中国航天员中心
ASTRONAUT CENTER OF CHINA

Novel network pharmacology methods for drug mechanism of action identification, pre-clinical drug screening and drug repositioning

用于药物作用机制研究、临床前药物筛选与药物重定位的网络药理学新方法

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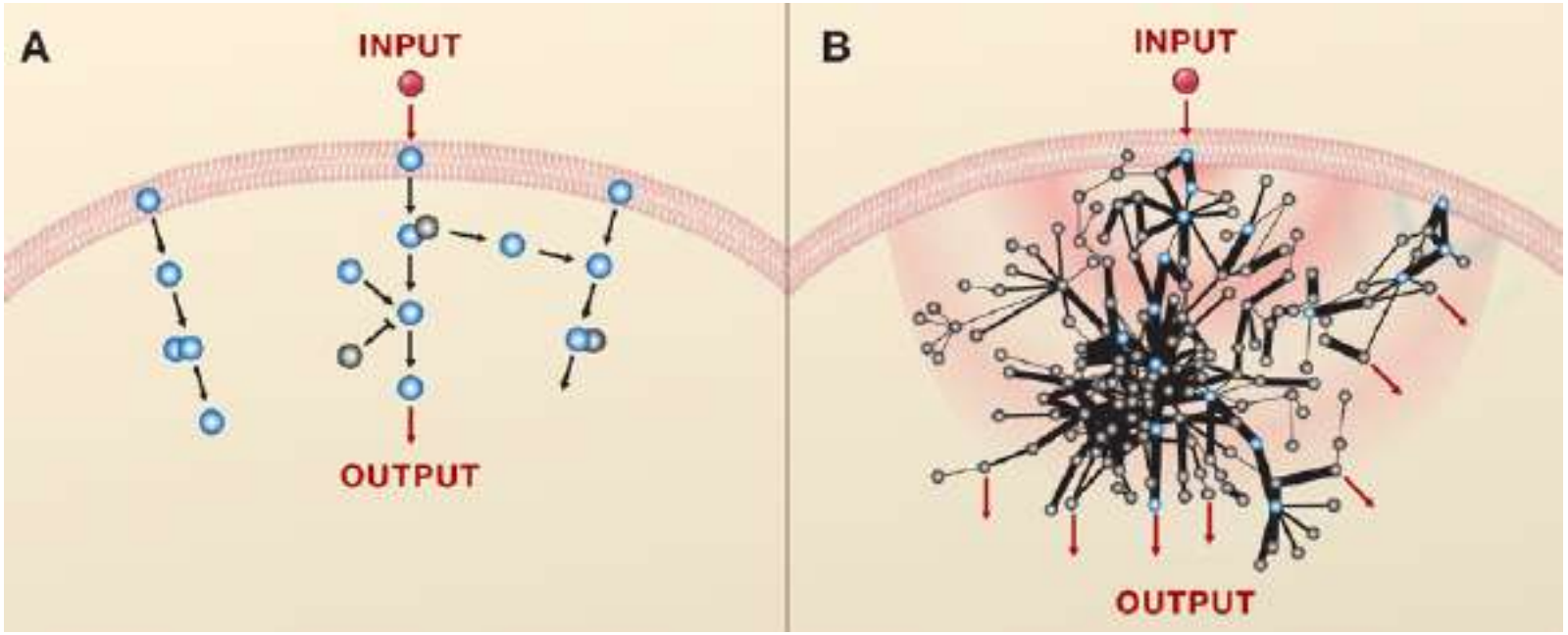
Bioinformatics group

Outline

- **Network pharmacology**
- **Case study I : Pre-Clinical Drug Prioritization via Prognosis-Guided Genetic Interaction Networks**
- **Case study II : Dynamic remodeling of context-specific miRNAs regulation networks facilitate in silico cancer drug screening**
- **What's next**

Network – a better knowledge representation

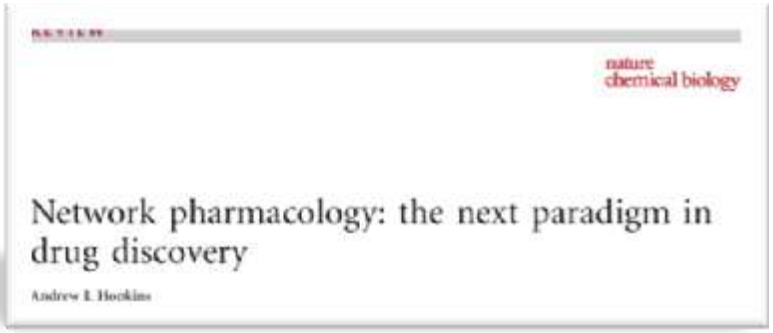


Linear pathway network

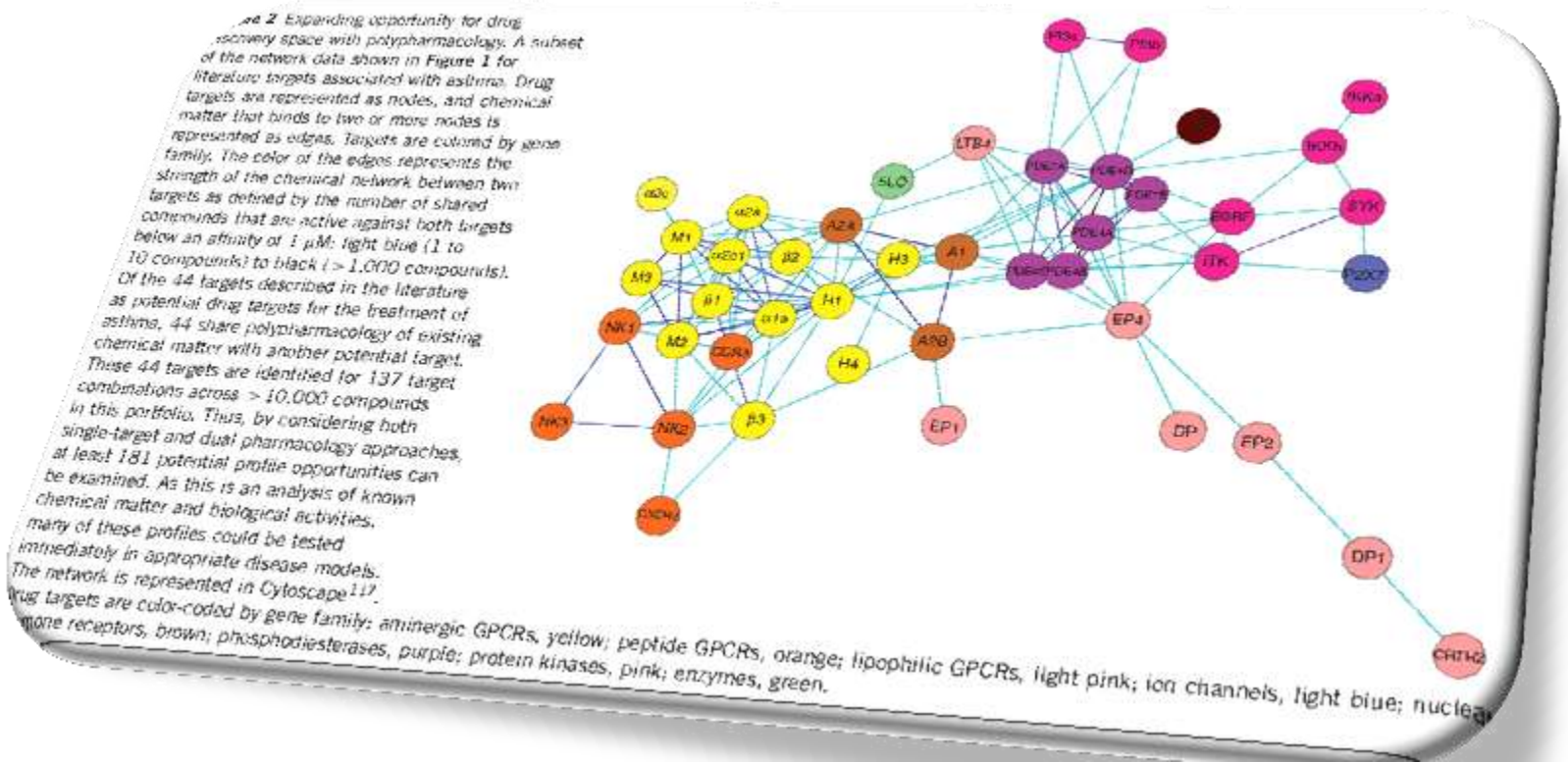
Leading Edge
Essay
Cell

Genetic Screening for Signal Transduction in the Era of Network Biology

Network pharmacology



Network Pharmacology attempts to model the effects of a drug action by simultaneously modulating multiple proteins in a network



Case Study I

Pre-Clinical Drug Prioritization via Prognosis-Guided Genetic Interaction Networks

Jianghui Xiong et al. PLoS ONE. 2010

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0013937

(Full text download)

Oncology Drug Development

One of most challenging scientific problems

Table 2 | **Cancer Phase I response**

Tumour type	Response number/ total (%)
Colorectal	2/476 (0.4%)
Lung	10/196 (5.1%)
Kidney	6/147 (4.1%)
Breast	5/94 (5.3%)
Prostate	4/88 (4.5%)
Sarcoma	2/86 (2.3%)
Ovarian	2/124 (1.6%)
Head and neck	1/41 (2.5%)
Melanoma	4/97 (4.1%)
Other	9/218 (4.1%)
Total	45/1612 (2.8%)

*Trials conducted between 1999 and 2002 according to standard clinical response criteria (from REF. 4). Note that due to dose-escalation protocols, drug dose in many patients in Phase I trials is below the target-inhibiting dose (see text).

What's wrong with our cancer models? NATURE REVIEWS DRUG DISCOVERY, 2005

What's wrong with our Disease Models

- The current models used for pre-clinical drug testing Do NOT accurately predict how new treatments will act in clinical trials
  - *Heterogeneity in patient populations*
  - Unpredictable physiology

Table 1. Mouse models of human cancer

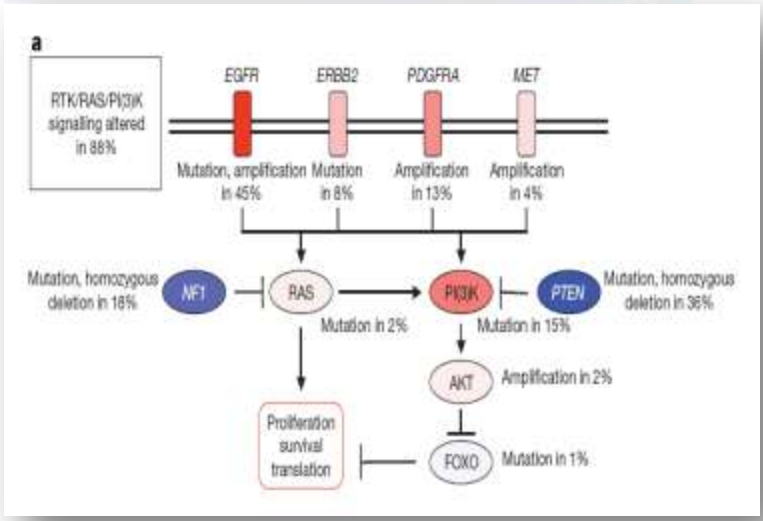
Cancer site	Mouse model	Refs
Brain		
Medulloblastoma	Ptc$^{+/-}$; p53, GFAP-Cre; Rb$^{lox/lox}$	[30]
Astrocytoma	GFAP-v-src, GFAP-HRas	[30]
Glioblastoma	NPcis	[31]
Breast		
Low-grade mammary intraepithelial neoplasia	MMTV-LTR/int3, MT/HGF	[32]
High-grade mammary intraepithelial neoplasia	C(3)1/SV40 tag, WAP/TGFα	[32]
Papillary carcinoma	MMTV-LTR/cyclin D1, MMTV-PyV-mt	[32]
Human ductal carcinoma in situ (DCIS)	MMTV-c-erb-B2	[32]
Colon		
Adenoma	Apc$^{Min/+}$; Apc$^{\Delta 716}$; Apc$^{\Delta 580/+}$	[33]
Adenocarcinoma	Mlh1$^{-/-}$; Apc$^{\Delta 580/+}$; Msh6$^{-/-}$; Apc$^{\Delta 580/+}$; Msh3$^{-/-}$; Apc$^{\Delta 580/+}$	[33]
Mucinous carcinoma	Tgfb$^{-/-}$; Rag2$^{-/-}$	[33]

Table 3 | Commonly used cancer models

Type	Subtype	Example
Human tumour cell line	Native Engineered	HCT116 colon FLT3-dependent BaF/3 cells
Human xenograft	Subcutaneous Orthotopic	PC-3 prostate PC-3 prostate implanted in prostate
Mouse tumour	Syngeneic implant Induced Genetically engineered	B16 melanoma Radiation-induced skin tumours RIP-Tag mouse pancreatic islet

?

THE CANCER GENOME ATLAS



Drug Discov Today Dis Models, 2008

What's wrong with our cancer models? NATURE REVIEWS DRUG DISCOVERY, 2005

Our proposal

1 Hypothesis

- The difficulty of identifying effective cancer cures (as evidenced by drug resistance) may be a consequence of the robustness of physiology-level (or microenvironment-level) network regulation
- **Network (robustness) as drug target**
  - Gene networks associated with cancer outcome in heterogeneous patient populations

2 Pre-clinical *in silico* Cancer Models for Drug Prioritization

- **Incorporating heterogeneity and in vivo physiology information, which MISSING in pre-clinical cancer models**

What type of gene network?

The NEW ENGLAND JOURNAL of MEDICINE

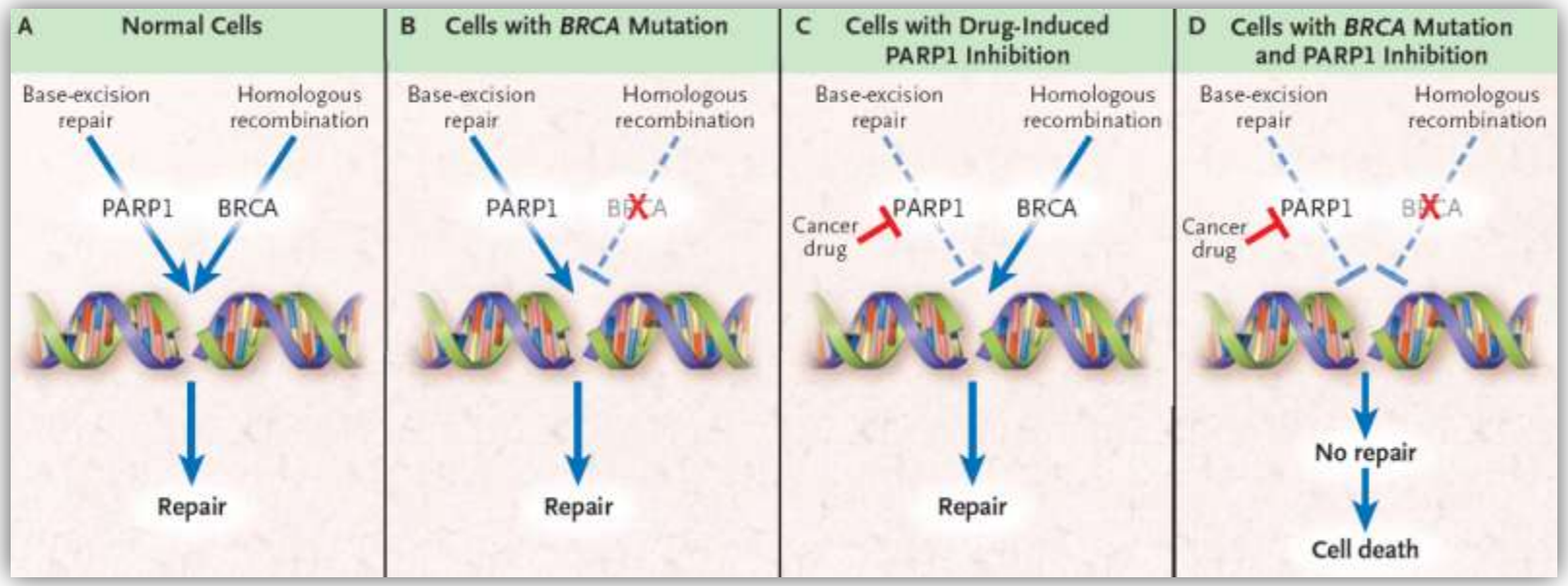
EDITORIALS

Synthetic Lethality — A New Direction in Cancer-Drug Development

J. Dirk Iglehart, M.D., and Daniel P. Silver, M.D., Ph.D.

a Synthetic lethality

Gene *A*	Gene *B*	
A	*B*	Viable
A	*b*	Viable
a	*B*	Viable
a	*b*	Lethal



Synthetic lethal provide approach for drug combination

446|12 April 2007|doi:10.1038/nature05697 nature

LETTERS

Synthetic lethal screen identification of chemosensitizer loci in cancer cells

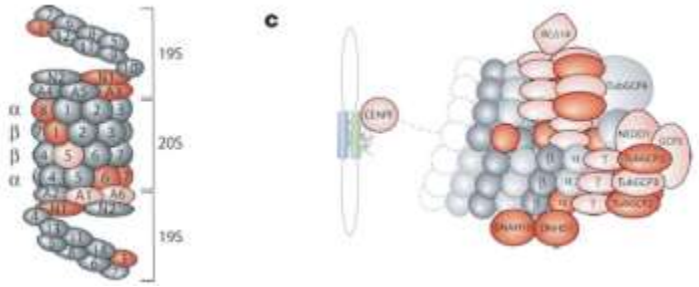
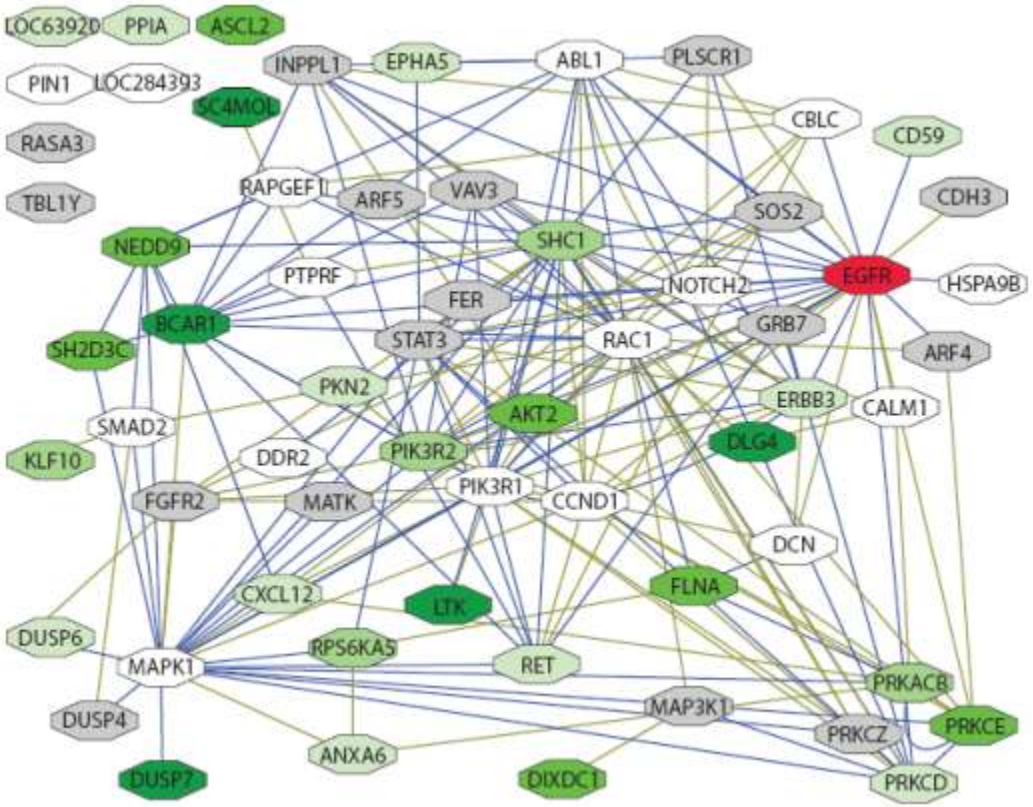


