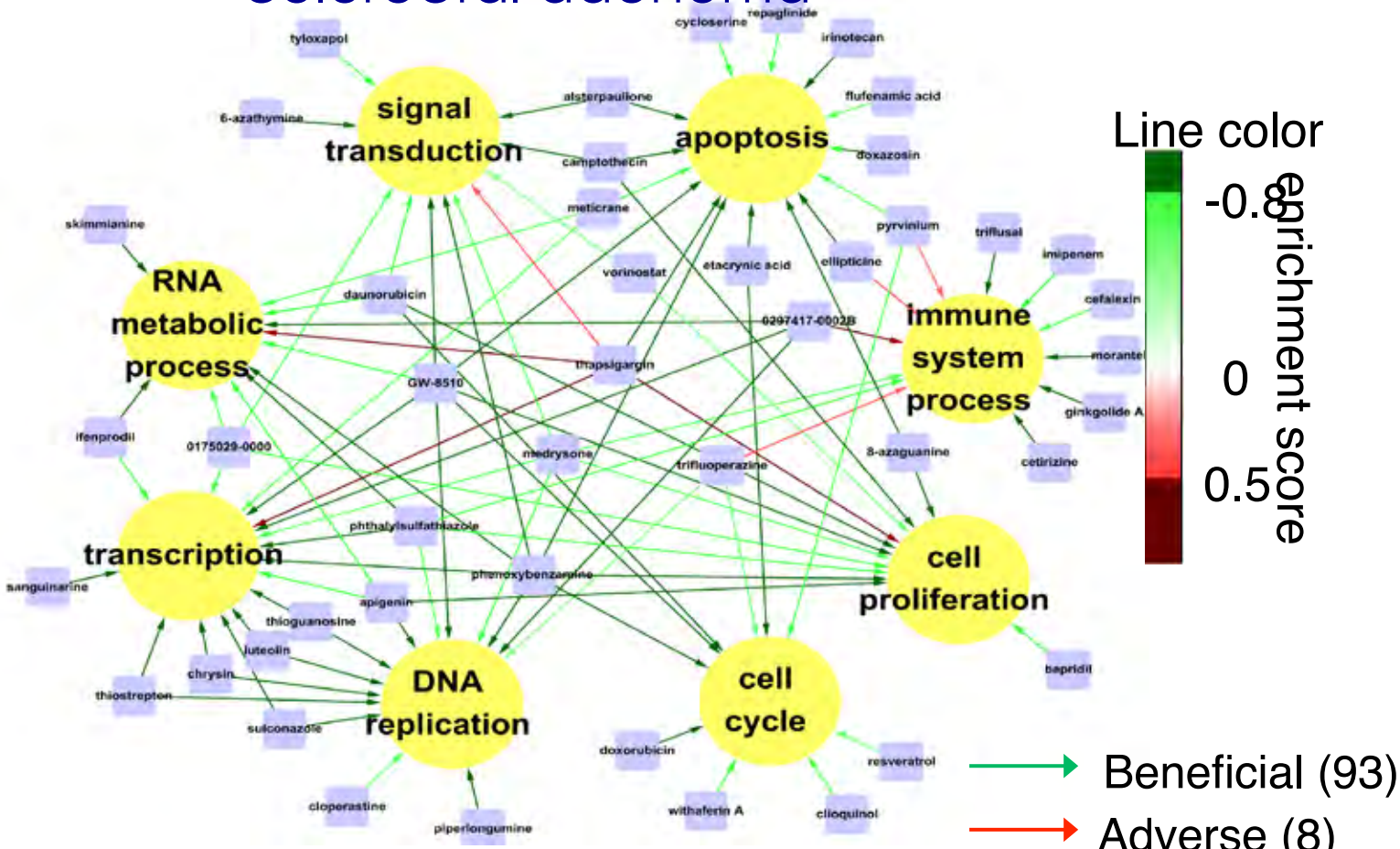


The Connectivity Map: using gene-expression signatures to connect small molecules, genes, and disease. *Science*. 2006 Sep 29;**313**(5795):1929-35.

Repurposed drug discovery for systems treatment of complex diseases 舊藥新用、西藥中用 (I)

- Cancer is a complex disease with multiple dysfucntions, requires systems treatment covering all affected functions
- Material - patient group microarray data
- Methods - GSToP, CMap, Functional Module CMap
- Result - Drug-disease association map indicates beneficial/ harmful effects drug to function

