Section 2-1: Genomics, Proteomics and Metabolomics in Drug Discovery and Target Validation

In silico Genetic Network Models for Pre-clinical Drug Prioritization

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Network pharmacology

nature chemical biology

Network pharmacology: the next paradigm in drug discovery

Andrew L. Hopkins

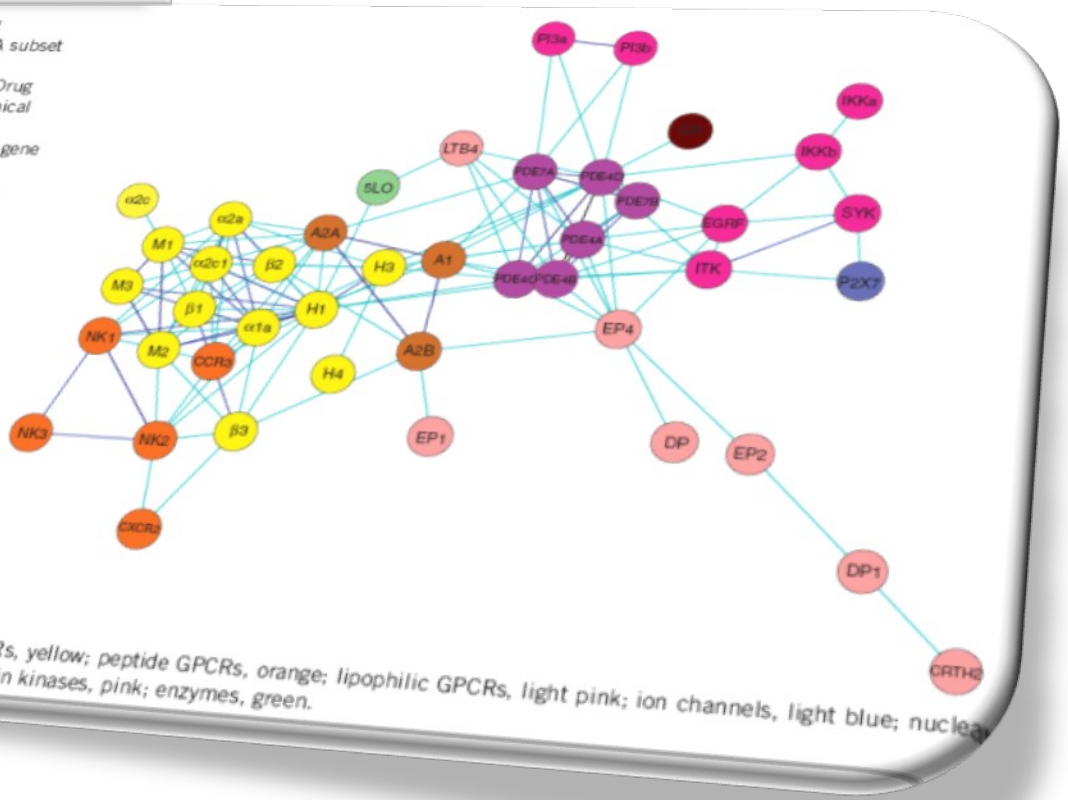


*Figure 2 Expanding opportunity for drug discovery space with polypharmacology. A subset of the network data shown in **Figure 1** for literature targets associated with asthma. Drug targets are represented as nodes, and chemical matter that binds to two or more nodes is represented as edges. Targets are colored by gene family. The color of the edges represents the strength of the chemical network between two targets as defined by the number of shared compounds that are active against both targets below an affinity of 1 μM: light blue (1 to 10 compounds) to black (> 1,000 compounds). Of the 44 targets described in the literature as potential drug targets for the treatment of asthma, 44 share polypharmacology of existing chemical matter with another potential target. These 44 targets are identified for 137 target combinations across > 10,000 compounds in this portfolio. Thus, by considering both single-target and dual pharmacology approaches, at least 181 potential profile opportunities can be examined. As this is an analysis of known chemical matter and biological activities, many of these profiles could be tested immediately in appropriate disease models. The network is represented in Cytoscape[117]. Drug targets are color-coded by gene family: aminergic GPCRs, yellow; peptide GPCRs, orange; lipophilic GPCRs, light pink; ion channels, light blue; nuclear hormone receptors, brown; phosphodiesterases, purple; protein kinases, pink; enzymes, green.*