Table 1 | High-confidence hit list

Symbol	Comments; motifs	Symbol	Comments; motifs
Proteasome		Transcription	
PSMA6	Proteasome subunit	RP9	ZnF_C2HC
PSMA7	Proteasome subunit	ZFPM1	ZnF_C2H2(x9)
PSMA8 (MGC26605)	Proteasome subunit	ZNF503	ZnF_C2H2
PSMB1	Proteasome subunit	ZNF585A	KRAB; ZnF_C2H2(x21)
PSMC3	Proteasome subunit	C11ORF30	ENT
PSMD1	Proteasome subunit	TRIM15	RING, BBOX, PRY, SPRY
PSMD3	Proteasome subunit		
		Translation	
Microtubule-related		RARSL	Arginyl-tRNA synthetase-like; Arg_S Core, tRNA-synt_1d_C
TUBGCP2	γ-TURC subunit; Spc97_Spc98	LOC390876	Similar to 60S ribosomal protein L35; coiled-coil
TUBA8	α-Tubulin	LOC388568	Similar to ribosomal protein S15 isoform
DNHD1 (FLJ32752)	Dynein heavy-chain subunit	SYMPK	
DNAH10 (FLJ43808)	Dynein heavy-chain subunit	SYNCRIP	RRM
TBL1Y	Transducin (β)-like 1Y-linked; LisH, WD40	BCDIN3 (FLJ20257)	Bin3, PrmA
MPP7	MAGUK family; L27, PDZ_signalling, SH3, GMPK	LOC144233	Bin3

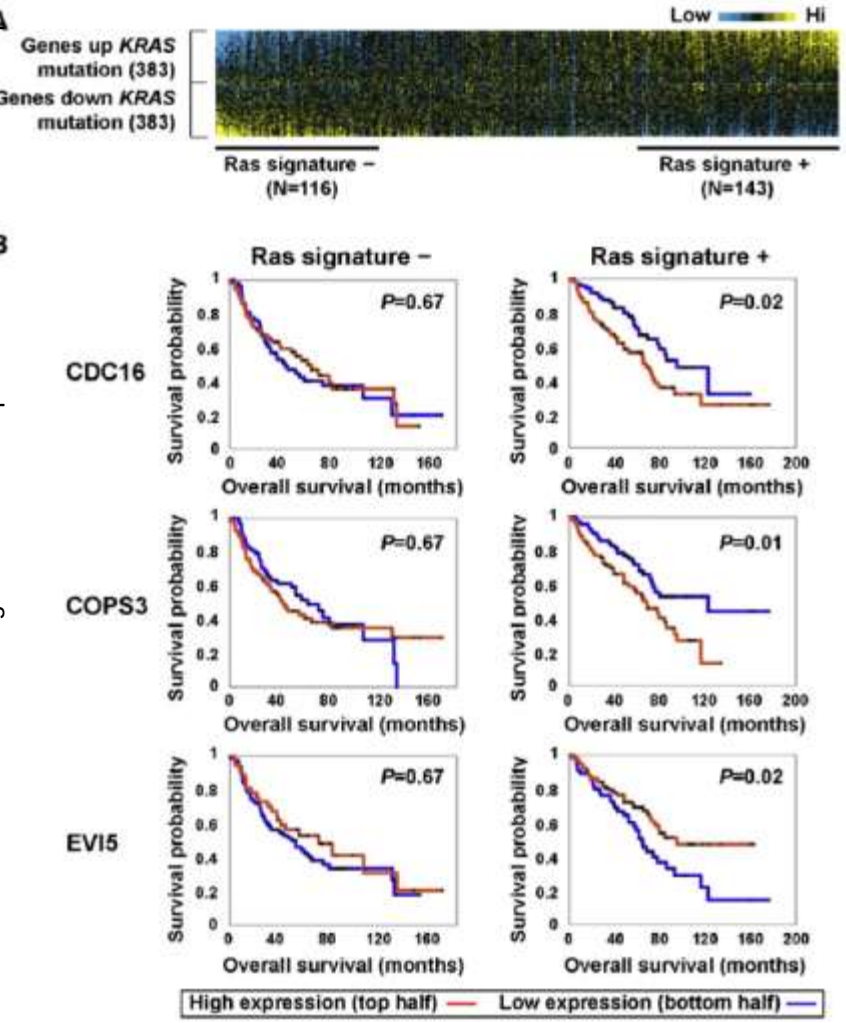
Synthetic lethal provide approach for improving targeted therapies (drug combination)

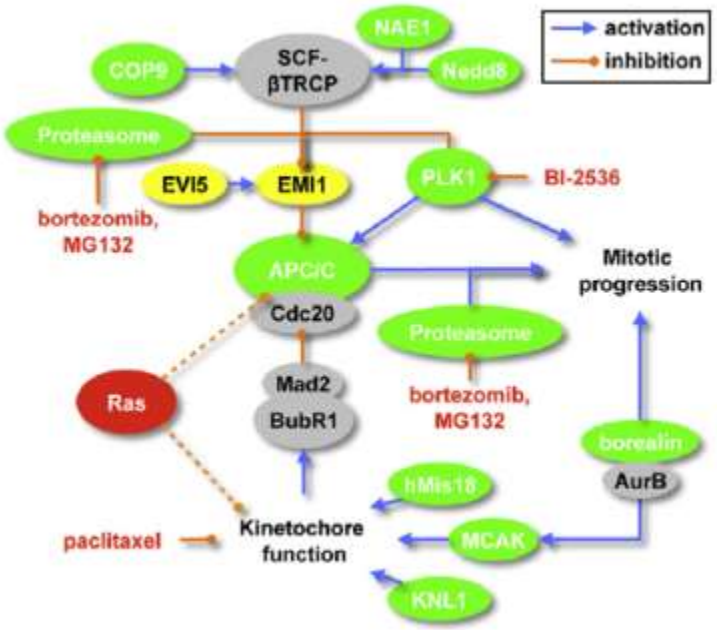


Science Signaling
AAAS

Synthetic Lethal Screen of an EGFR-Centered Network to Improve Targeted Therapies
Igor Astsaturov, Vladimir Ratushny, Anna Sukhanova, Margret B. Einarson,

Synthetic lethal provide approach for personalized therapy





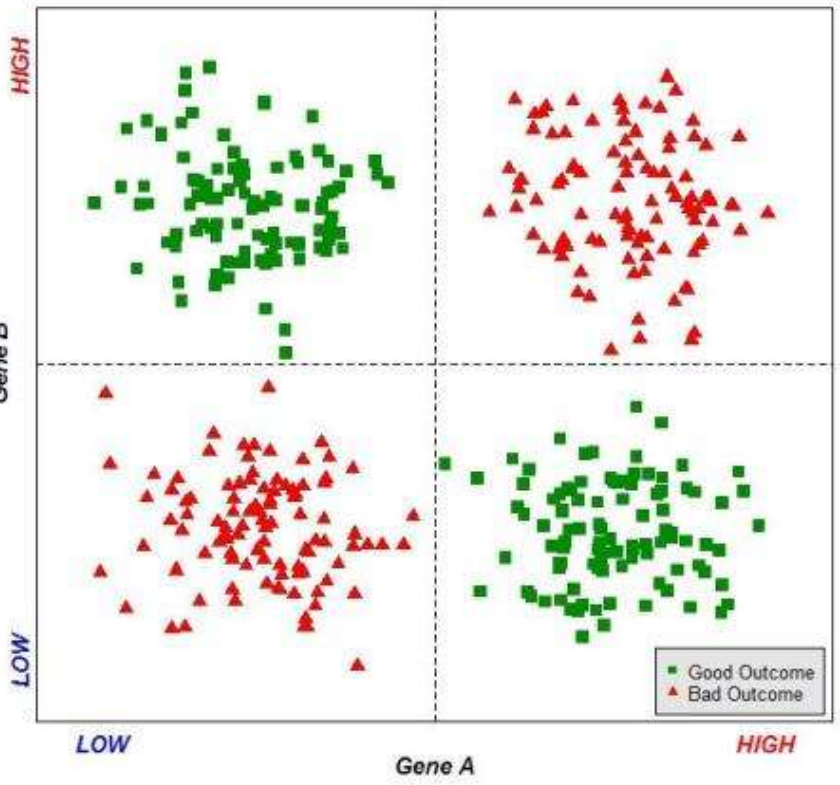
A Genome-wide RNAi Screen Identifies Multiple Synthetic Lethal Interactions with the Ras Oncogene

What type of gene network?

– **We proposed a novel *in vivo* genetic interaction between genes as 'synergistic outcome determination' (SOD), in a similar way to 'synthetic lethality'**

SOD (Synergistic Outcome Determination)

-- not Superoxide dismutase ☺



SOD is defined as the synergy of a gene pair with respect to cancer patients' outcome, whose correlation with outcome is due to cooperative, rather than independent, contributions of genes.

Synergistically Infered Nexus (SIN)

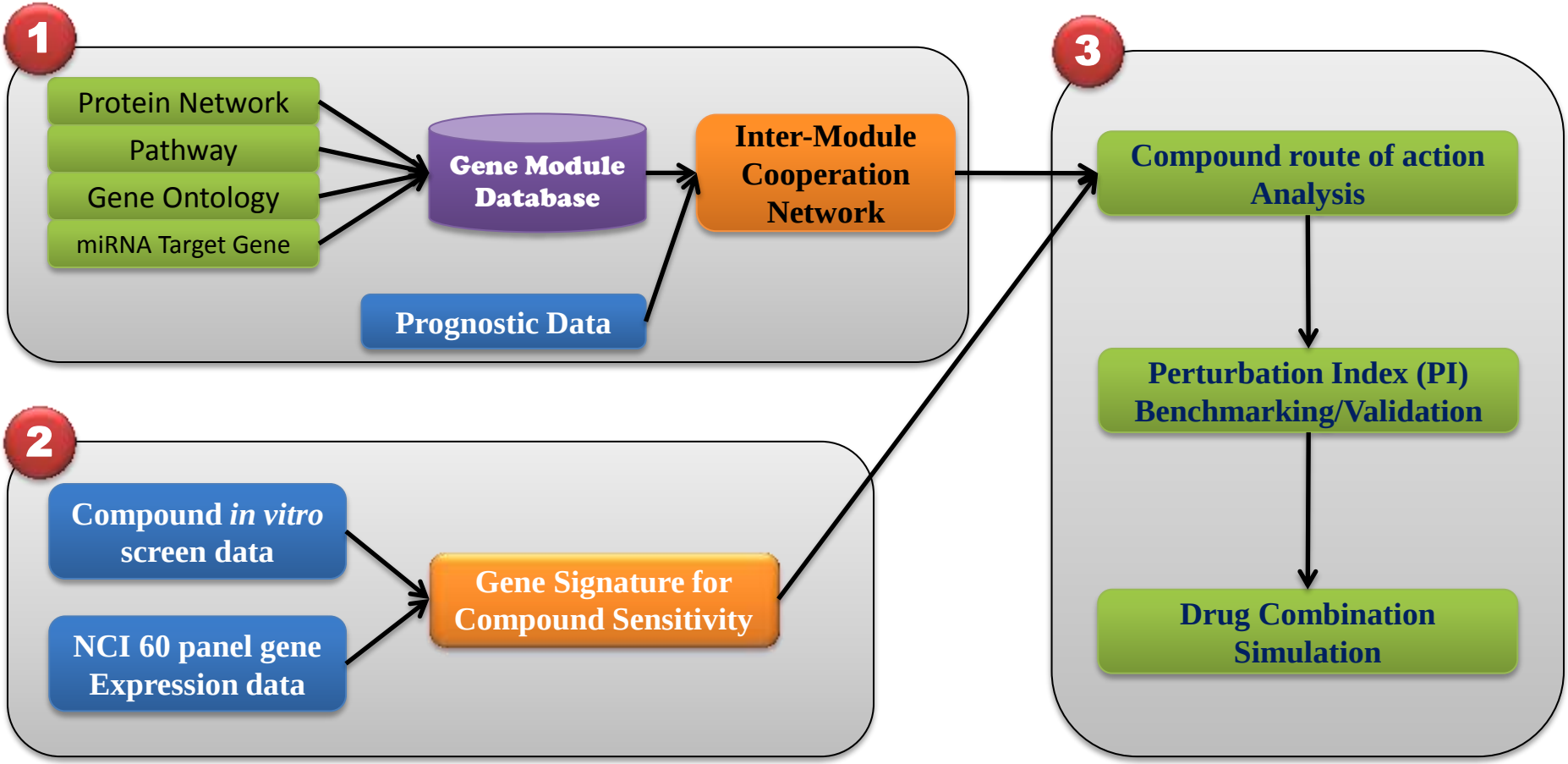
$$Syn(G_1, G_2; C) = I(G_1, G_2; C) - [I(G_1; C) + I(G_2; C)]$$

$$I(X;Y) = \sum_x \sum_y p(x,y) \log_2 \frac{p(x,y)}{p(x)p(y)}$$

SOD (Synergistic Outcome Determination) vs Synthetic Lethality

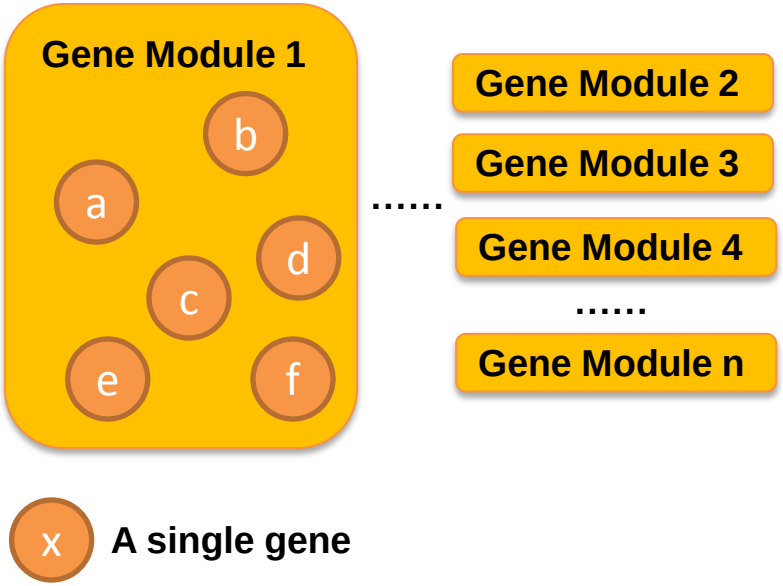
Feature compared	SOD	Synthetic Lethality
Phenotype	Survival outcome of individual patient	Cell death/growth
Systems Level	**human body**	Cell
Data Accessible	Human population (via computation)	Yeast (SGA); Human cell lines; ~~Human population~~

The pipeline

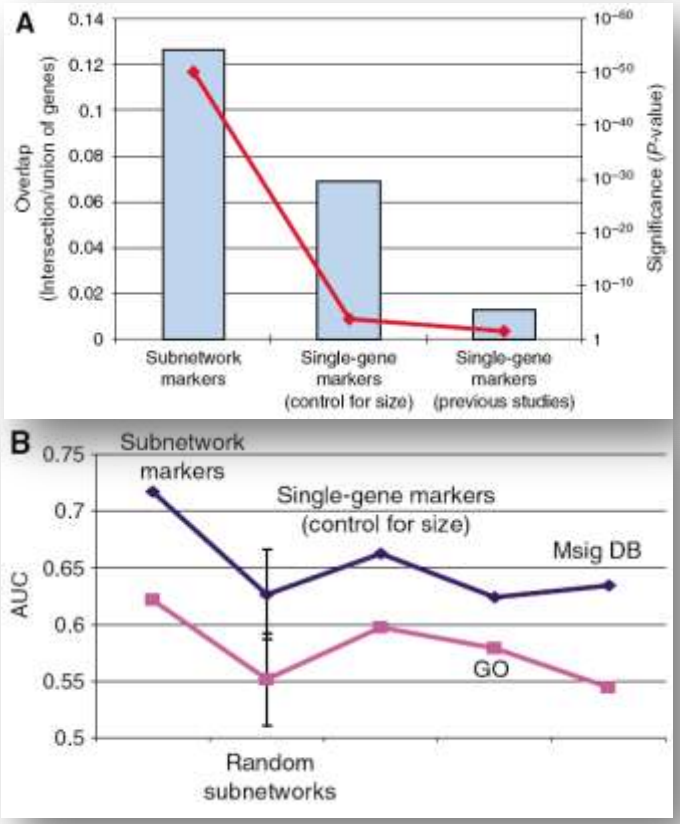


What is Gene Module?
And Why We use it instead of the single genes?