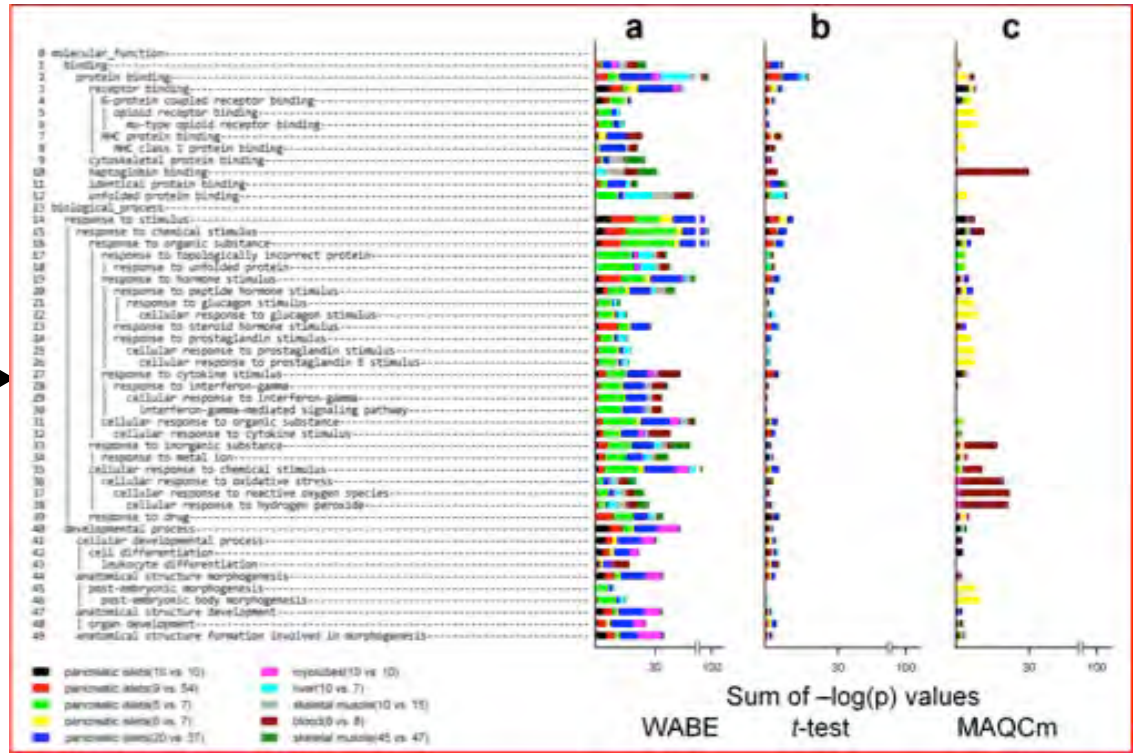
Drug-disease association map for colorectal adenoma



FH Chung, et al. PLoS ONE 9(1): e86299 (2014)

Functional genomic studies of some other complex diseases

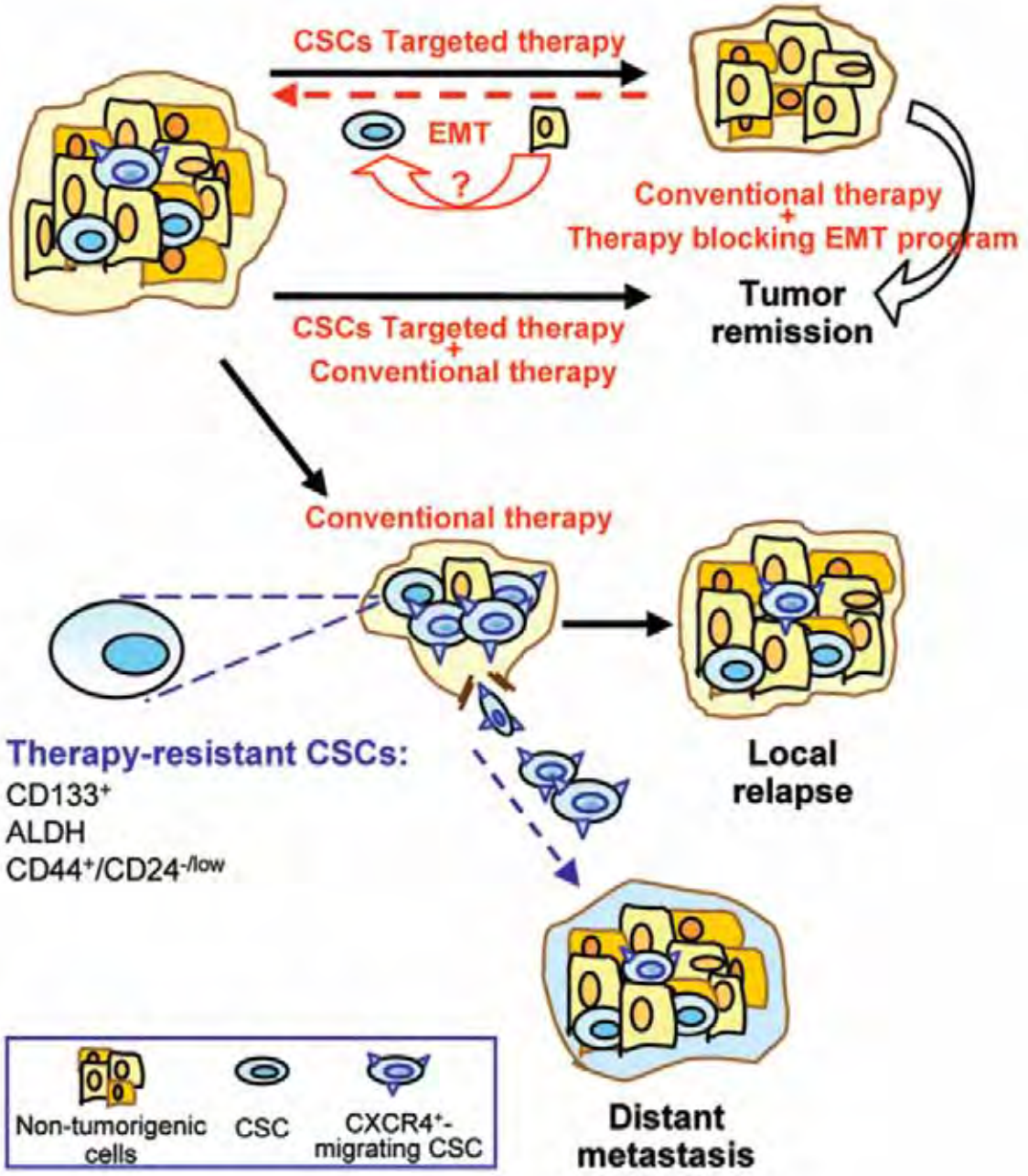
- Lung cancer
- Psychiatric disorders (bipolar, …)
- Type 2 diabetes
- Aging