The information to deliver

- **Network could be drug target**

- Jianghui Xiong etc., Pre-clinical drug prioritization via prognosis-g
  PloS ONE 2010

- "For more than a decade, scientists in systems biology have promised that real breakthrough in genetic medicine will come when we stop mapping individual genes to phenotypes and instead start looking at interacting networks. Yet, not much has happened. The field is still struggling to define relevant networks and to interpret data in terms of those networks.

  The paper by Xiong et al adds considerably to the progress of **network-based genetic medicine**. It is highly relevant, original and interesting."

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,

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

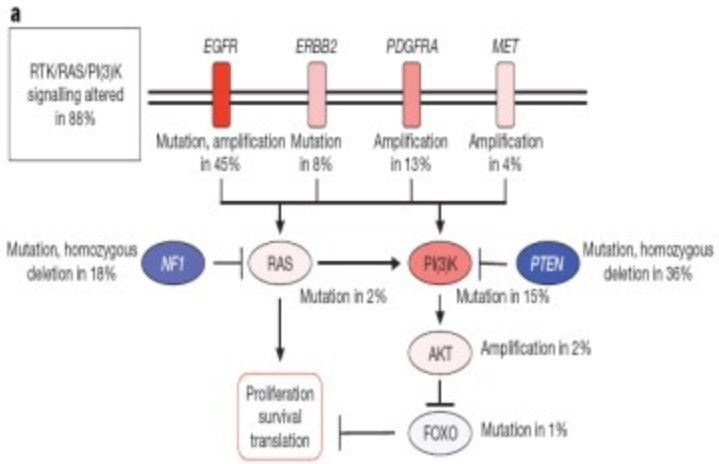
Cancer site	Mouse model	Refs
Brain		
Medulloblastoma	$Ptc^{+/-}$; p53, GFAP-Cre; $Rb^{lox/lox}$	[30]
Astrocytoma	GFAP-v-src, GFAP-HRas	[30]
Glioblastoma	NPcis	[31]
Breast		
Low-grade mammary intraepithelial neoplasia	MMTV-LTR/int3, MT/HGF	[32]
High-grade mammary intraepithelial neoplasia	C(3)1/SV40 tag, 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	$Apc^{min/+}$; $Apc^{\Delta 716}$; $Apc^{1638N/+}$	[33]
Adenocarcinoma	$Mlh1^{-/-}$; $Apc^{1638N/+}$; $Msh6^{-/-}$; $Apc^{1638N/+}$; $Msh3^{-/-}$; $Apc^{1638N/+}$	[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,

Our proposal

1 **Hypothesis**

- Considering gene networks associated with cancer outcome in heterogeneous patient populations
- The difficulty of identify effective cancer cures (as evidenced by drug resistance) may be a consequence of the robustness of this network
- **Network (robustness) as drug target**