Gene Module:
a group of genes which share similar function

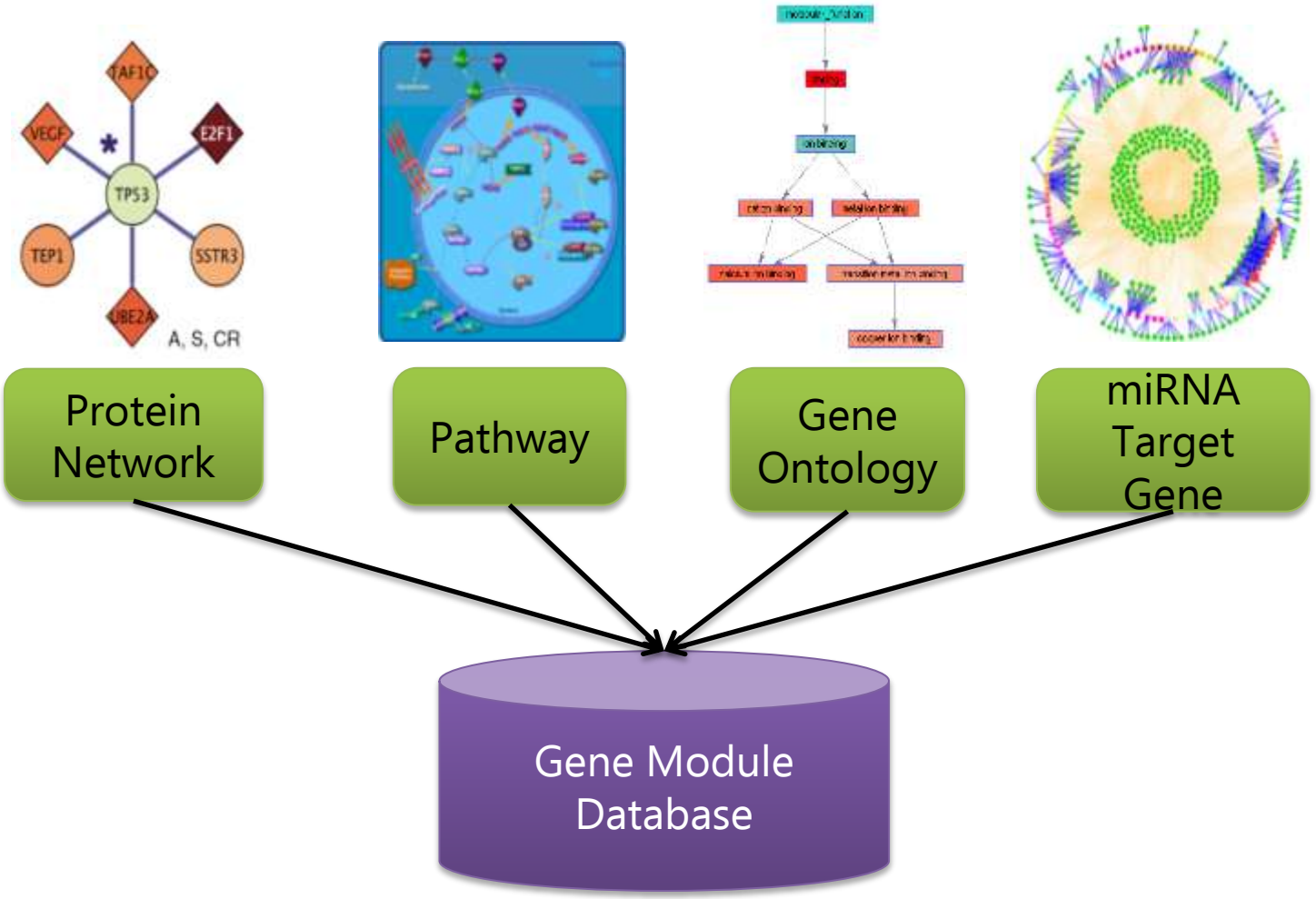


Gene Module:
robust/reproducible features rather than single genes




EPORT
letwork-based classification of breast cancer

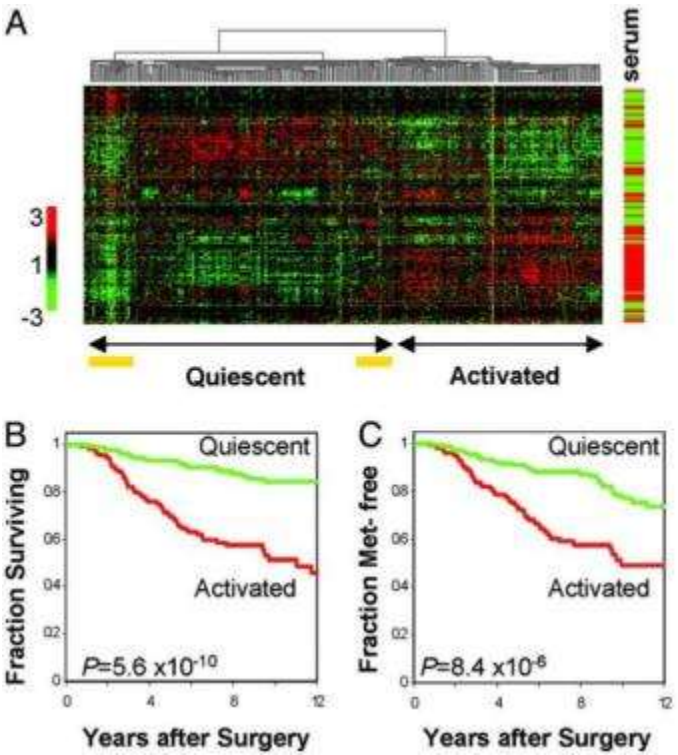
Gene Module Database



Prognosis Data
-- data associated gene expression with patients' phenotype (prognosis)

Prognosis Data Instance

a "wound response" gene expression signature in predicting breast cancer progression

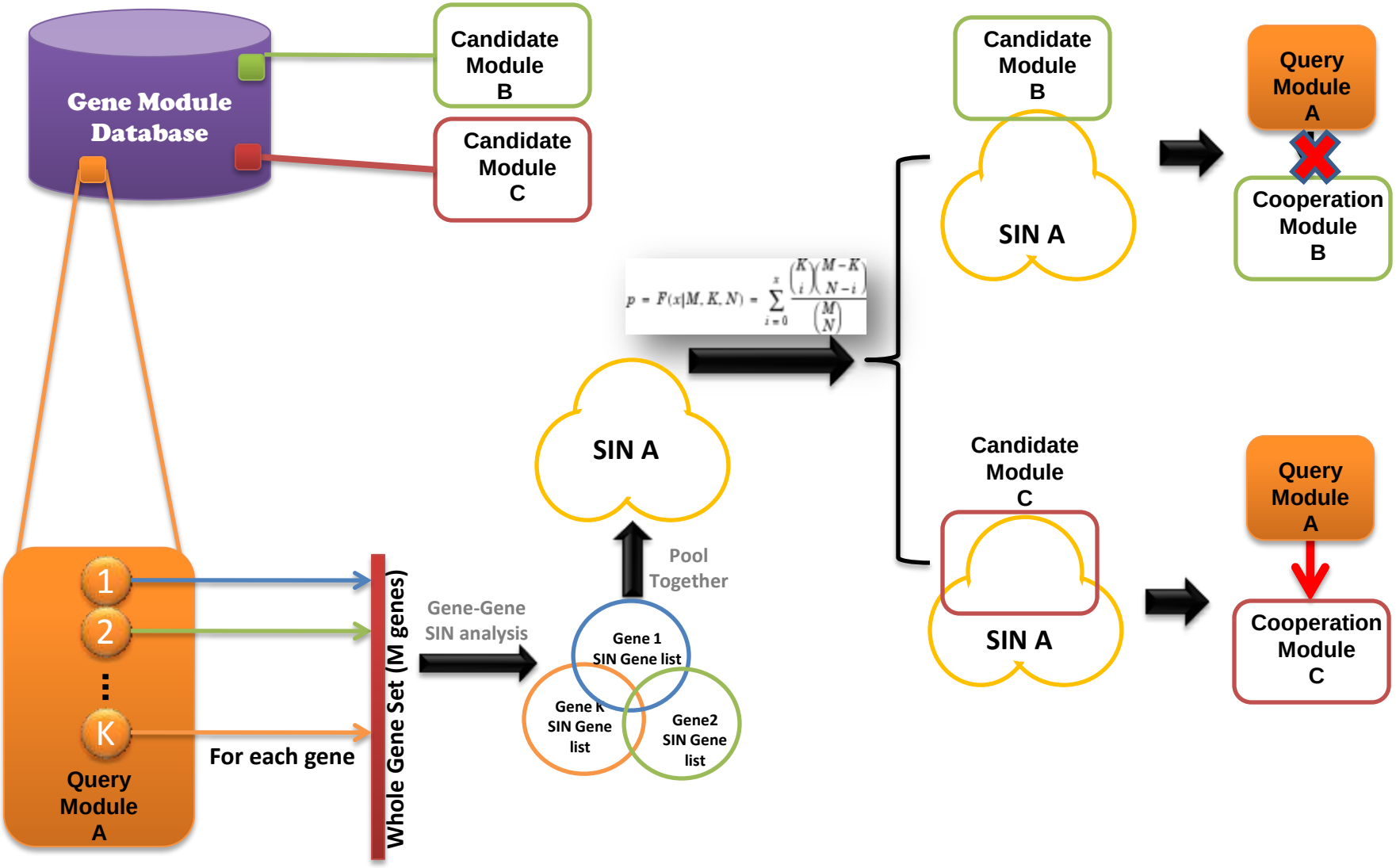


Benefit of Prognosis Data

- Natural population
  - Heterogeneity
- Tumor tissue
  - Microenvironment reflection
- Final point phenotype
  - Survival time
- Comprehensive genomic characterization
- Large Data Set

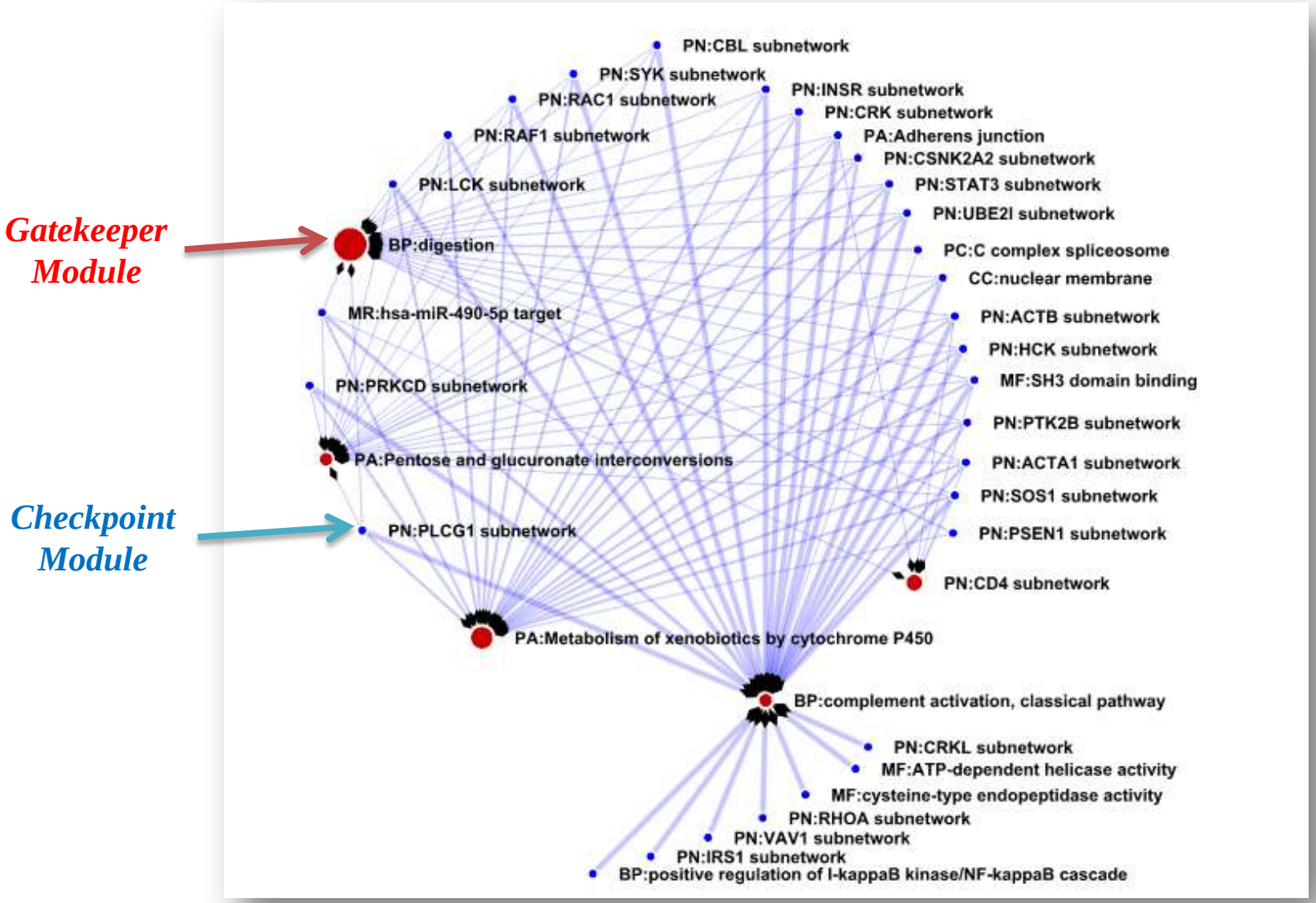
Chang H Y et al. PNAS 2005;102:3738-3743

Module-module cooperation network



Inter-Module Cooperation Network (IMCN)

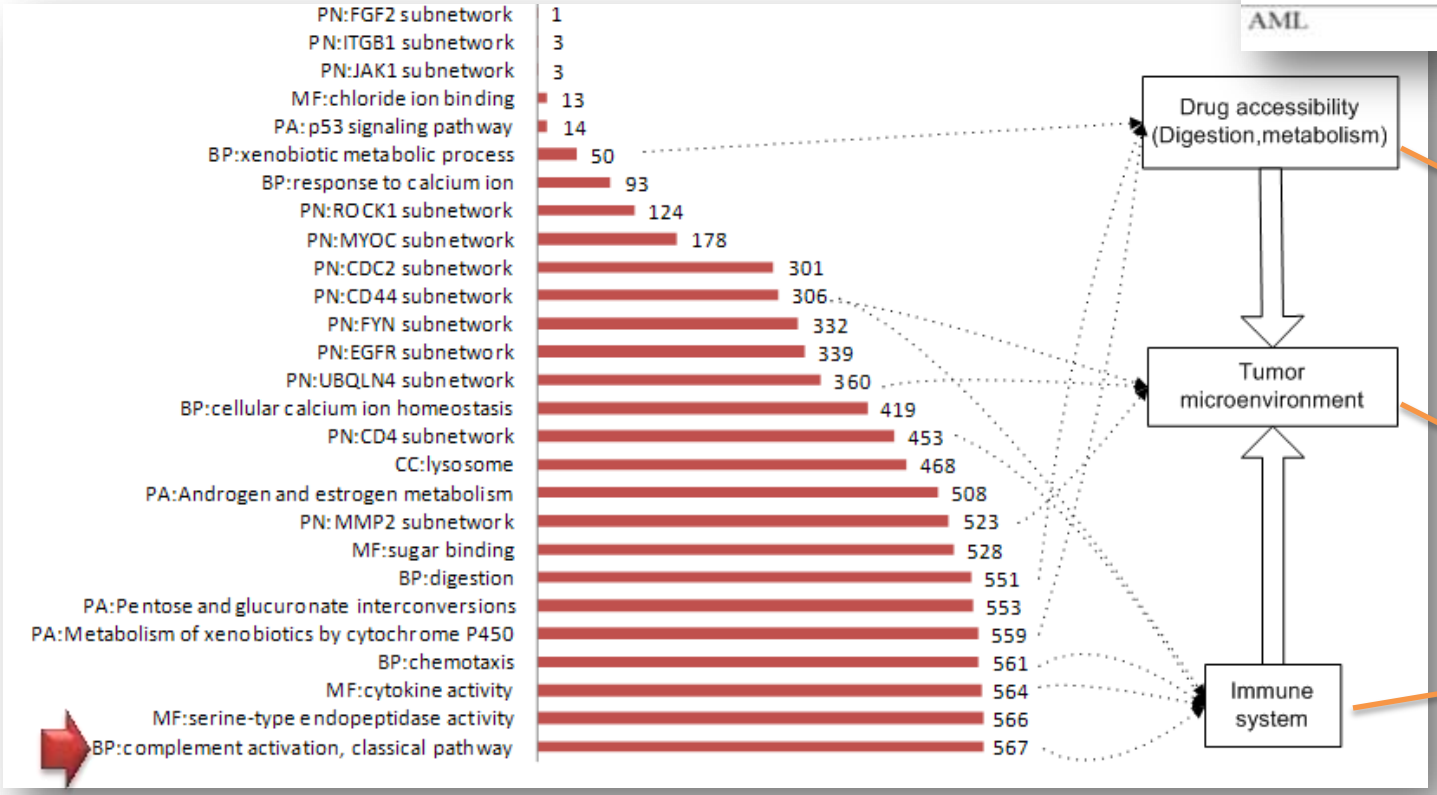
for lung cancer suggests that the network robustness highly dependent on **gatekeeper modules**



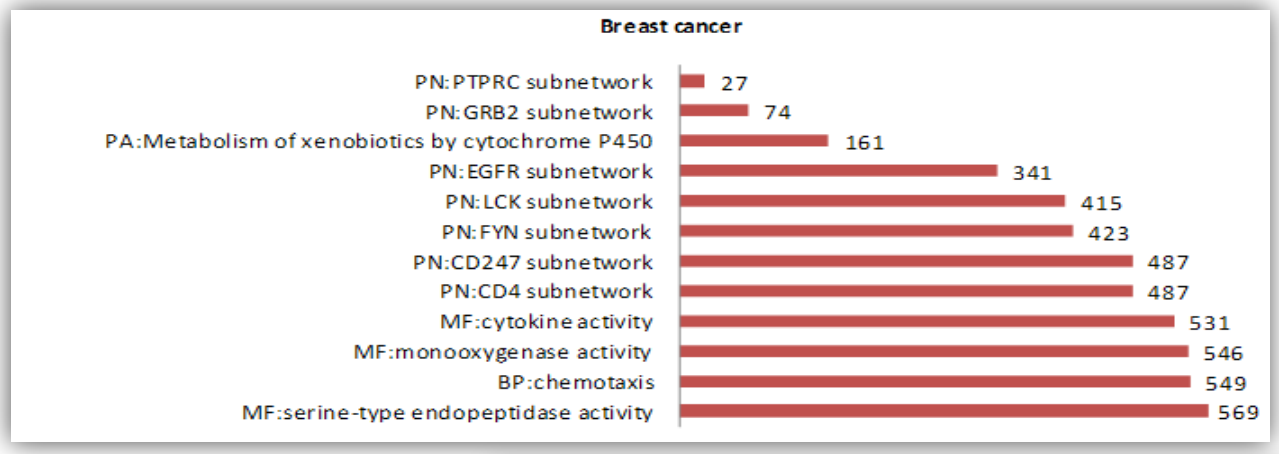
The biological themes of the most highly connected gatekeeper modules in multiple types of cancer