Cancer Stem Cells

- Failure of standard treatments, including chemotherapy and radiotherapy, for preventing cancer relapses have been recently often attributed to a small set of drug resistant tumor cell

- These cell have stem cell-like properties and are commonly referred to as "cancer stem cells" (CSC)



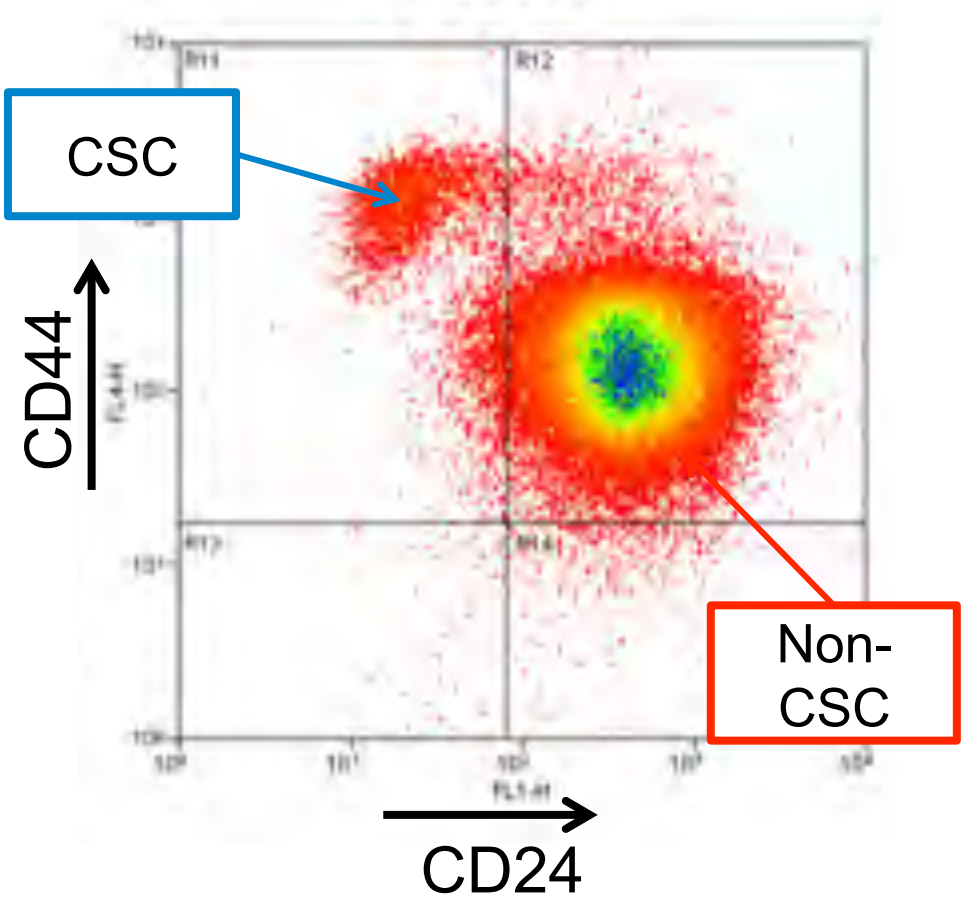
Giulia, et al., Cell Cycle 2010

Characteristic of Cancer Stem Cells (CSCs)

1. *self-renewal*
2. *tumor initiation*
3. *invasive*
4. *metastatic*
5. *therapy-resistant*

CSC data source

- CSC can be isolated experimentally and there microarray data on CSC of multiple cancer types Gene Expression Omnibus (GEO) database.
- We collected 14 CSCs and 4 control high quality data sets for functional genomic analysis



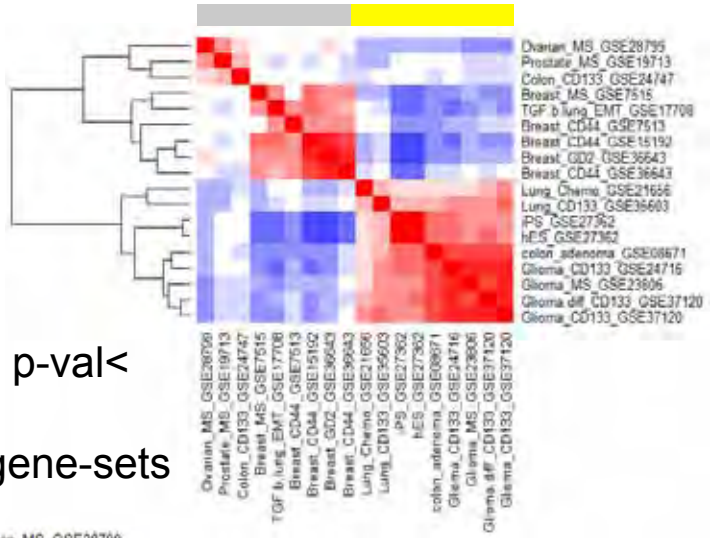
Sendurai A, et al., Cell, 2008.