2 **Pre-clinical *in silico* Cancer Models for Drug action study**

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

The NEW ENGLAND JOURNAL of MEDICINE

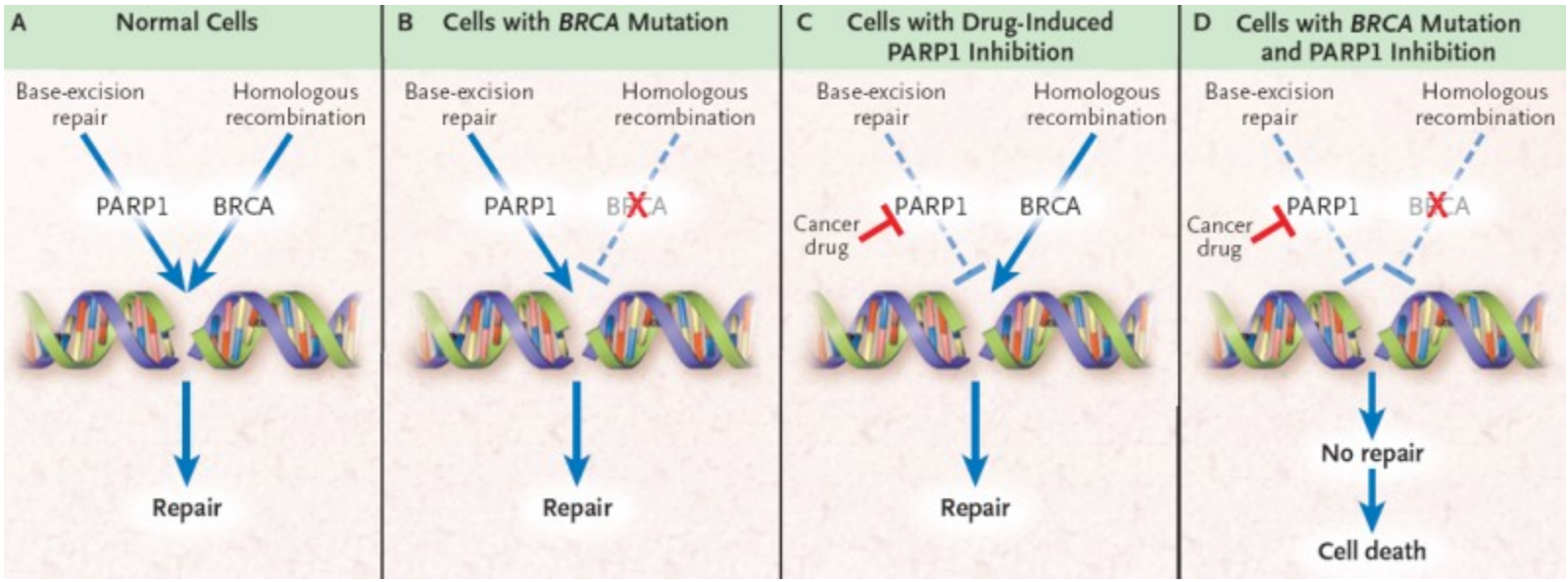
EDITORIALS

Synthetic Lethality — A New Direction in Cancer-Drug Development

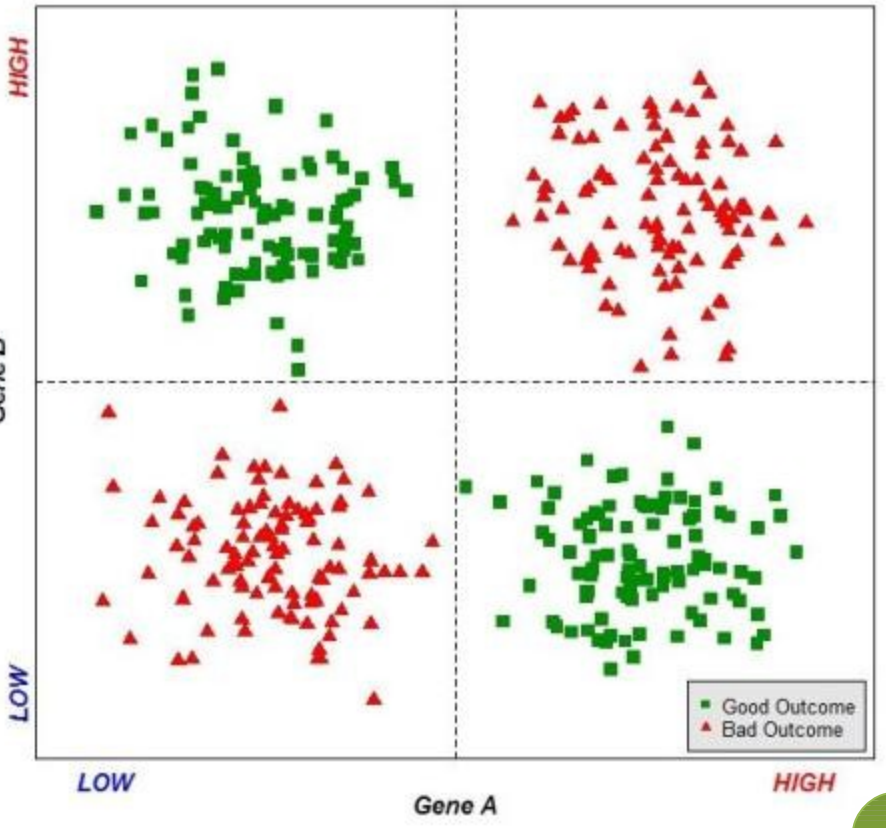
I. Dirk Iglehart, M.D., and Daniel P. Silver, M.D., Ph.D.