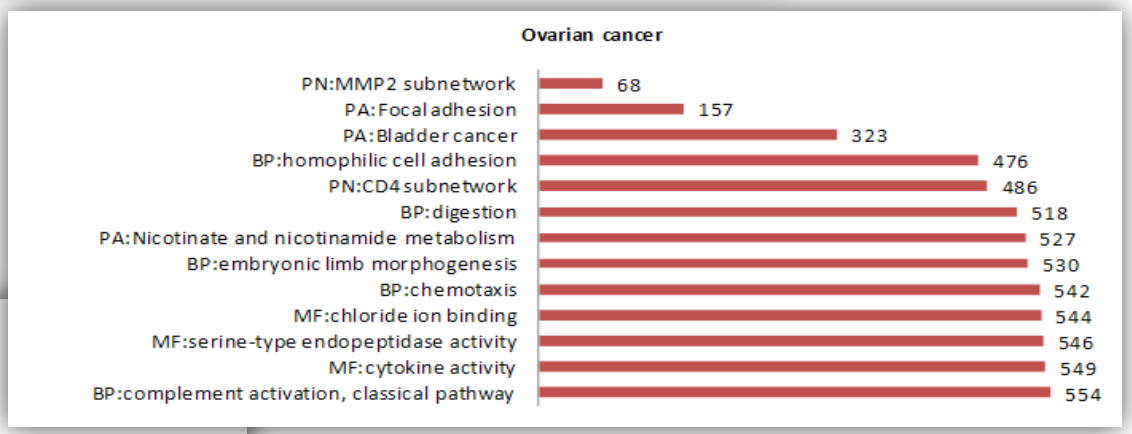
Cancer type	GEO data set
Lung cancer (NSCLC)	GSE3593
Breast cancer	GSE2034
Ovarian cancer	GSE3149
AML	GSE12417

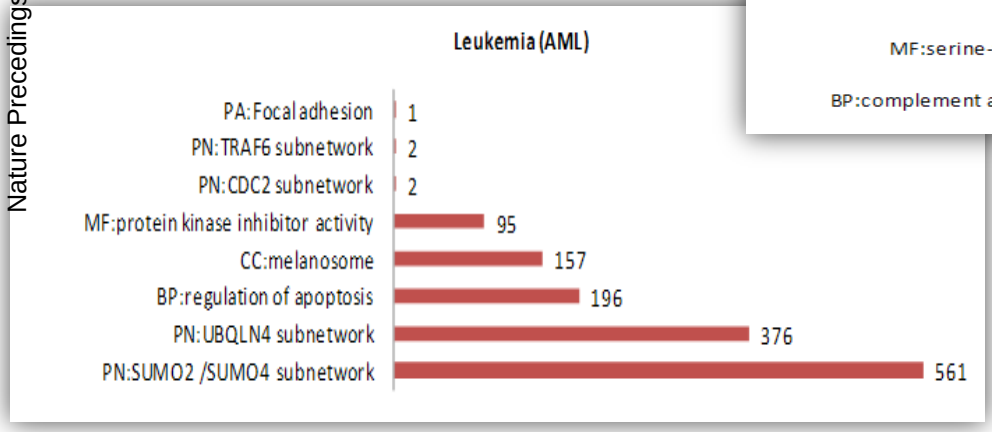
'Gatekeeper' modules for lung cancer (NSCLC)



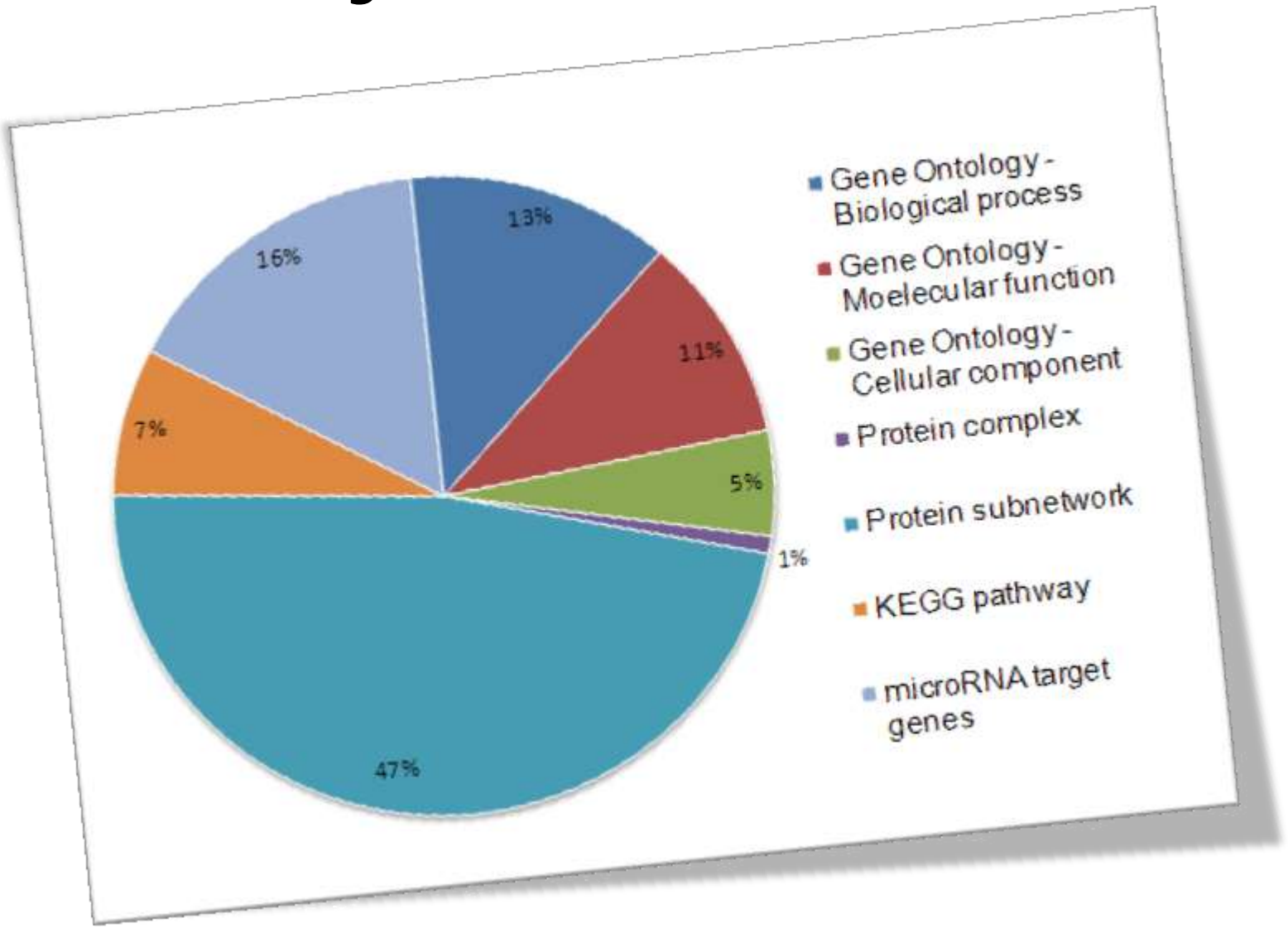
These common themes indicate the pivotal role of the *in vivo* tumor microenvironment, and the efficacy of drugs could be regulated by these components



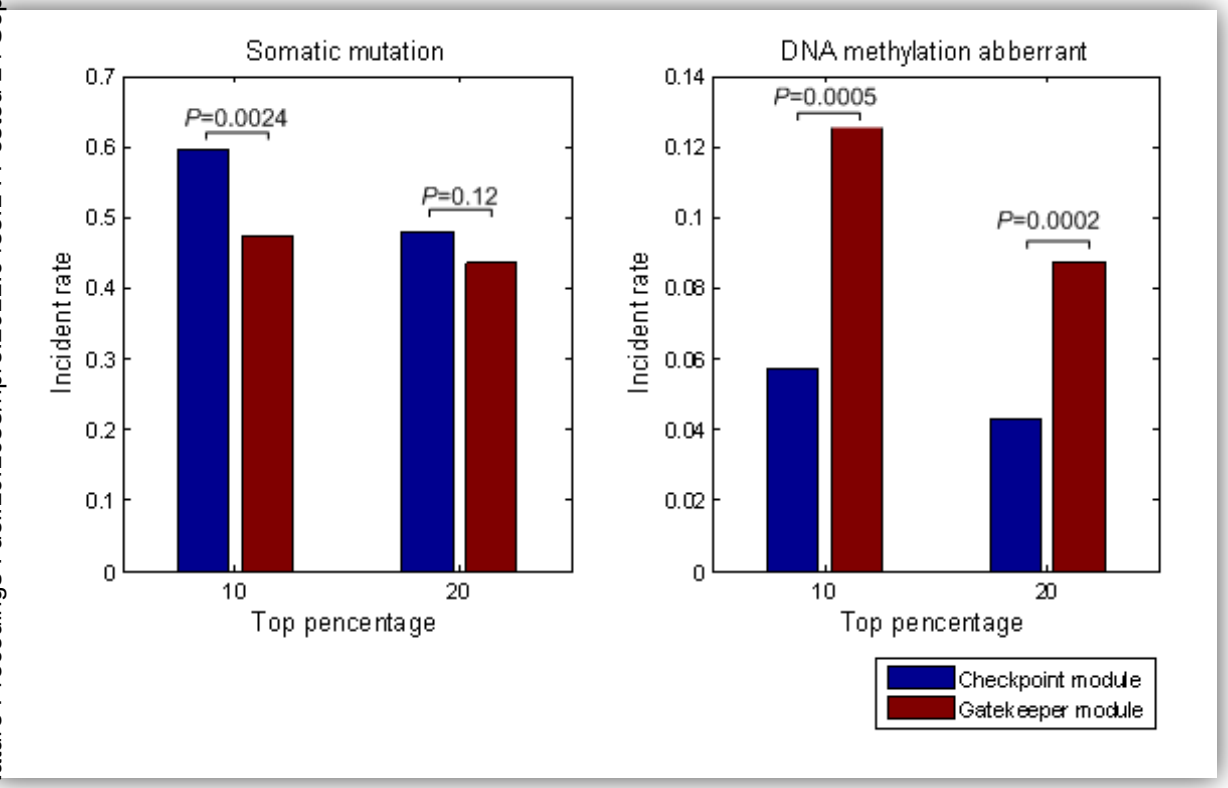




Contribution of various evidence sources for gene module definition



Association of gatekeeper modules with genetic and epigenetic aberration events

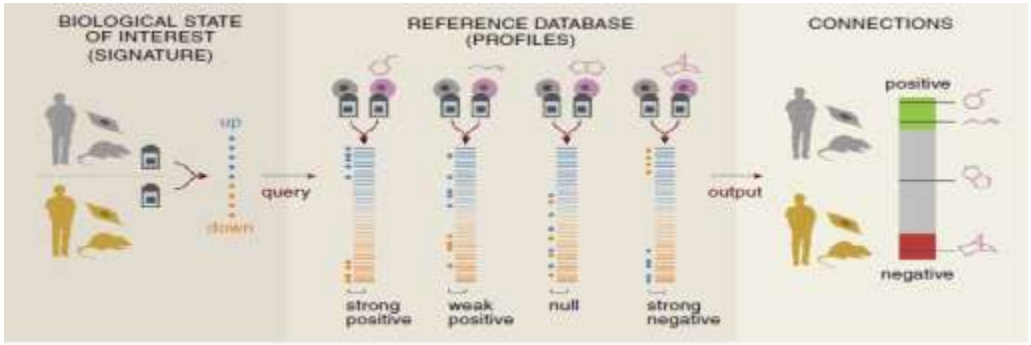


- Comparing genetic (somatic mutation) and epigenetic (DNA methylation) aberration rate (in tumor vs. normal) of two types of modules
- Top 10% or 20% of genes which highly used (i.e. one gene involved in multiple gene modules) as representative of each types of modules

- **Gatekeeper modules have a significantly lower incident rate of somatic gene mutation, but a notably higher incident rate of DNA methylation aberration**
- **Supporting the role of epigenetic plasticity in tumor phenotype**

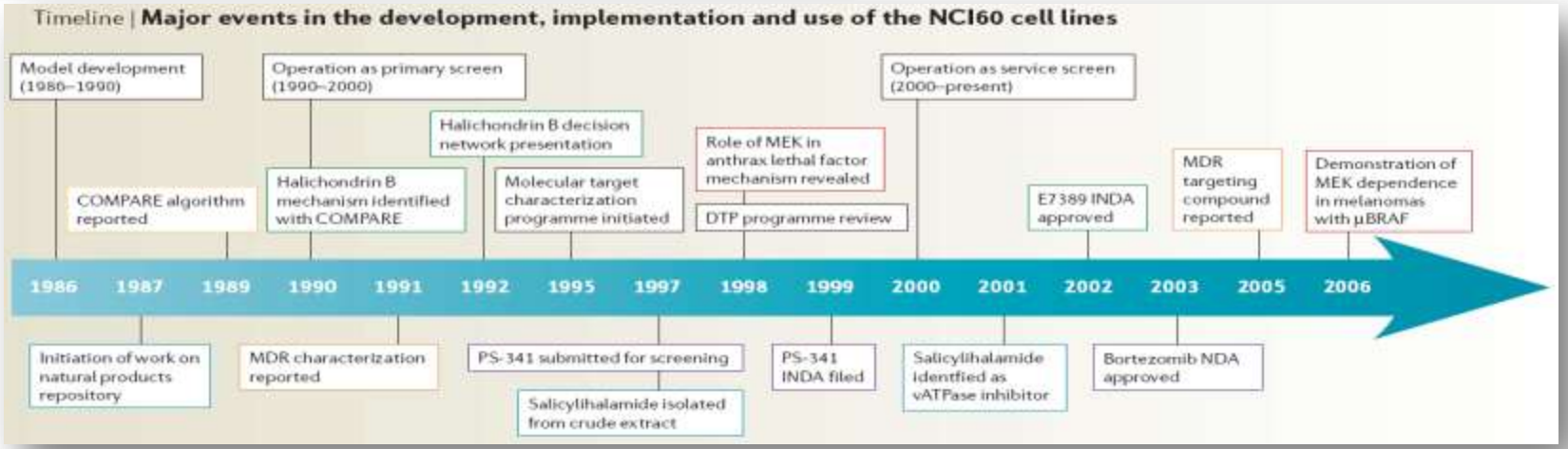
Mapping compound action into gene networks

Connectivity MAP

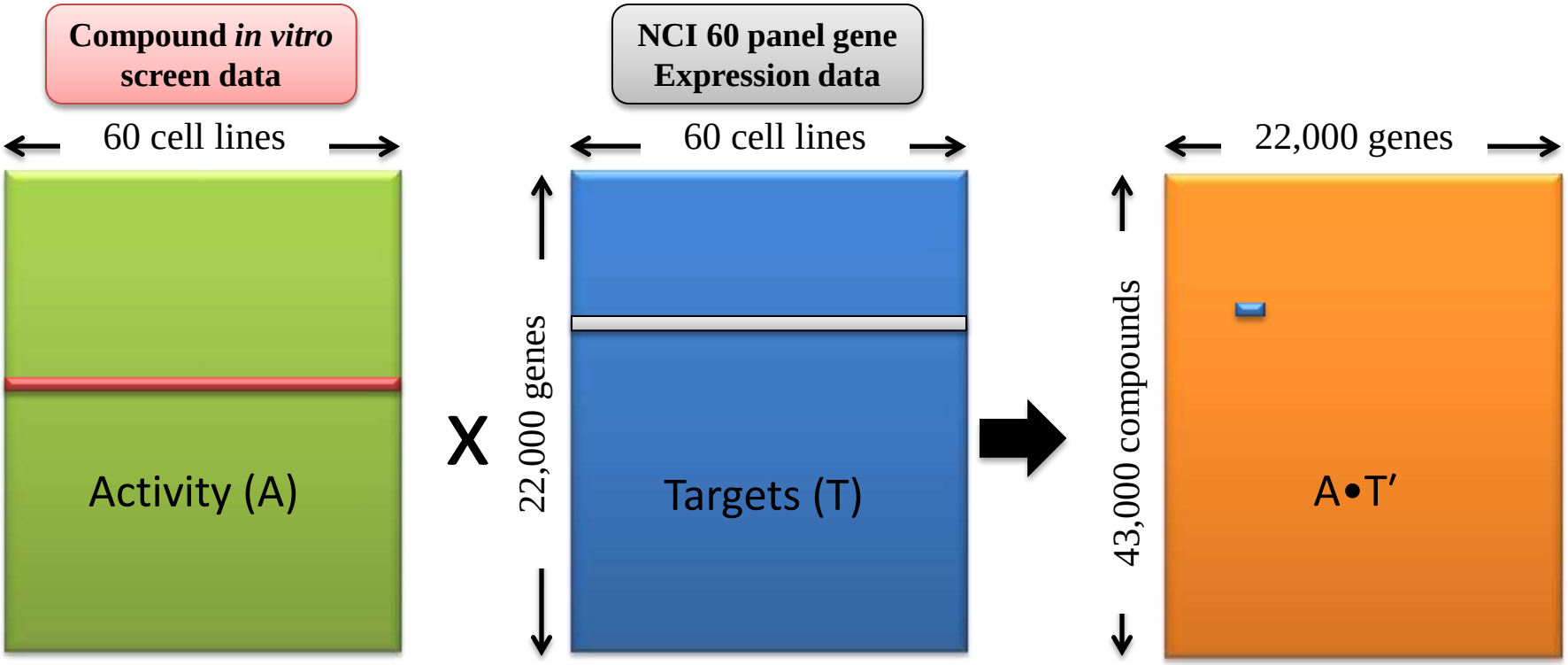


The Connectivity Map: Using Gene-Expression Signatures to Connect Small Molecules, Genes, and Disease
Justin Lamb, *et al.*
Science 313, 1929 (2006);

NCI 60 in vitro Drug screen Project



Compound-Gene Correlations



Activity

Compound/drug A's there are a measurement of drug activity (A) cross 60 cell line is determined by GI 50 (the 50% growth inhibition values) , the concentration of the drug necessary to reduce the growth rate of cells by 50% to that of controls.