Gene-set analysis (GSA) versus individual gene analysis (IGA)

- GSA is based on functional genomic profile, samples characterized by differentially enriched functions.
  - We used the method Gene Set Enrichment Analysis (GSEA); Subramanian et al. Science (2005)
- IGA is based on genomic profile, samples characterized by differentially expressed genes (DEG)

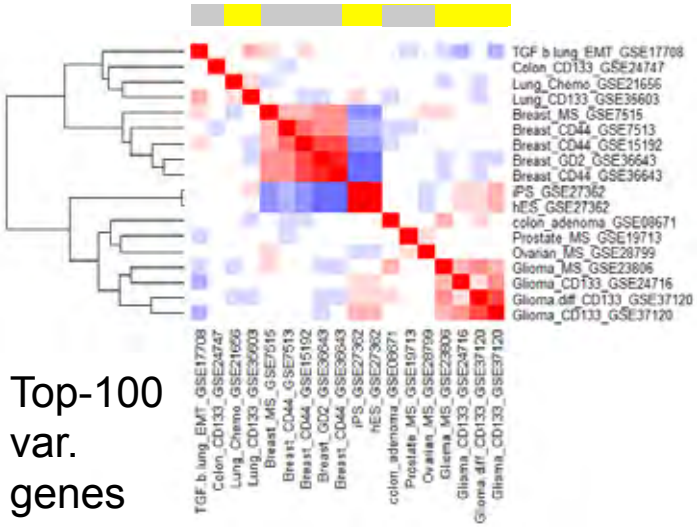
Sample clustering by content overlap – No clustering in IGA; into same two distinct groups in GSA using three methods