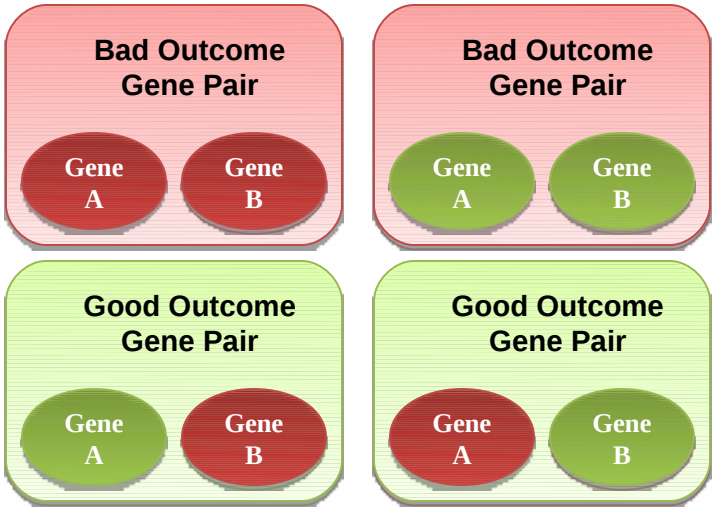
a Synthetic lethality

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



SOD (Synergistic Outcome Determination)





Synergistically Infered Nexus (SIN)

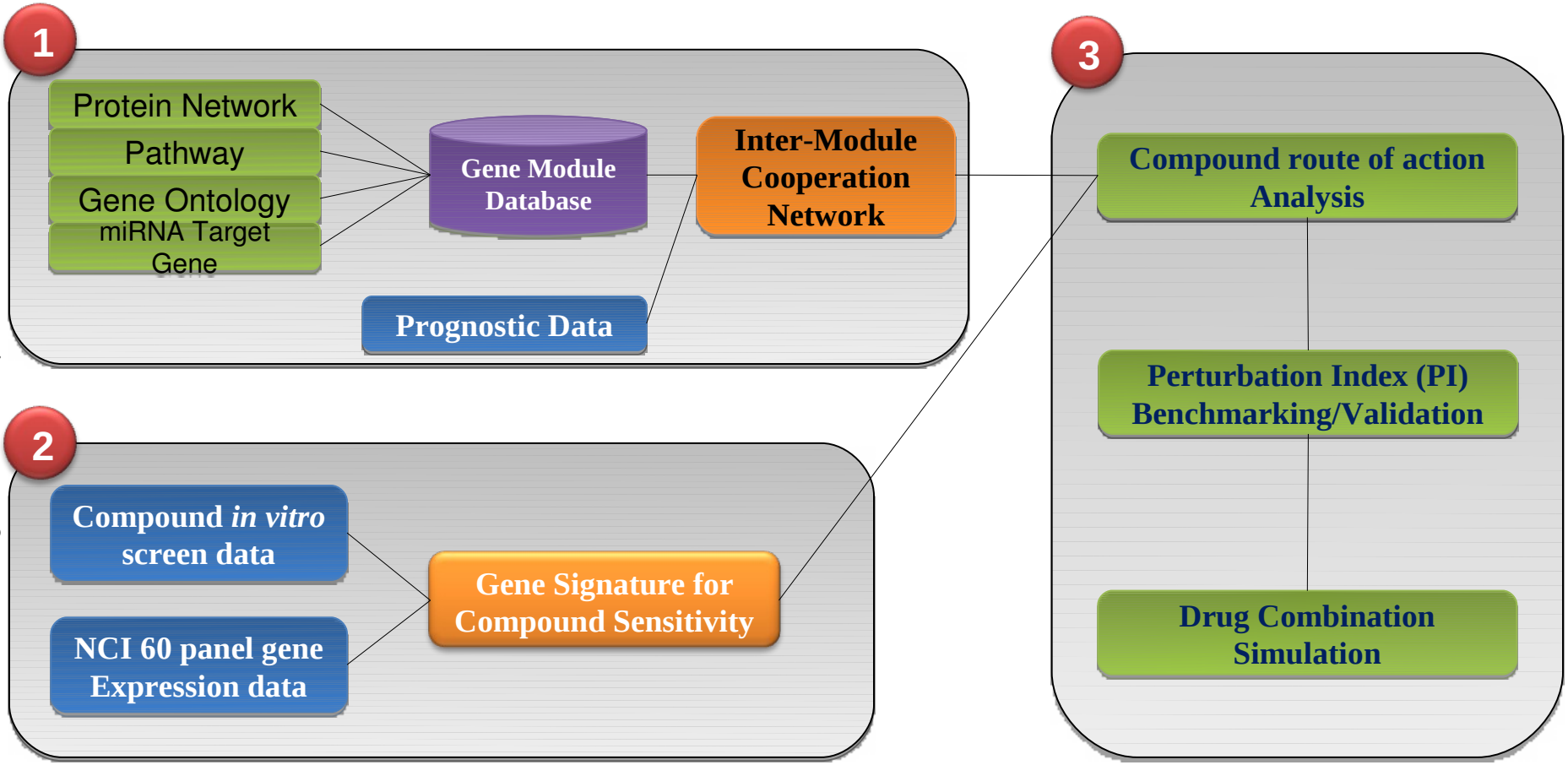
$$\square\square\square\square_1,\square_2;\square\square = \square\square\square_1,\square_2;\square\square - \square\square\square\square_1;\square\square + \square(\square_2;\square)\square$$