Activity (A) = -log10(GI50)

Sensitivity

"Sensitivity" = the sensitivity of one particular cell lines to a drug.

if drug *d1* can effectively inhibit the cell growth of cell line *c1*, we say " cell line *c1* is sensitive to drug *d1"*

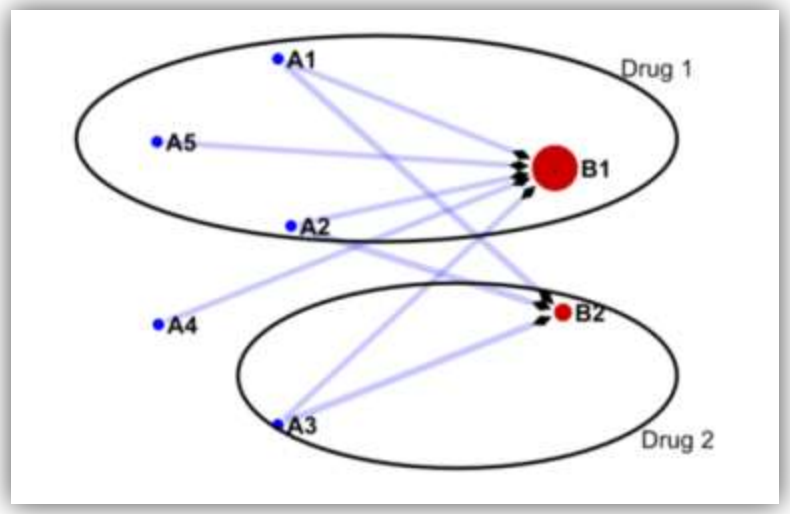
Define Perturbation Index (PI) to quantify Drug action

Hypothesis

- **To disrupt/perturb cancer network, the key to success is to simultaneously perturbs the corresponding gatekeeper modules with the checkpoint modules (for better exploit the gene synergy)**

$$PI(c) = \frac{\sum_{i=1}^{N}(H_i \times L_i)}{G(c)}$$

- *H*i -- the number of hits by compound *c*
- *L*i -- the active links (i.e. links in which both source node and target node are matched by compound *c*)
- *N* -- the number of gatekeeper modules

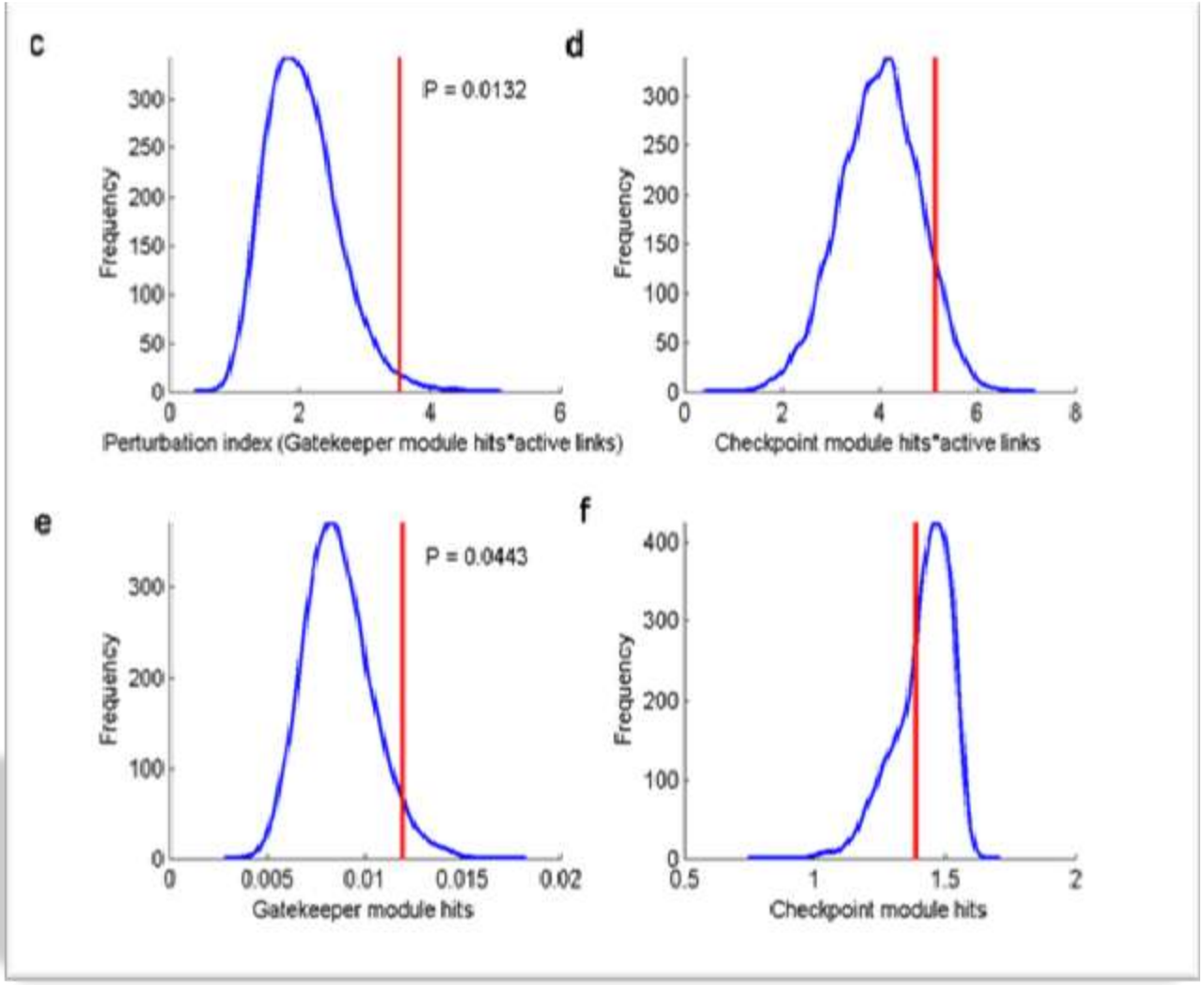


Benchmarking for pre-clinical drug prioritizing

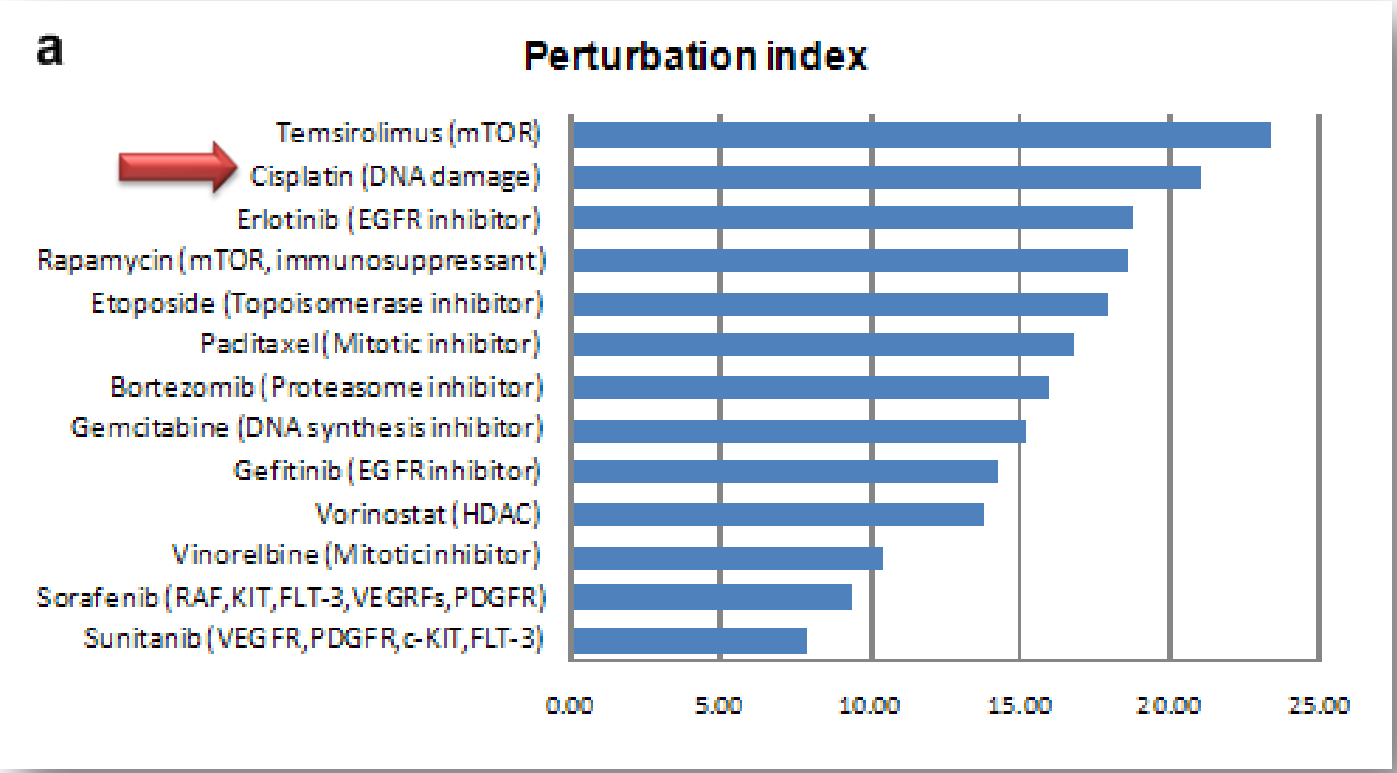
- **Why test?**
  - Assess the potential application for prioritizing compounds for clinical trials, based on the information available in pre-clinical stage
- '***Standard Agent Database***'
  - Originally created by Boyd [29] and ultimately finalized by the NCI
  - Compounds which have been submitted to the FDA for review as a New Drug Application
  - OR compounds that have reached a particular high stage of interest at the NCI
- **Successful drug list - FDA approved and routinely used drugs**
- **Candidate list - the remainder**
- **Test what?**
  - **Whether we could statistically discriminate between these two compound lists using the perturbation index**

Bootstrapping-based assessment of Perturbation Index on discriminating successful drugs from the candidate

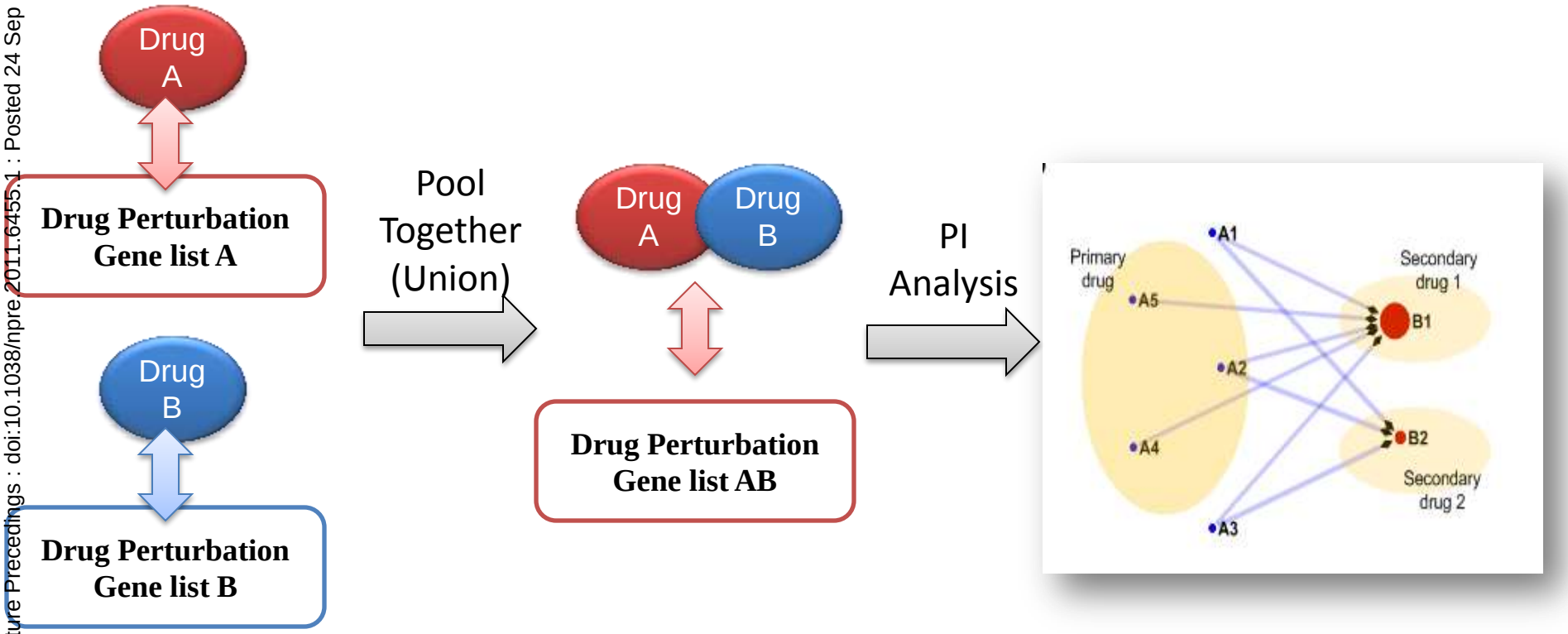
$$PI(c) = \frac{\sum_{i=1}^{N}(H_i \times L_i)}{G(c)}$$



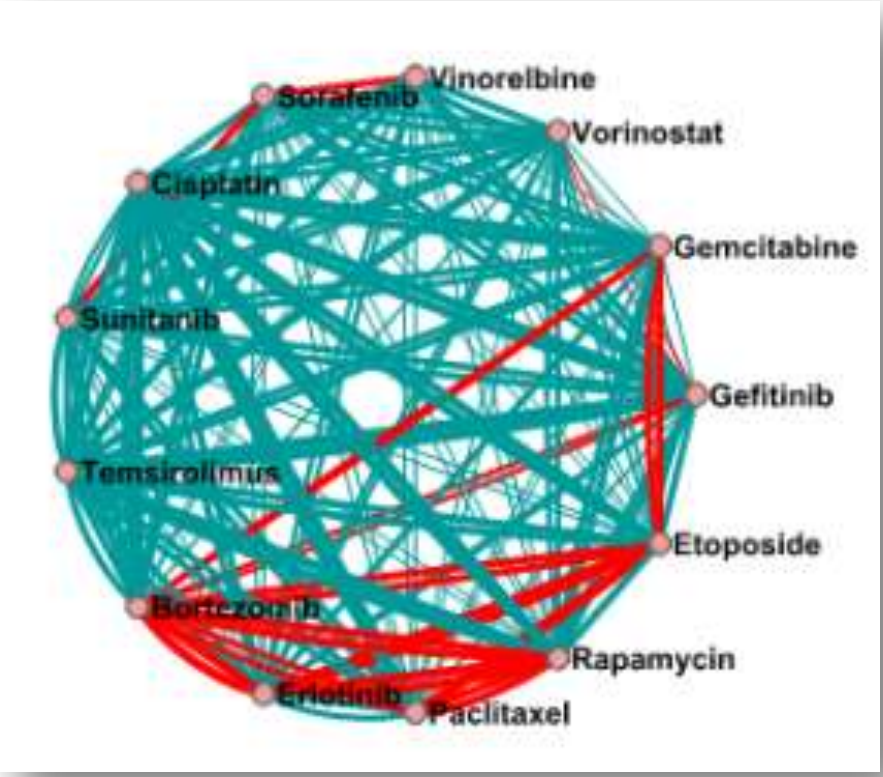
Rank of drugs and agents in clinical development for lung cancer according to their Perturbation Index



How to quantify synergistic effect of Drug Combination?



The Perturbation Index of pair-wise combination of lung cancer agents



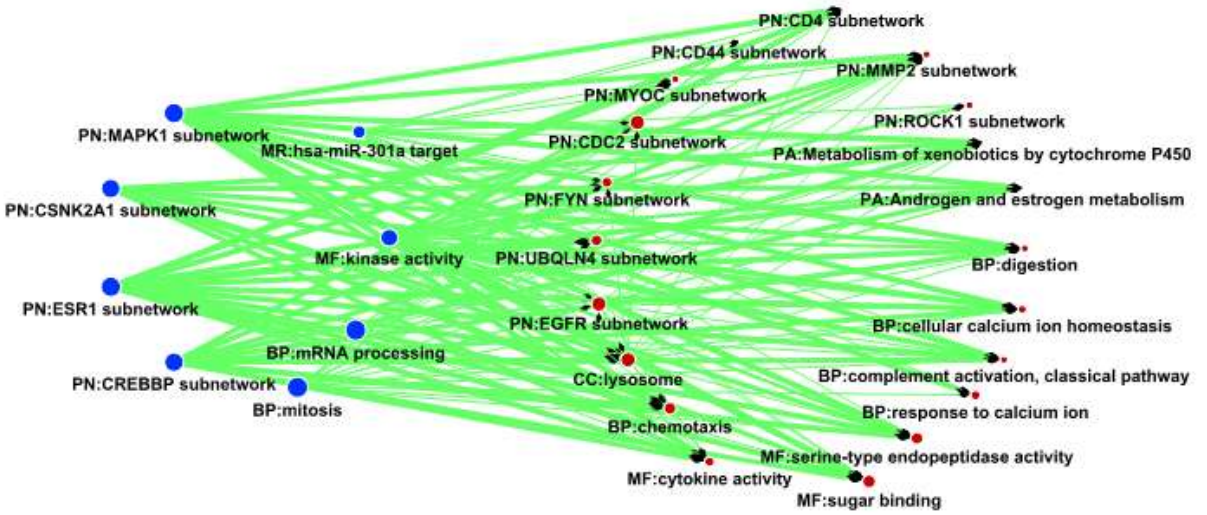
- Combination of Bortezomib-Gemcitabine supported by phase II clinical trial evidence
  - Notable survival benefits in lung cancer patients using a Bortezomib + gemcitabine/carboplatin combination as first-line treatment (phase II clinical trial reported)
    - Davies, A.M. et al. ***J Thorac Oncol*** 4, 87-92 (2009)
- Combination of Bortezomib-Paclitaxel supported by literatures
  - In an RNA interference (RNAi)-based synthetic lethal screen for seeking paclitaxel chemosensitizer genes in human NSCLC cell line, proteasome is the most enriched gene group
    - Whitehurst, A.W. et al. ***Nature*** 446, 815-819 (2007)