GSEA



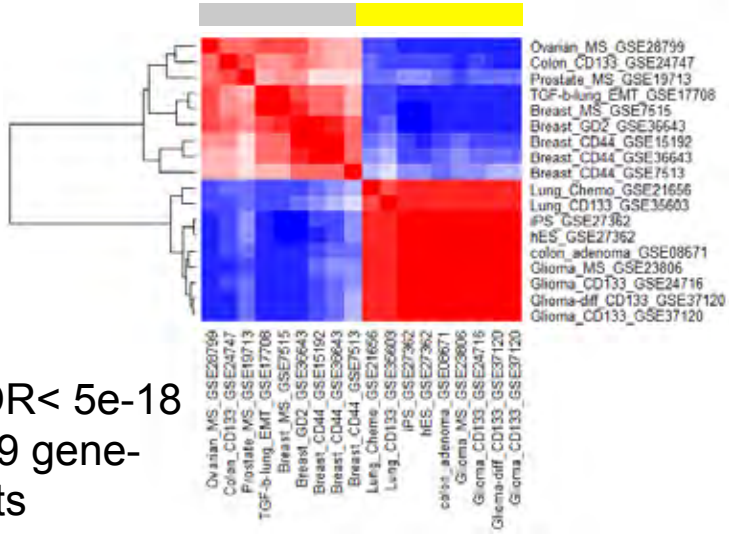
NOM p-val< 0.05
44 gene-sets

IGA



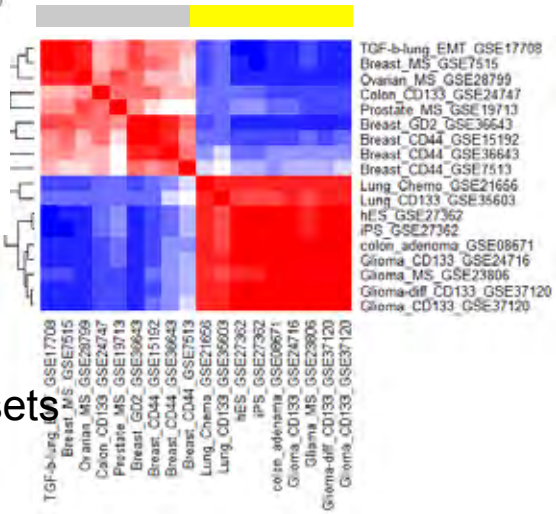
Top-100 var. genes

PAGE

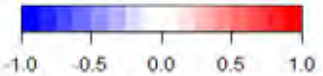


FDR< 5e-18
209 gene-sets

GAGE

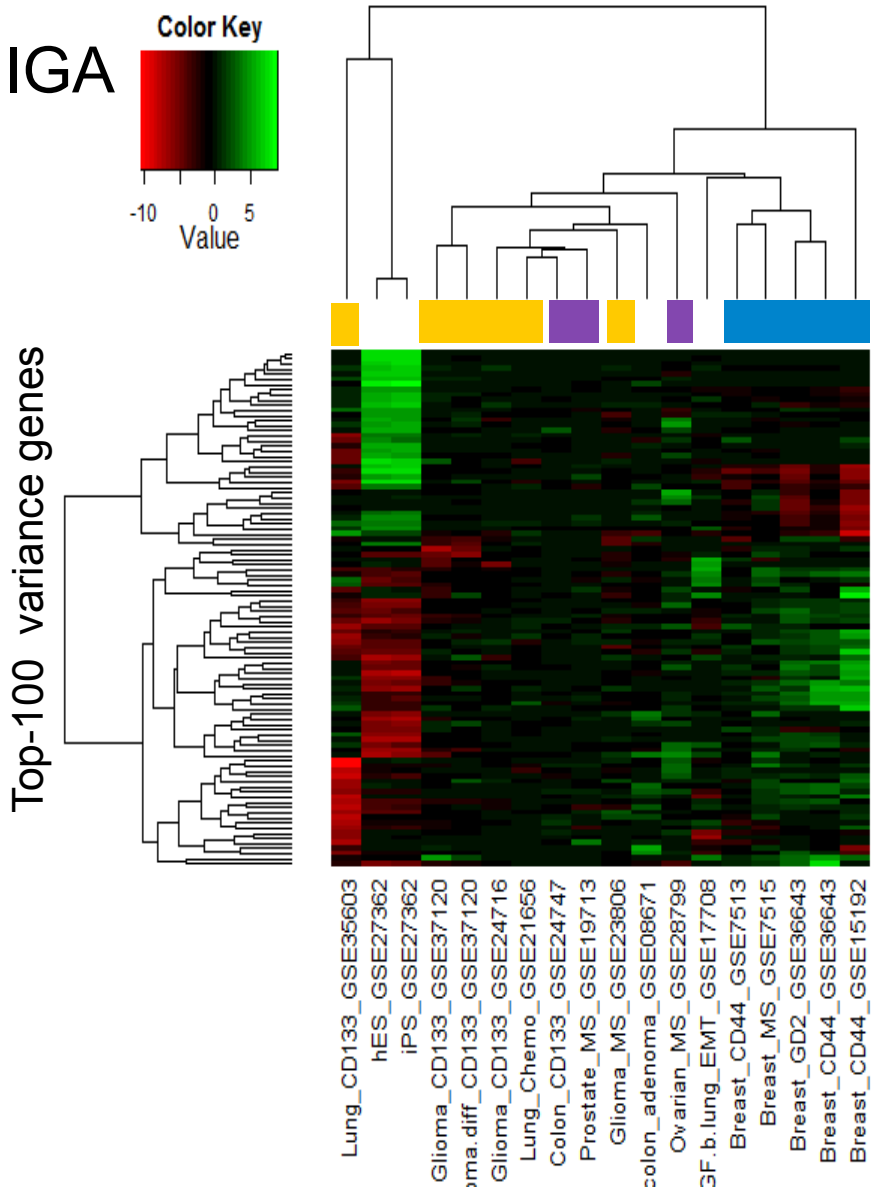