$$\square\square\square;\square\square = \sum_{\square}\sum_{\square} \square\square\square,\square\square\log_2\frac{\square(\square,\square)}{\square\square\square\square(\square)}$$

SOD (Synergistic Outcome Determination) vs Synthetic Lethality

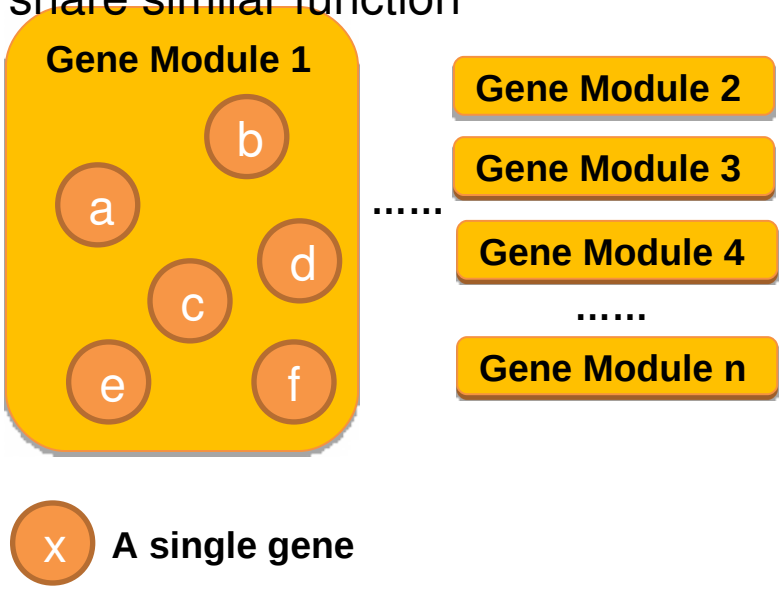
Feature compared	SOD	Synthetic Lethality
Phenotype	Survival outcome of individual patient	Cell death/growth
Level	Individual	Cell
Data Accessible	Human population (via computation)	Yeast (SGA); Human cell lines; ~~Human population~~