Bortezomib-Gemcitabine Combination

Nature Precedings : doi:10.1038/npre.2011.6455.1 : Posted 24 Sep 2011

Gemcitabine

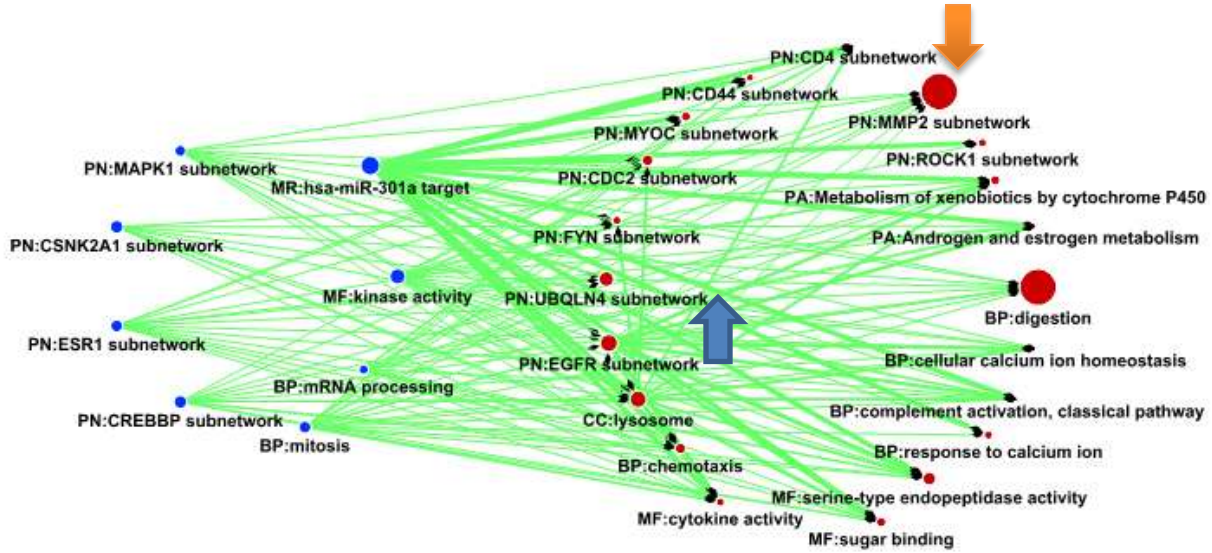
baseline perturbation



Gemcitabine

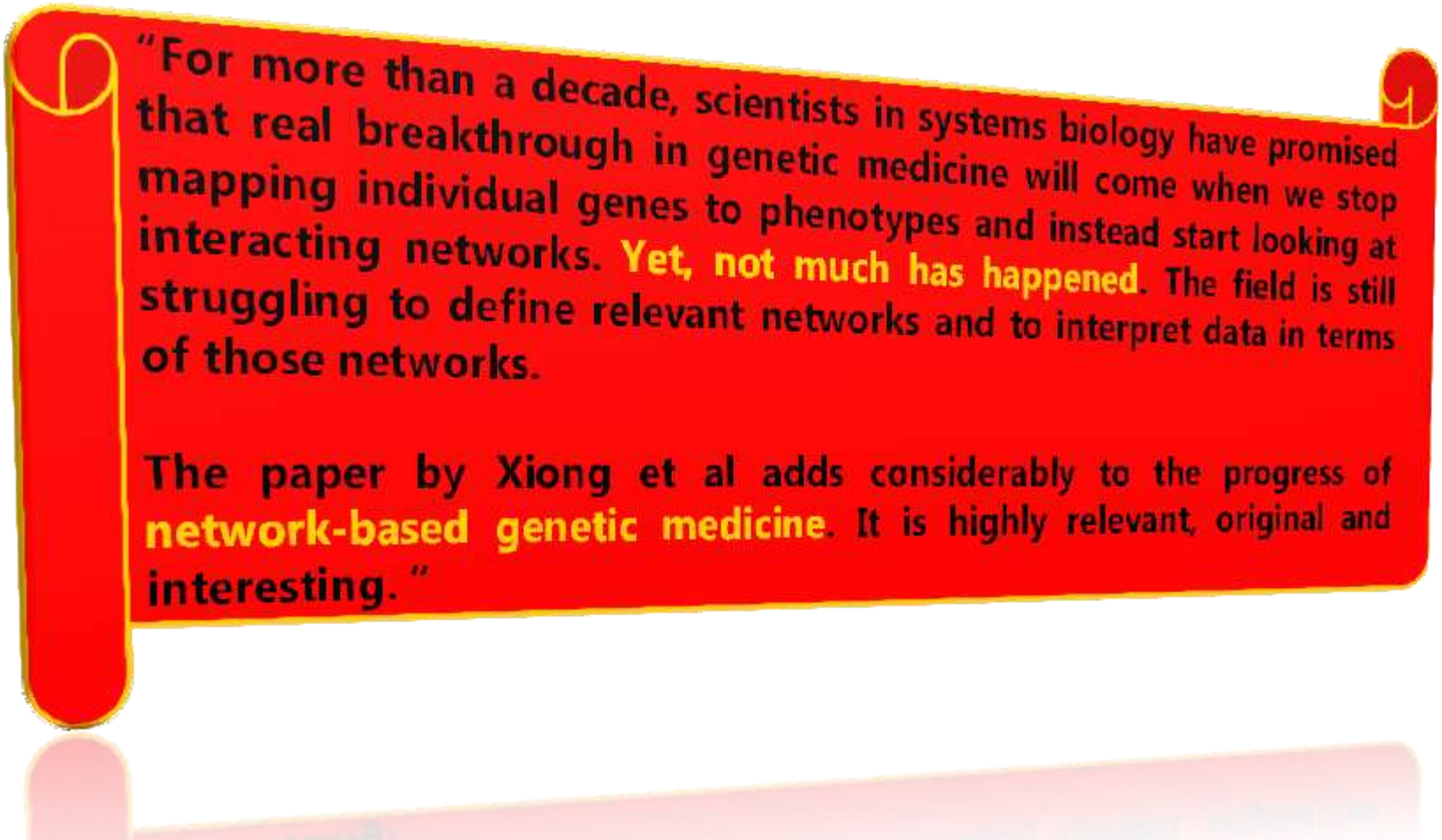
Bortezomib

add a focused perturbation on key gatekeeper modules

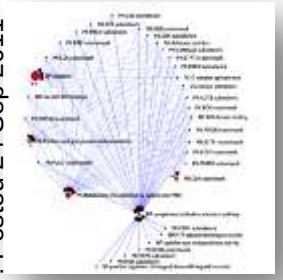


Discussion (1): As preclinical cancer modeling tool

- Mirroring drug behavior on heterogeneous patients population
- Cost-effectiveness
- Easy to integrate drug action mechanisms/patterns



Discussion (2) : novel strategy against cancer

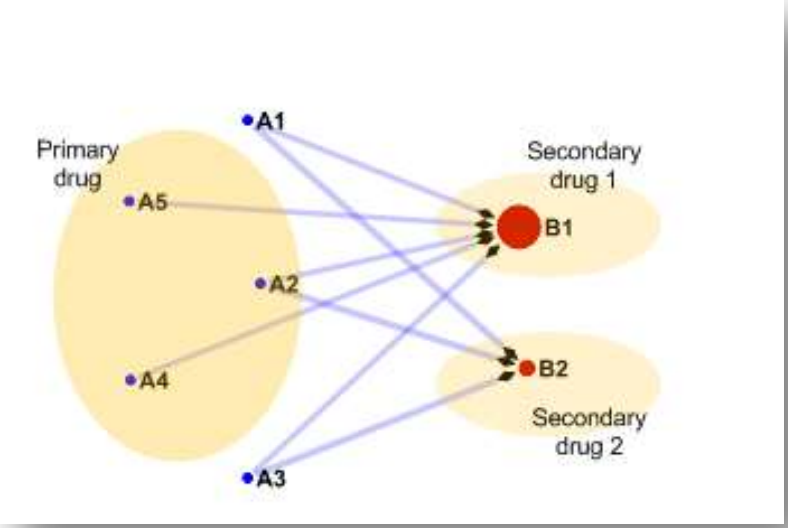


- Gatekeeper modules as rate-limiting steps in therapeutic treatment
  - Drug metabolism and accessibility
  - Microenvironment
  - immune system modulation
- Epigenetic plasticity on gatekeeper modules could exploited by tumor for attaining resistance to treatment
- **Suggest a novel strategy against cancer**
  - **Traditional strategy: dig the history of tumorigenesis <etiology, TCGA effort> to find drug target ?**
  - **Alternative strategy: predict future survival strategy of tumor under therapeutic interventions**
- **Systems biology modeling could provide prediction of the tumor survival strategy**

The next generation therapeutic strategy

Etiology-based strategy → Prediction-based strategy

Discussion (3) : Traditional Chinese Medicine



Based on this method, we could interrogate different roles of the gene modules
& their cooperation effects

- 君 - King
- 臣 - Minister
- 佐 - Assistant
- 使 - Ambassador

provide new perspective to understand principle of drug combination

provide approach for rational design of drug combination

Case Study II

Dynamic remodeling of context-specific miRNAs regulation networks facilitate in silico cancer drug screening

Reference

- Lida Zhu, …, **Jianghui Xiong****. Dynamic remodeling of context-specific miRNAs regulation networks facilitate in silico cancer drug screening. Proceedings of 2011 IEEE International Conference on Systems Biology (ISB). 2011
- Xionghui Zhou, …**, Jianghui Xiong****. Context-Specific miRNA Regulation Network Predicts Cancer Prognosis. Proceedings of 2011 IEEE International Conference on Systems Biology (ISB). 2011

in silico drug screening

- **Virtual drug screening** is a computational technique used in drug discovery research.
- ***In silico*** is an expression used to mean "performed on computer or via computer simulation".
- In silico drug screening is thought to have the potential to speed the rate of discovery while reducing the need for expensive lab work and clinical trials.

Drug repositioning

-- the application of known drugs and compounds to new indications

PERSPECTIVE

GENOMIC MEDICINE

The Emergence of Genome-Based Drug Repositioning

Yves A. Lussier[1,2,3*] and James L. Chen[4*]

Science Translational Medicine AAAS

Discovery and Preclinical Validation of Drug Indications Using Compendia of Public Gene Expression Data

Marina Sirota, *et al.*

Sci Transl Med **3**, 96ra77 (2011);

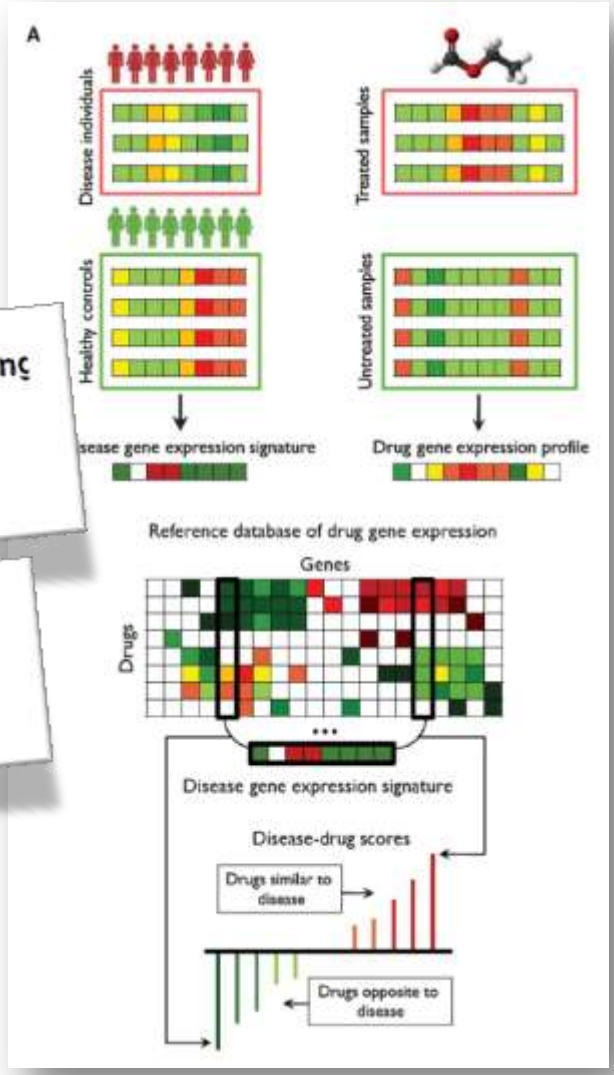
DOI: 10.1126/scitranslmed.3001318

Science Translational Medicine AAAS

Computational Repositioning of the Anticonvulsant Topiramate for Inflammatory Bowel Disease

Joel T. Dudley, *et al.*

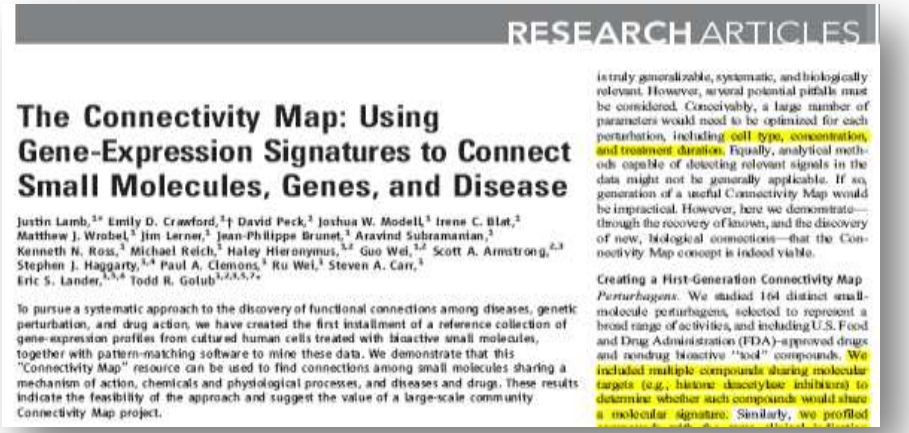
Sci Transl Med **3**, 96ra76 (2011);



Connectivity MAP (CMAP)

BROAD INSTITUTE

The Broad Institute is a research collaboration of MIT, Harvard and its affiliated Hospitals, and the Whitehead Institute, created to bring the power of genomics to medicine.



RESEARCH ARTICLES

The Connectivity Map: Using Gene-Expression Signatures to Connect Small Molecules, Genes, and Disease

Justin Lamb,[1*] Emily D. Crawford,[2†] David Peck,[1] Joshua W. Modell,[1] Irene C. Blat,[1] Matthew J. Wrobel,[1] Jim Lerner,[1] Jean-Philippe Brunet,[1] Aravind Subramanian,[1] Kenneth N. Ross,[1] Michael Reich,[1] Haley Hieronymus,[1,2] Guo Wei,[1,2] Scott A. Armstrong,[2,3] Stephen J. Haggarty,[1,4] Paul A. Clemons,[1] Ru Wei,[1] Steven A. Carr,[1] Eric S. Lander,[1,5,6] Todd R. Golub[1,2,5,7*]

To pursue a systematic approach to the discovery of functional connections among diseases, genetic perturbation, and drug action, we have created the first installment of a reference collection of gene-expression profiles from cultured human cells treated with bioactive small molecules, together with pattern-matching software to mine these data. We demonstrate that this "Connectivity Map" resource can be used to find connections among small molecules sharing a mechanism of action, chemicals and physiological processes, and diseases and drugs. These results indicate the feasibility of the approach and suggest the value of a large-scale community Connectivity Map project.

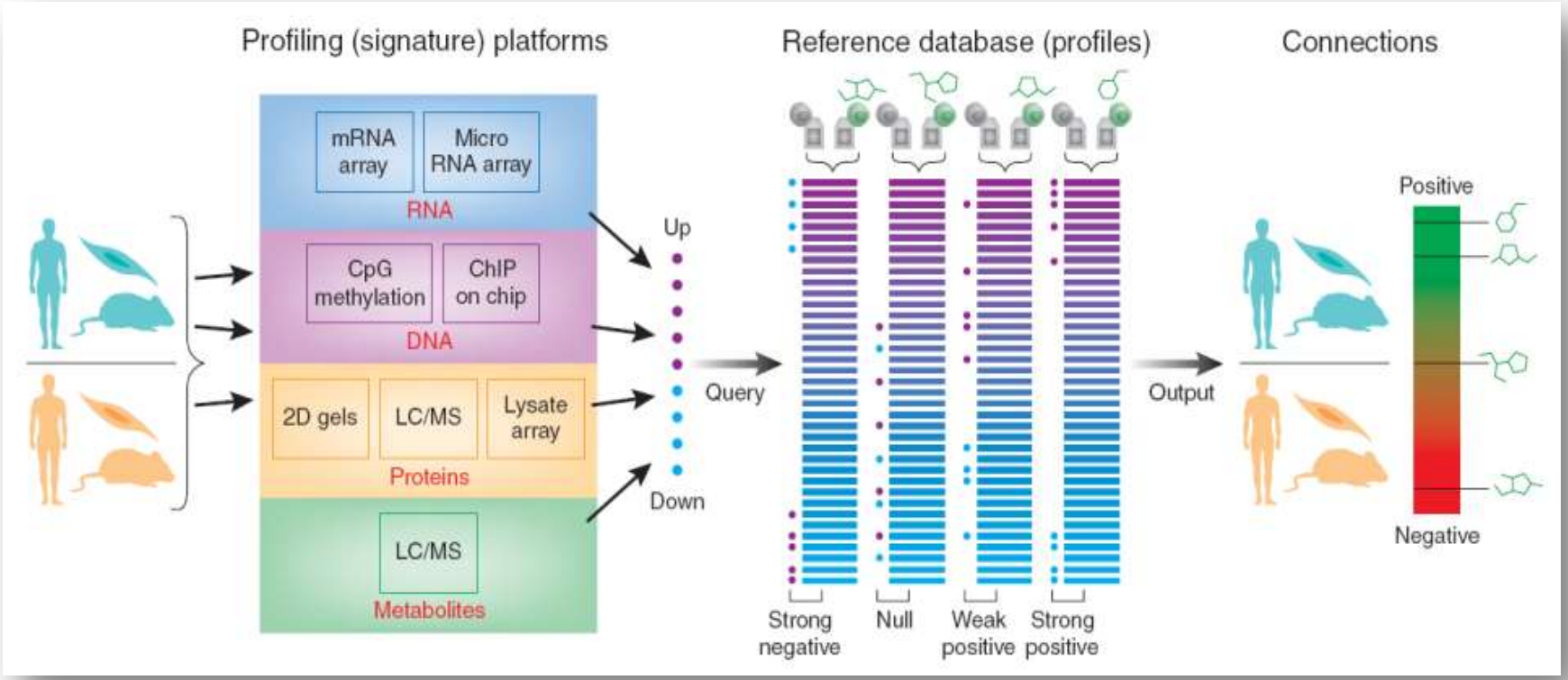
is truly generalizable, systematic, and biologically relevant. However, several potential pitfalls must be considered. Conceivably, a large number of parameters would need to be optimized for each perturbation, including cell type, concentration, and treatment duration. Equally, analytical methods capable of detecting relevant signals in the data might not be generally applicable. If so, generation of a useful Connectivity Map would be impractical. However, here we demonstrate—through the recovery of known, and the discovery of new, biological connections—that the Connectivity Map concept is indeed viable.