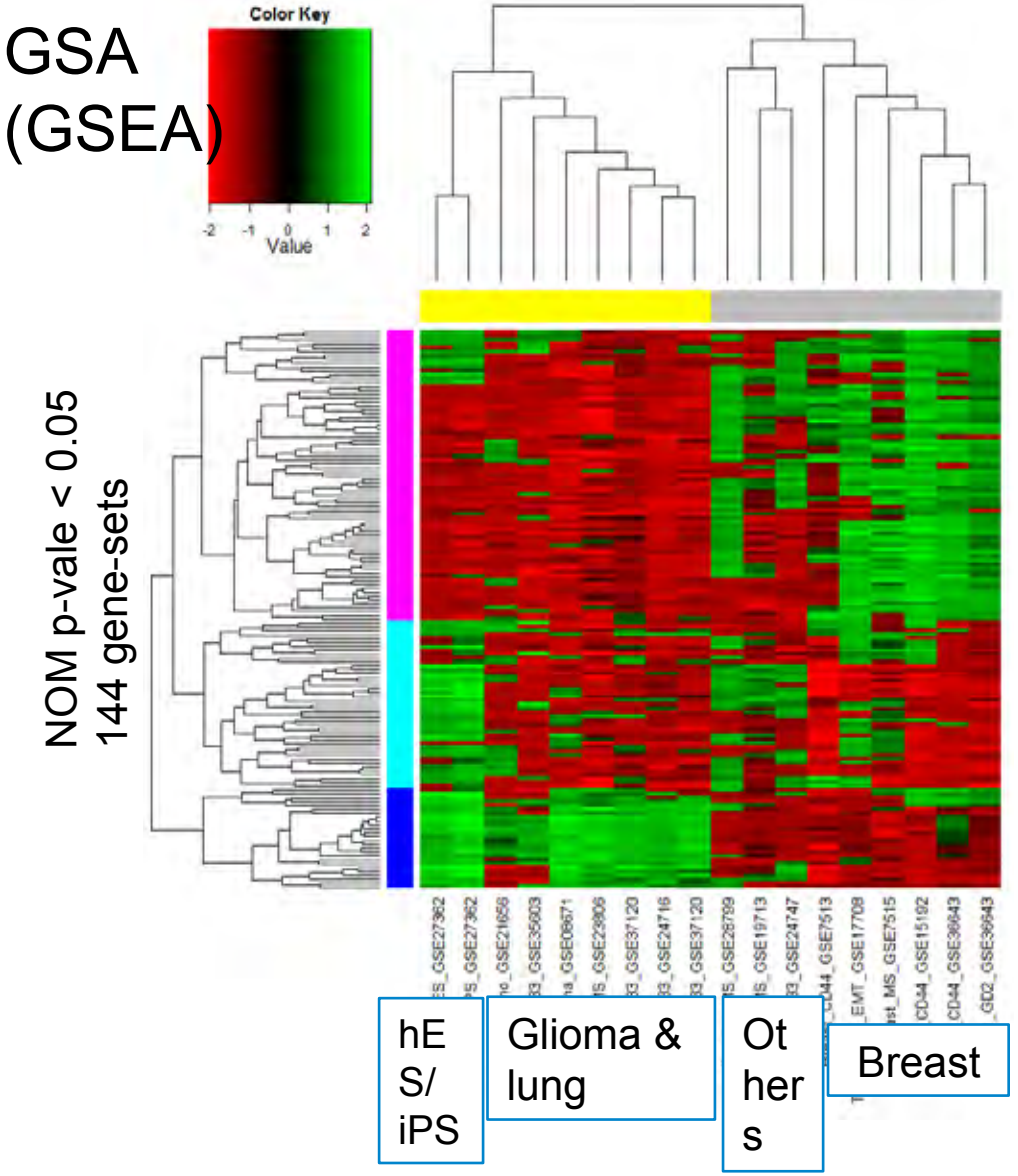
FDR< 5e-7
196 gene-sets



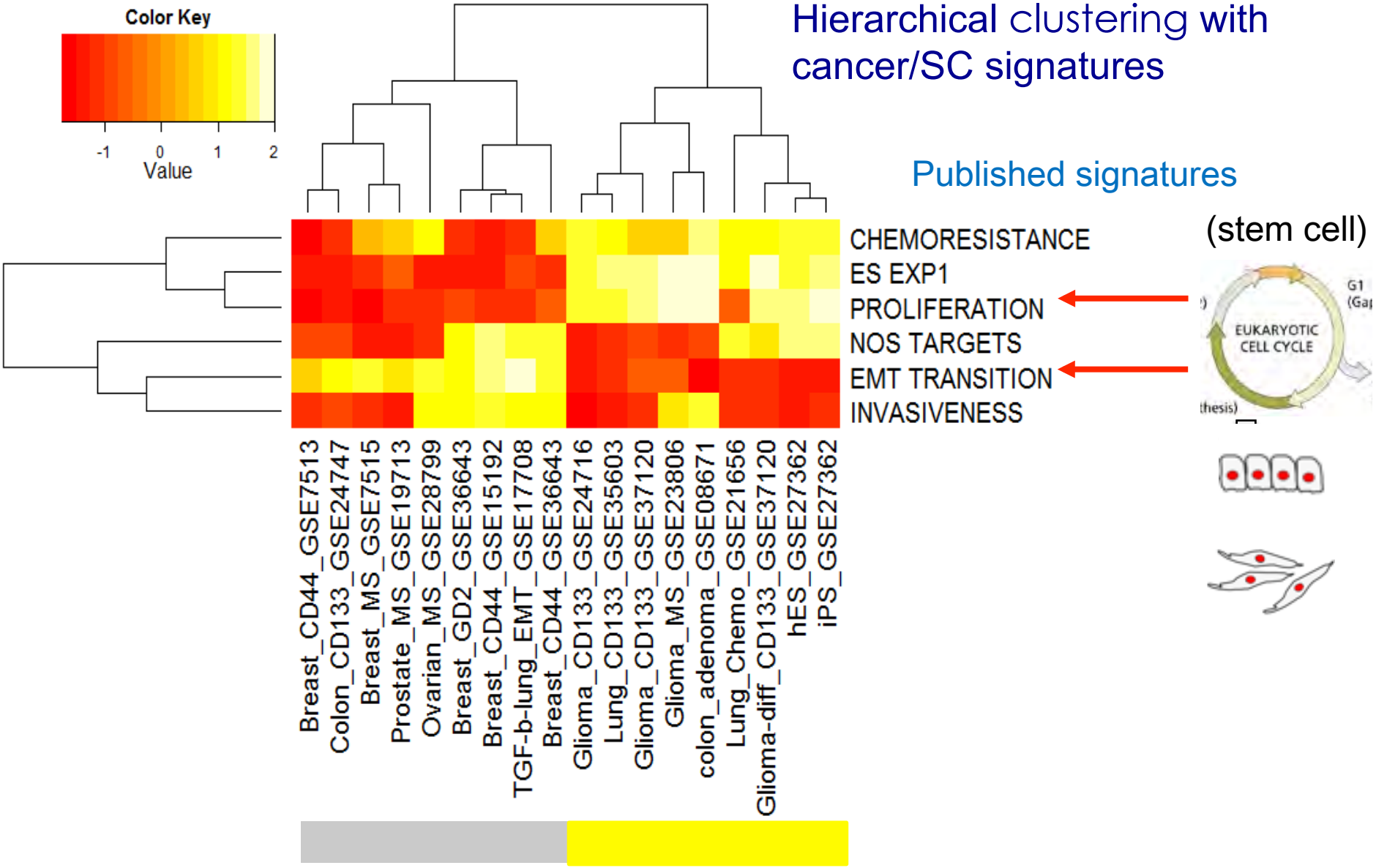
Correlation *r*

Two-way clustering of differentially expressed content by GSA (but not IGA) classifies samples into two types