The pipeline

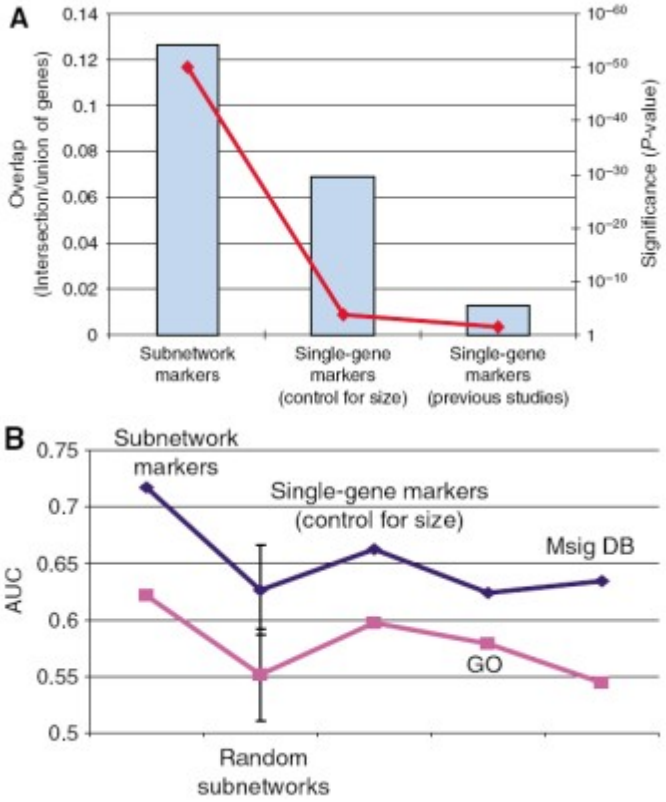


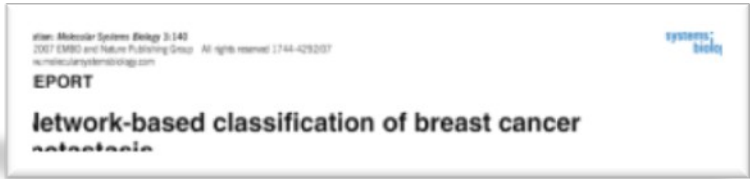
What is Gene Module?
And Why We use it instead of the single genes?