Creating a First-Generation Connectivity Map

Perturbagens. We studied 164 distinct small-molecule perturbagens, selected to represent a broad range of activities, and including U.S. Food and Drug Administration (FDA)–approved drugs and nondrug bioactive "tool" compounds. We included multiple compounds sharing molecular targets (e.g., histone deacetylase inhibitors) to determine whether such compounds would share a molecular signature. Similarly, we profiled

- mRNA-CMAP:
  - Data source: human gene mRNA expression.
  - Method: GSEA
  - This project set out to create a reference collection of gene expression profiles from cultured human cells treated with bioactive small molecules, and can be used to *discover connections among small molecules sharing a mechanism of action, chemicals and physiological process.*

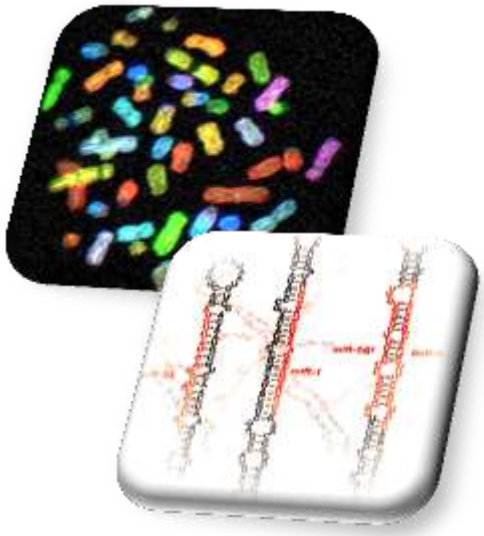
Connectivity MAP (CMAP)



The Connectivity Map: Using Gene-Expression Signatures to Connect Small Molecules, Genes, and Disease .

Lamb et al. **Science** .29 September 2006: 1929-1935

MicroRNAs (miRNAs)



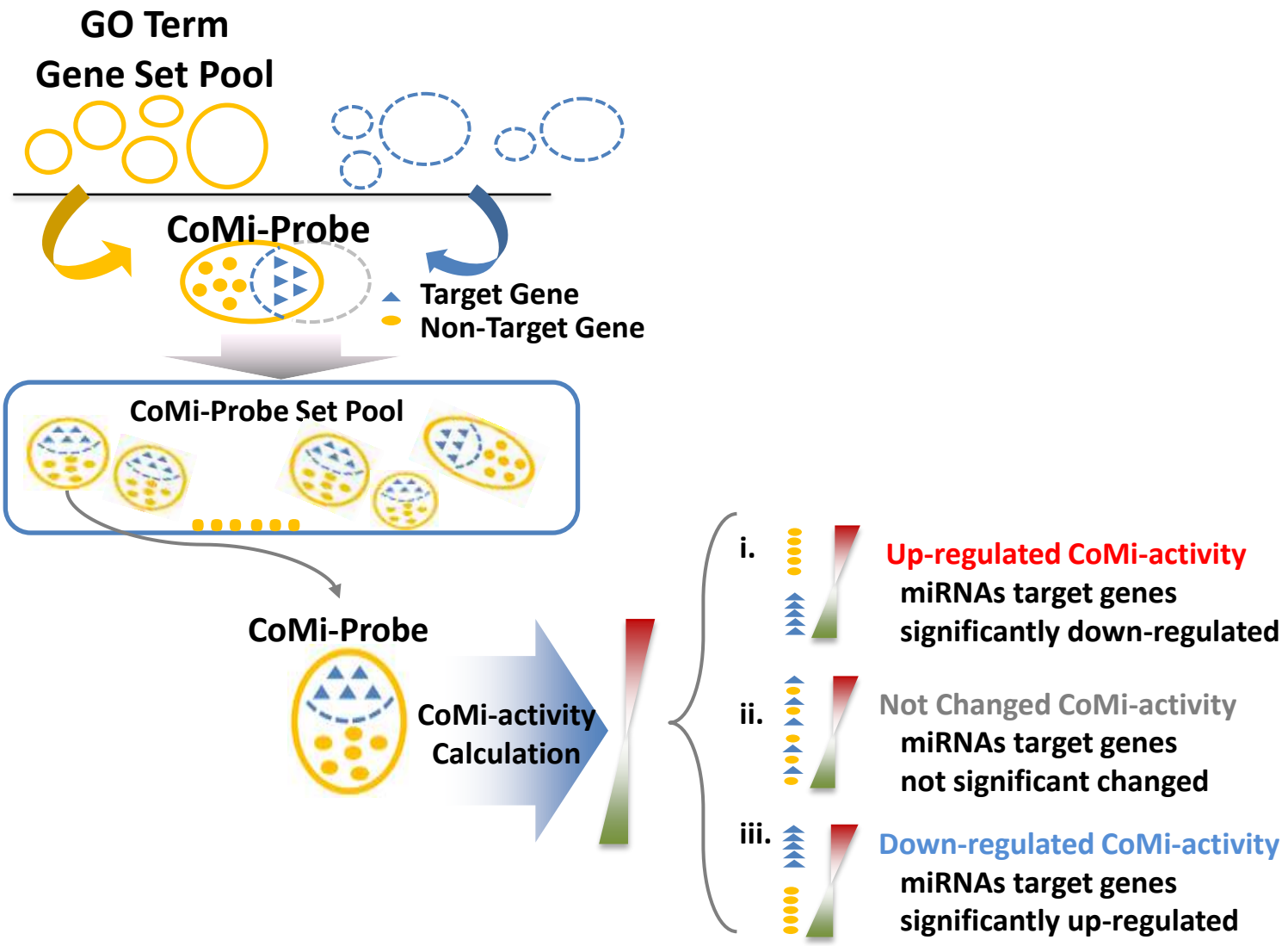
- MicroRNAs (miRNAs) play a key role in the regulation of the transcriptome.
- miRNAs have been identified as a key mediator in human disease and drug response.

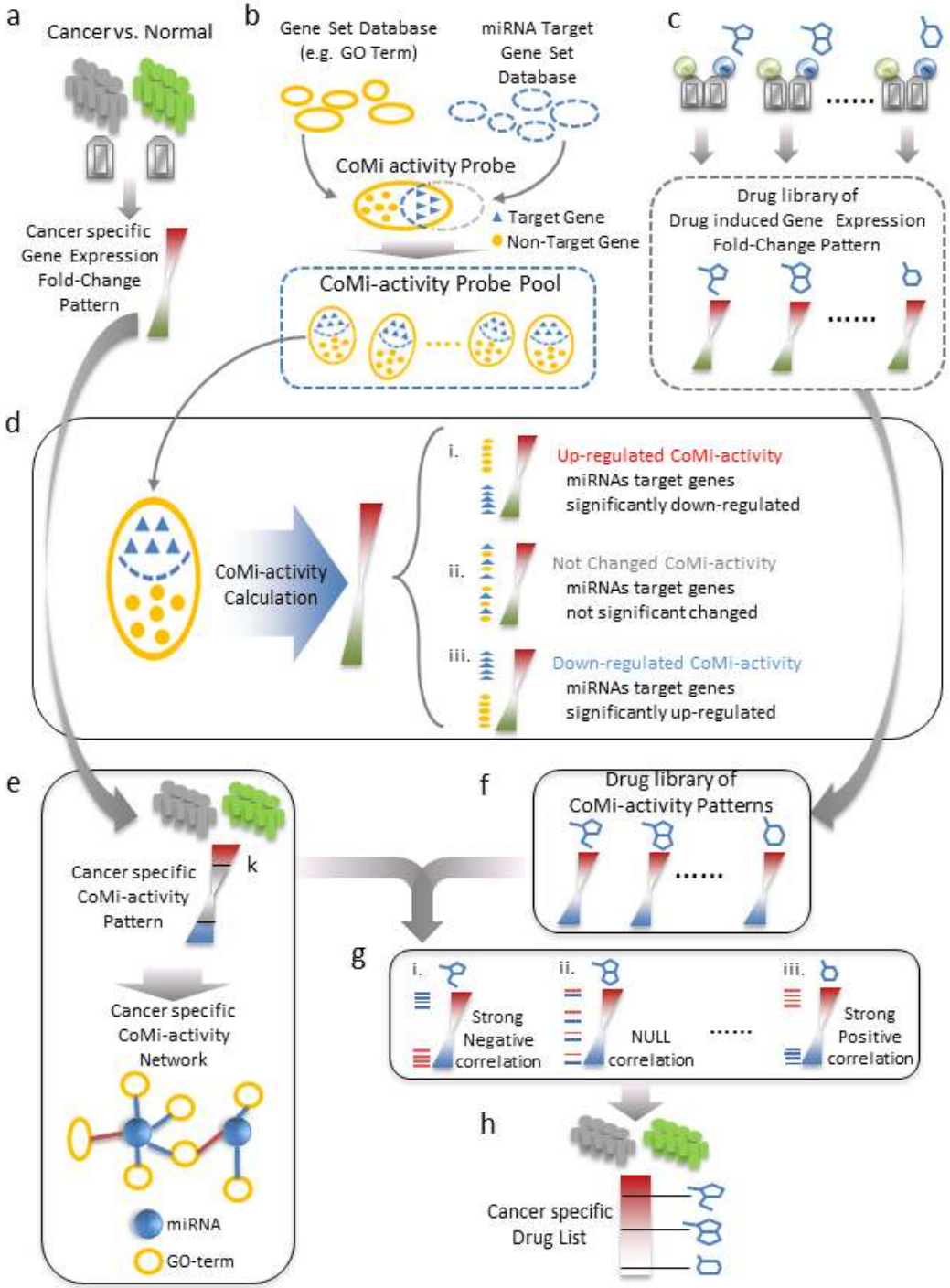
However, in methodology,
even if miRNA expression can be precisely detected,
the information regarding miRNAs action
on a particular part of the transcriptome is still lacking…

We proposed to

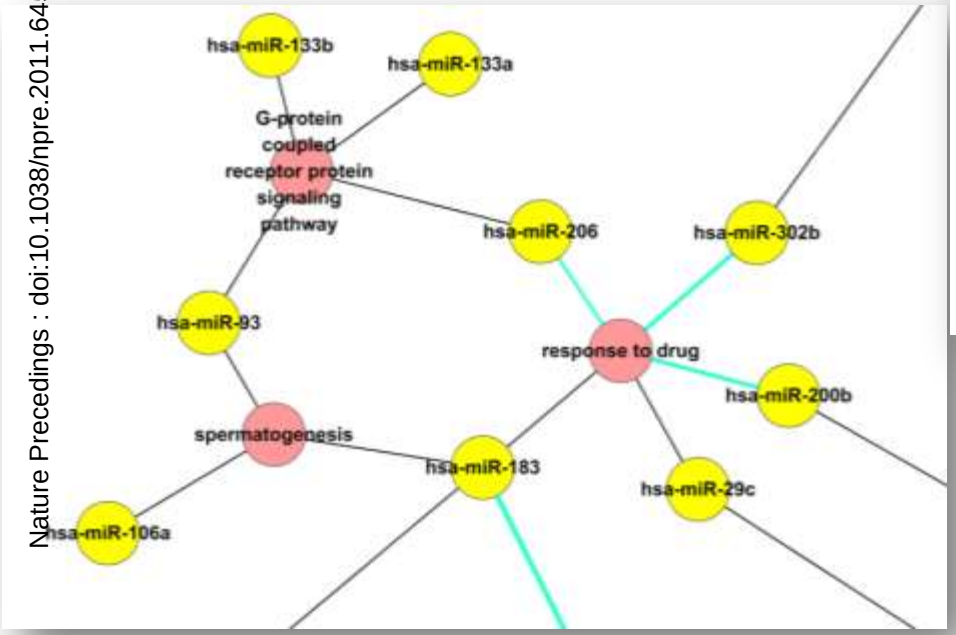
- Reveal the global network of **miRNAs action on specific part of the transcriptome**
- Use this network to understand drug Mechanism of Action (MOA)
- Demo its application on drug screening (drug positioning)

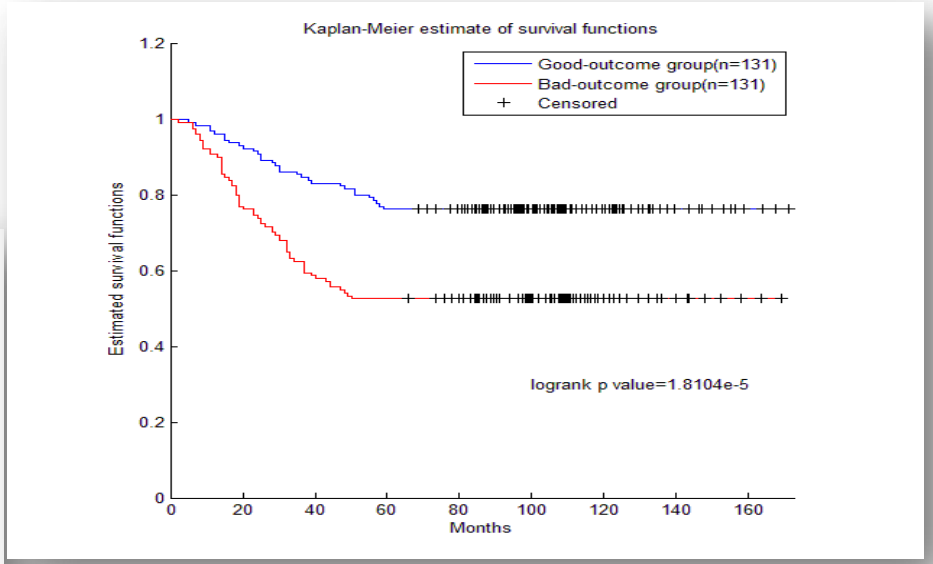
Context-specific miRNA activity (CoMi activity)





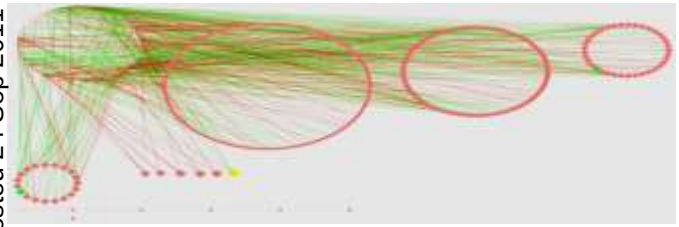
Previously we demoed its application on cancer prognosis prediction

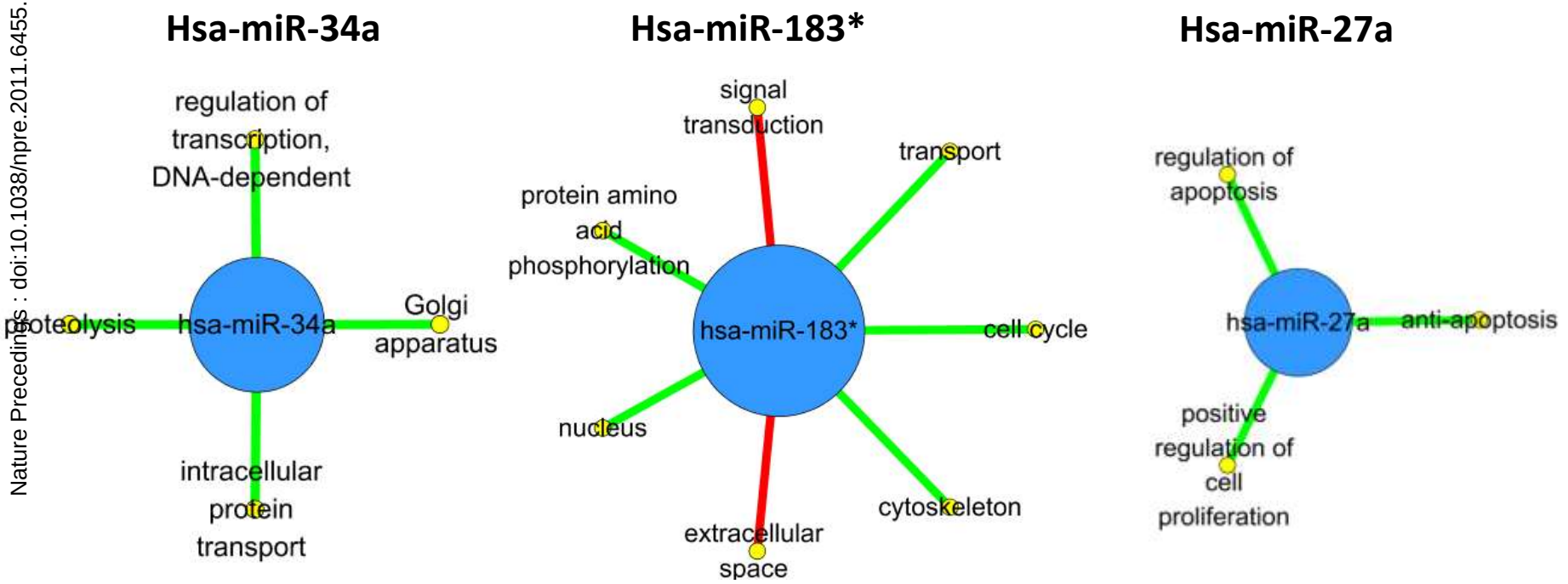




- Xionghui Zhou, …, **Jianghui Xiong****. **Context-Specific miRNA Regulation Network Predicts Cancer Prognosis**. Proceedings of 2011 IEEE International Conference on Systems Biology (ISB). 2011

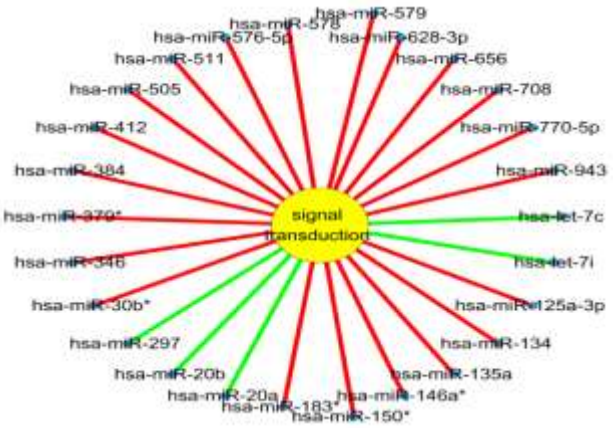
CoMi activity network (Breast cancer) could highlight key onco-miRNAs and tumor supressor miRNAs