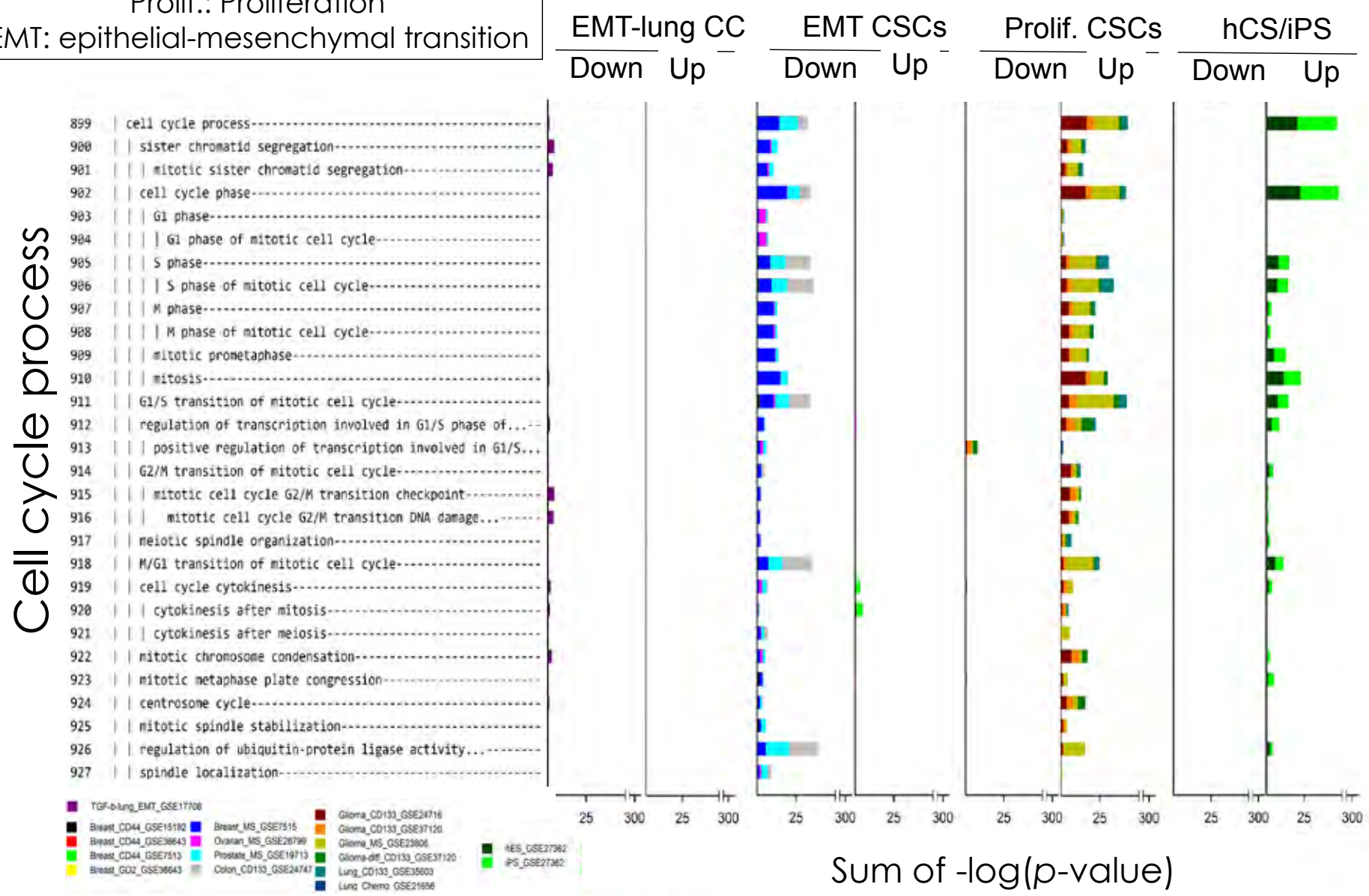


Two groups essentially characterized by two cancer/SC signatures: proliferation & EMT transition