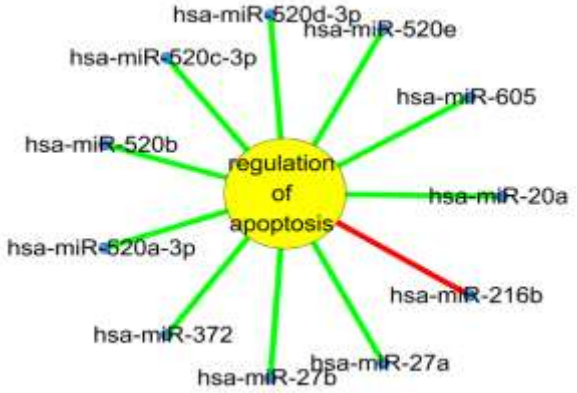


known onco-miRNAs (hsa-miR-183*, has-miR-27a) , tumor suppressor miRNAs (hsa-miR-34a)

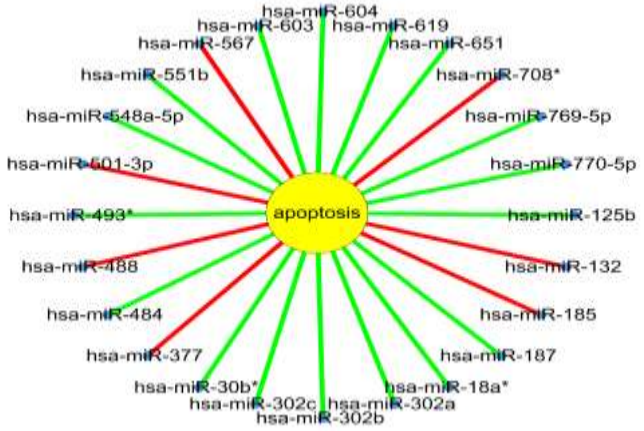
CoMi activity network (Breast cancer) highlighted key pathways in cancer



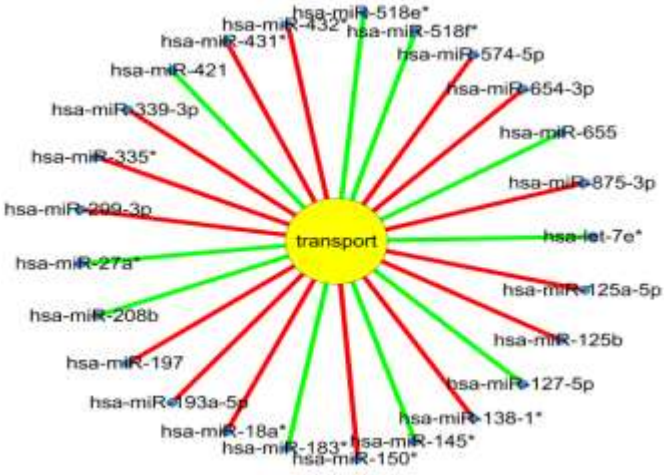
GO: Signal transduction



GO: regulation of apoptosis



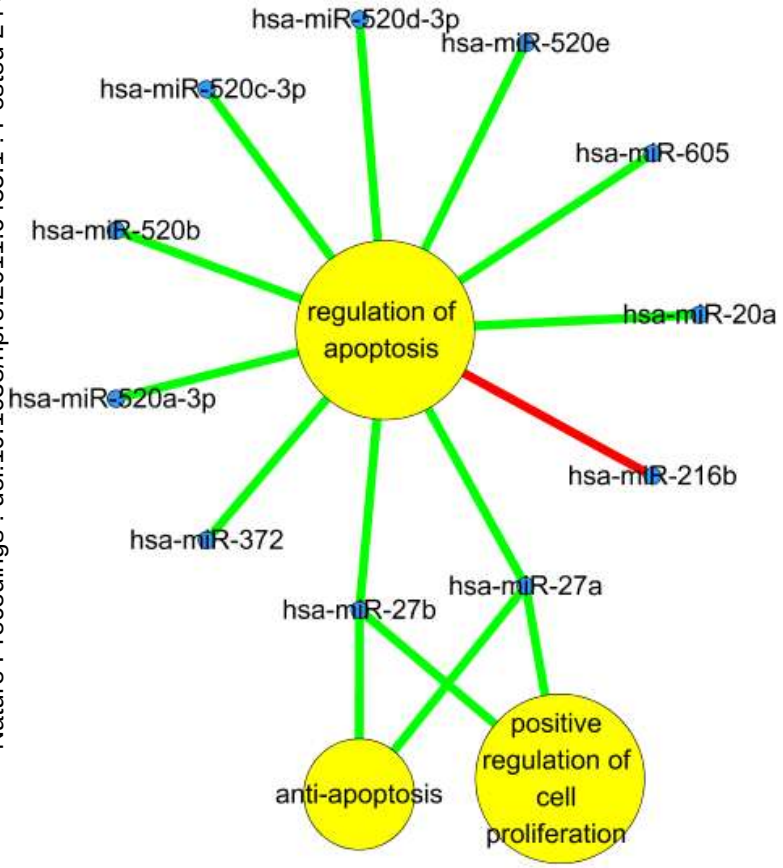
GO: Apoptosis

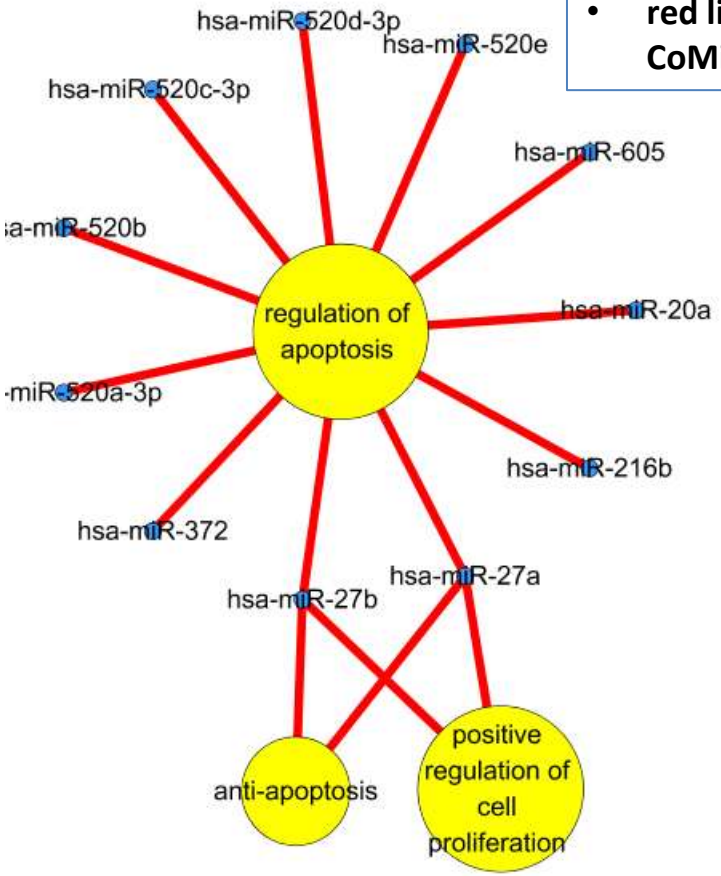


GO: Transport

CoMi network provide a promising way to understand the Mechanism of action of Paclitaxel on breast cancer

- green lines = down-regulated CoMi
- red lines= up-regulated CoMi





Dys-regulated network in Breast cancer

Paclitaxel can counteract the network (green lines → red lines)

Performance benchmarking as drug screening (drug repositioning) method

- Standard Agent Database：
  - 17 drugs mapping with CMAP，103 Instances.
- Breast cancer treatment:
  - Paclitaxel
  - Tamoxifen
  - Mitoxantrone
  - Vinblastine sulfate

  - 19 Instances of treatment. 19/103;4/17

- We tests which method could ranked the treatment drugs on the top of the drug ranked list.

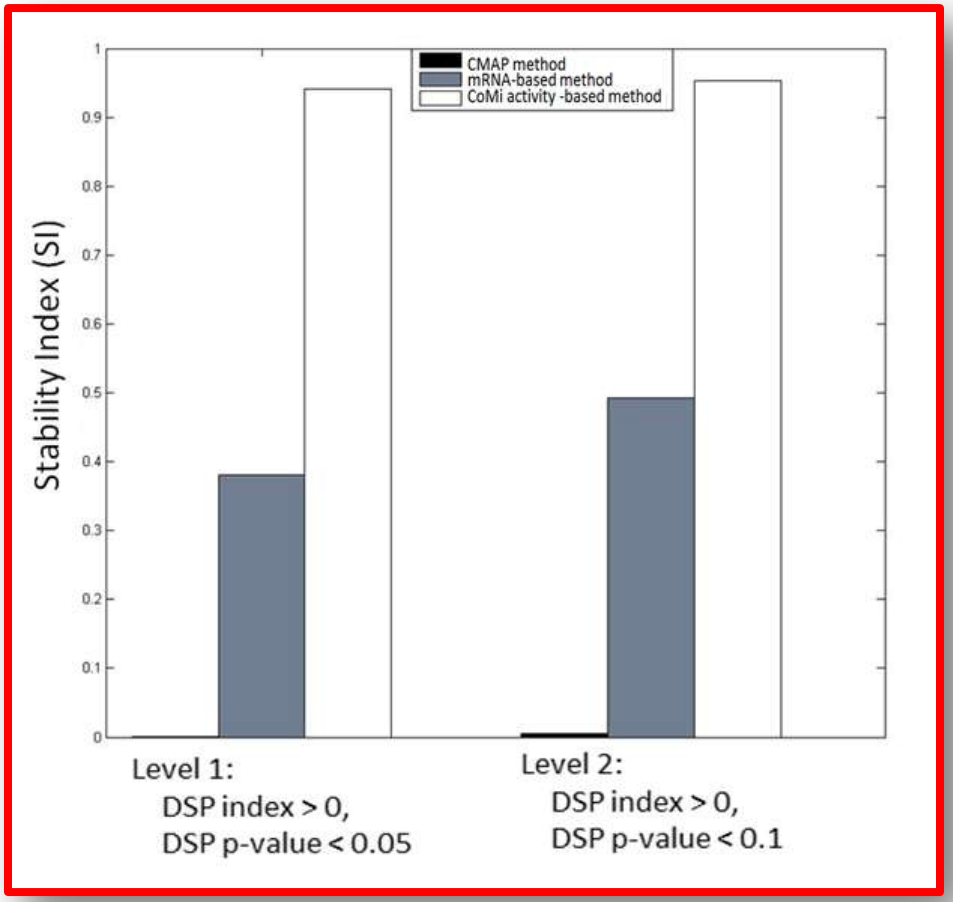
CoMi –based method has the best stability index as drug screening system

(i) CMAP method
(ii) mRNA-based method
(iii) CoMi activity –based method

$$\text{Stability Index (SI)} = \frac{\text{Count of the acceptable DSP index}}{N}$$

DSP: Drug screening performance

Level 1:
DSP index > 0
DSP p-value < 0.05
Level 2:
DSP index > 0
DSP p-value < 0.1



Comparison between drug list
CoMi activity-based method vs. CMAP method

Drug list of CoMi activity-based method			Drug list of CMAP method		
Rank	Drug	KS Score	Rank	Drug	KS Score
1	mercaptopurine	0.9417	1	decitabine	0.6893
2	***mitoxantrone***	***0.6214***	2	lomustine	0.4587
3	***vinblastine***	***0.5825***	3	***tamoxifen***	***0.4397***
4	daunorubicin	0.5073	4	procarbazine	0.4369
5	doxorubicin	0.4563	5	chlorambucil	0.4223
6	lomustine	0.4029	6	***mitoxantrone***	***0.3883***
7	***tamoxifen***	***0.3329***	7	***paclitaxel***	***0.3576***
8	***paclitaxel***	***0.2427***	8	etoposide	0.2646
	azacitidine	-0.2524		daunorubicin	-0.3811
	methotrexate	-0.2755		tetrandrine	-0.4393
	etoposide	-0.3107		methotrexate	-0.4660
	hycanthone	-0.3131		***vinblastine***	***-0.4919***
	tetrandrine	-0.3204		hycanthone	-0.4951
	chlorambucil	-0.3981		doxorubicin	-0.5146
	procarbazine	-0.5696		azacitidine	-0.5728
	decitabine	-0.8835		mercaptopurine	-0.9417

Wrong prediction!

- Our method successfully boost all positive drugs within the top 8
- Traditional CMAP method made a wrong prediction

Summary for CoMi method

- **CoMi network provide a promising way to understand the Mechanism of action of drugs**

- **As a drug screening/drug repositioning method, CoMi method strikingly outperformed the traditional CMAP method**

What's next?

- **Network models library is the infrastructure of Network pharmacology efforts**

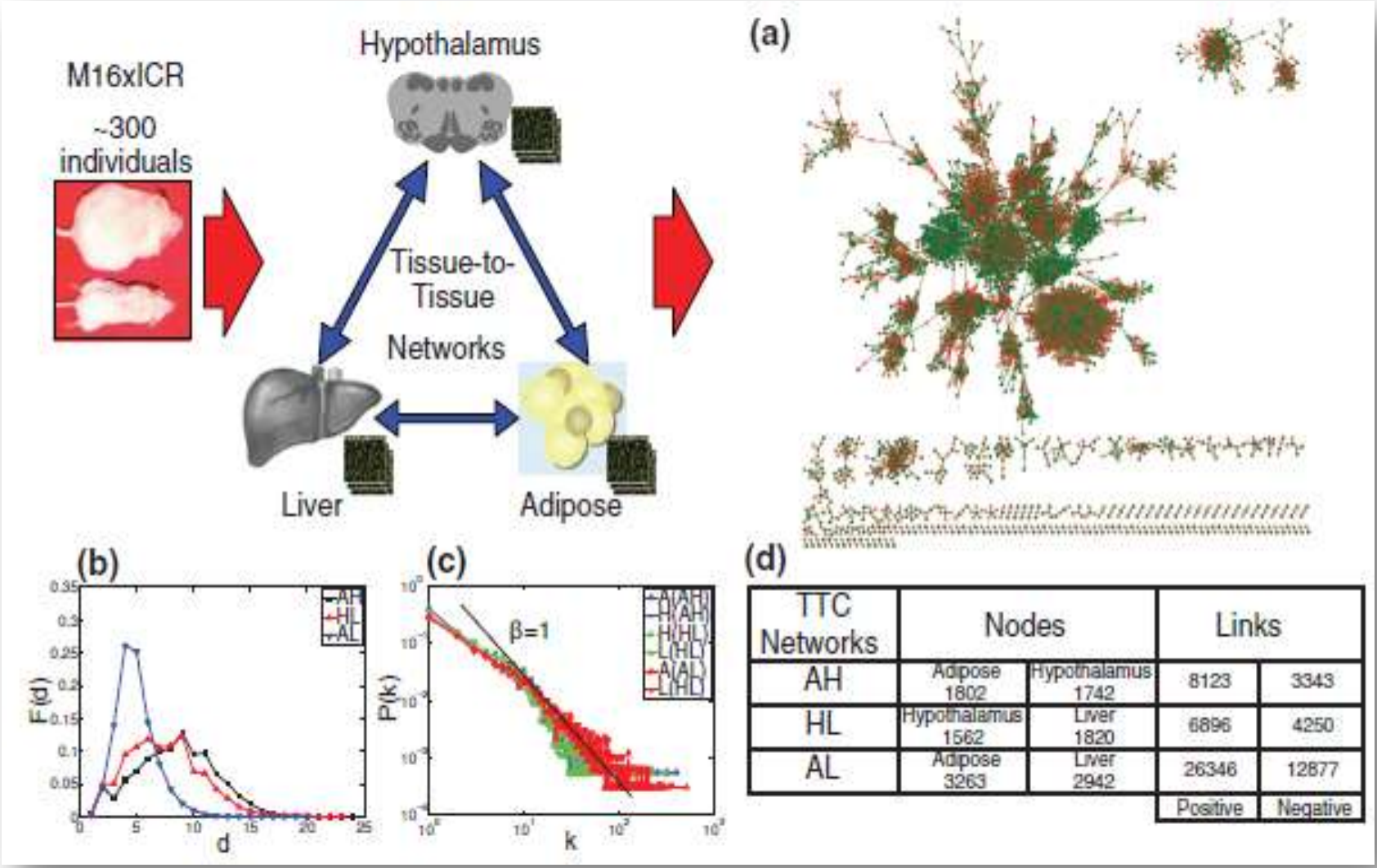
There are huge innovative opportunities on establishing diverse network, we set out to compile a comprehensive Network models library

- **Diverse types of node**
  - Gene
  - Gene modules
  - microRNAs
  - Long non-coding RNAs …
- **Diverse types of edge (interaction)**
  - Physical interaction
  - Genetic interaction
  - Co-expression
  - Bayesian …
- **Various metric for target identification**
  - Connectivity (hub)
  - Bridging centrality
  - Hierarchy…

Network models library?

- For genetic interaction
  - Different phenotype define different type of networks
  - Different experimental methods
  - Different context (cell lines, tissue source..)
- Not all biologists are computational biologists, we need pre-defined network models
- "The library of Network Models"
  - Annotate
  - Benchmark/validate
  - Updating
  - Integrating

Inter-organ network



TTC Networks	Nodes		Links	
AH	Adipose 1802	Hypothalamus 1742	8123	3343
HL	Hypothalamus 1562	Liver 1820	6896	4250
AL	Adipose 3263	Liver 2942	26346	12877
			Positive	Negative

Multi-tissue coexpression networks reveal unexpected subnetworks associated with disease

Radu Dobrin*, Jun Zhu*, Cliona Molony*, Carmen Argman*, Mark L Parrish*, Sonia Carlson*, Mark F Allan*§, Daniel Pomp*‡ and Eric E Schadt*¶

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- Juan Liu (Wuhan University)
- Jingfang Ju (Stony Brook University, USA)
- Wenxia Zhou (Beijing Institute of Pharmacology and Toxicology)

- Fengji Liang (Electrical and Computer Engineering)
  - NGS
  - Long ncRNAs

Lida Zhu (Computer Science)
- Drug screening/drug repositioning
- miRNAs network

- Xionghui Zhou (Computer Science)
  - microRNAs regulation network

Wenyan Qiao (Biology)
- Drug – miRNAs association

"What we observe is not nature itself, but nature exposed to our method of questioning."

Werner Karl Heisenberg

"我们所观测到的不是自然本身，而是自然根据我们探索它的方法的展现"

——维尔纳·海森堡 ("测不准原理", 量子力学，1932年诺贝尔物理学奖)

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