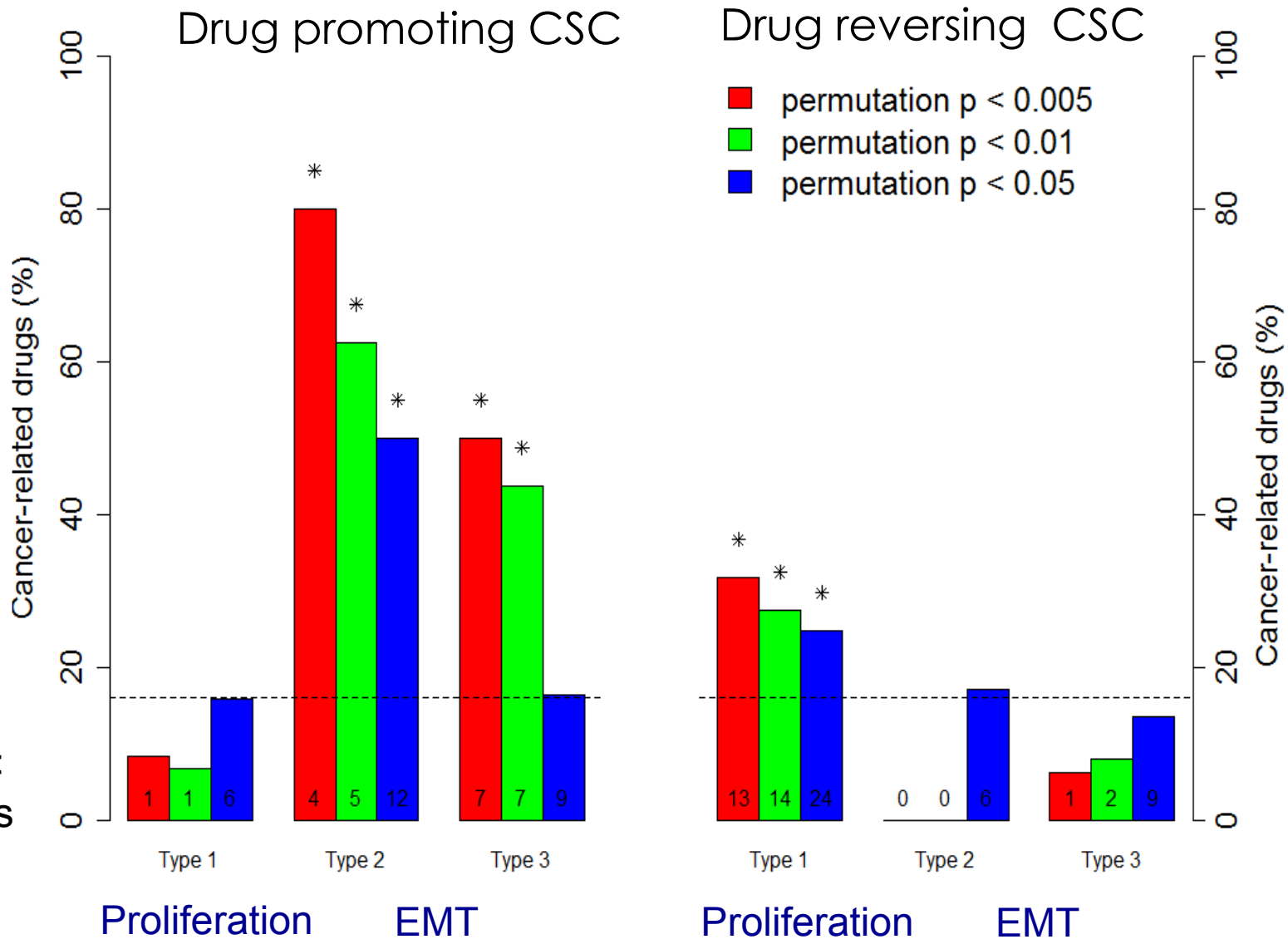
Cell cycle process over-enriched in proliferation-type CSCs but depleted in EMT-type CSCs

Prolif.: Proliferation
EMT: epithelial-mesenchymal transition



Drug analysis (CMap) suggests most cancer drugs have tendency to enhance CSC properties in EMT-type CSCs

C-Map queried by type-specific small p-value gene-sets



* represents $p < 0.05$ by Fisher's exact test

Summary

- GSA, but not IGA, classified 14 CSC samples into two subtypes
- The two CSC subtypes were characterized by two important cancer/SC signatures, proliferation (mainly breast cancer) and EMT (glioma)
- Cell cycle processes were over-enriched in proliferation-type CSCs but depleted in EMT-type CSCs
- Many cancer drugs effective for proliferation-type CSCs tended to enhance CSC properties in EMT-type CSCs

Conclusion

- Functional genomics is one link in, and a powerful tool for, systems biology studies, and may be applied to many biomedical related fields, including understanding diseases and stem cells, and repurposed drug discovery

- When coupled with experiments (not reported here) it becomes more powerful

- Being computer based, it allows (relatively) resource poor, tiny groups (such as ours) to do interesting and useful research

- Work done by:
  - Dr. Feng-Hsiang Chung, PDF
  - JL Hsu, TT Hsu, YH Tien, YH Peng, PhD students
  - Dr. Chih-Hao Chen, PDF

- Supported by
  - Ministry of Education
  - National Research Council/Ministry of Science & Technology
  - National Central University-Cathay General Hospital Joint Research Center
  - Center for Dynamical Biomarkers and Translational Medicine, National Central University

Thank you for your attention

National Central University
Zhongli, Taiwan

(views from my office building)