Gene Module:
a group of genes
which
share similar function



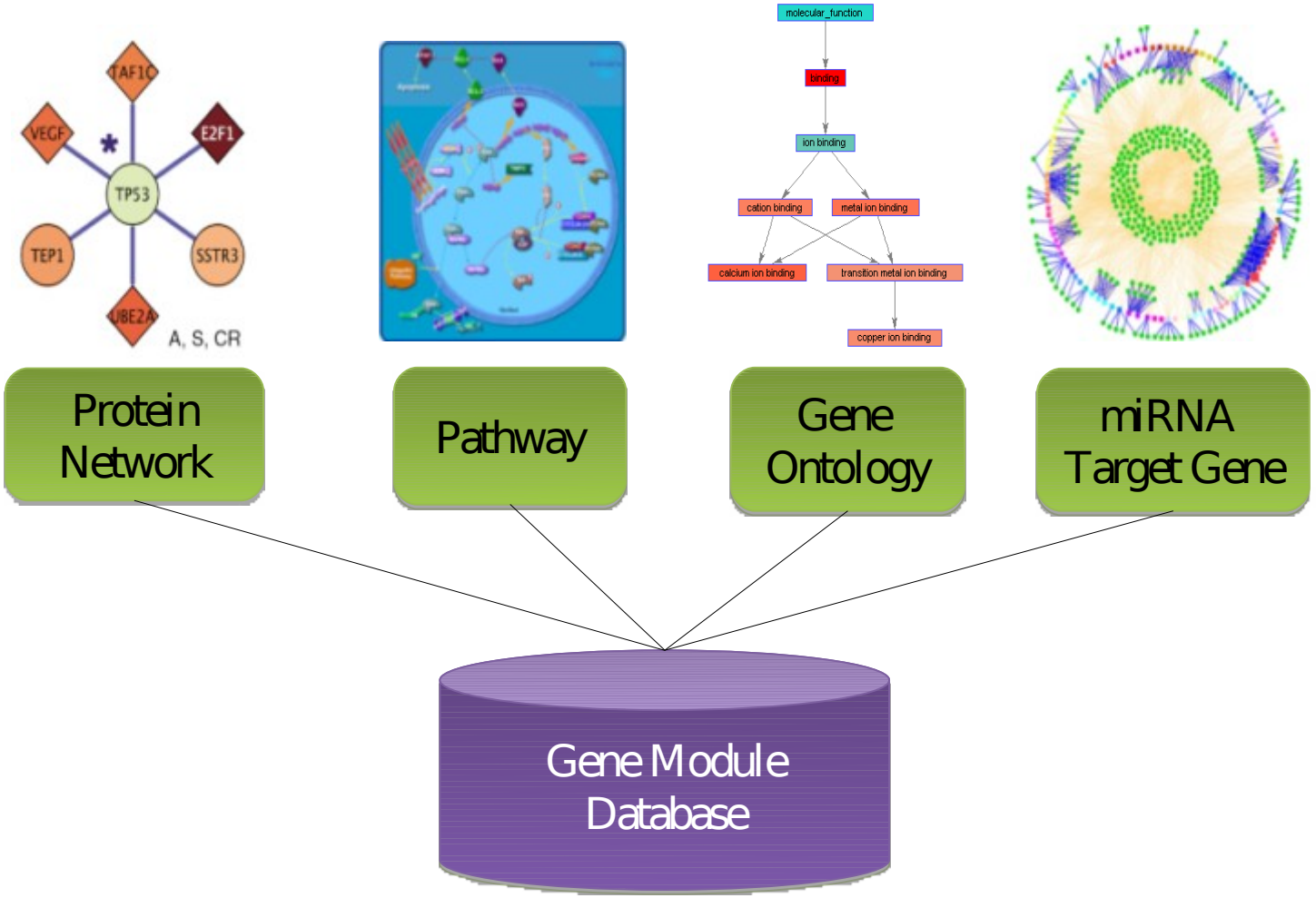
Gene Module:
robust/reproducible features rather than single gene




EPORT

letwork-based classification of breast cancer

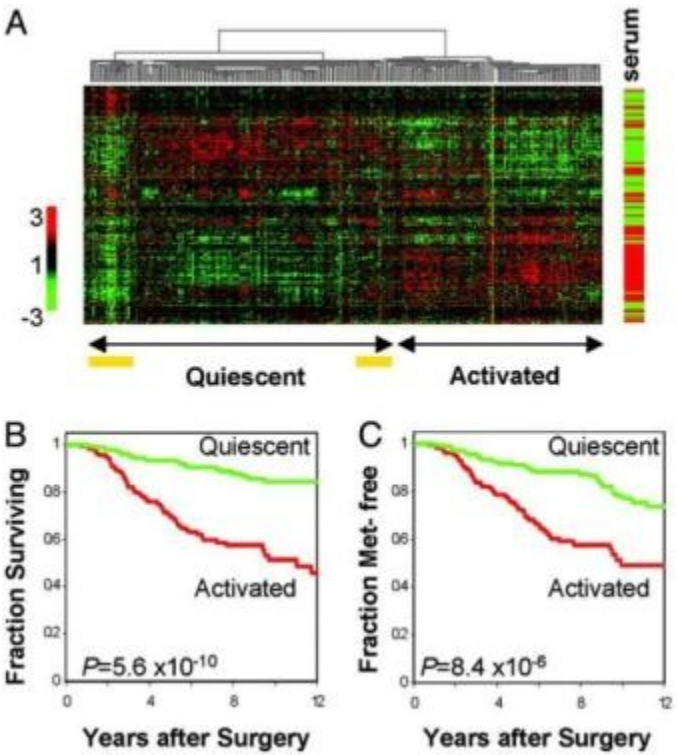
Gene Module Database



Prognosis Data
-- data associated gene expression with patients' prognosis

Prognosis Data Instance

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

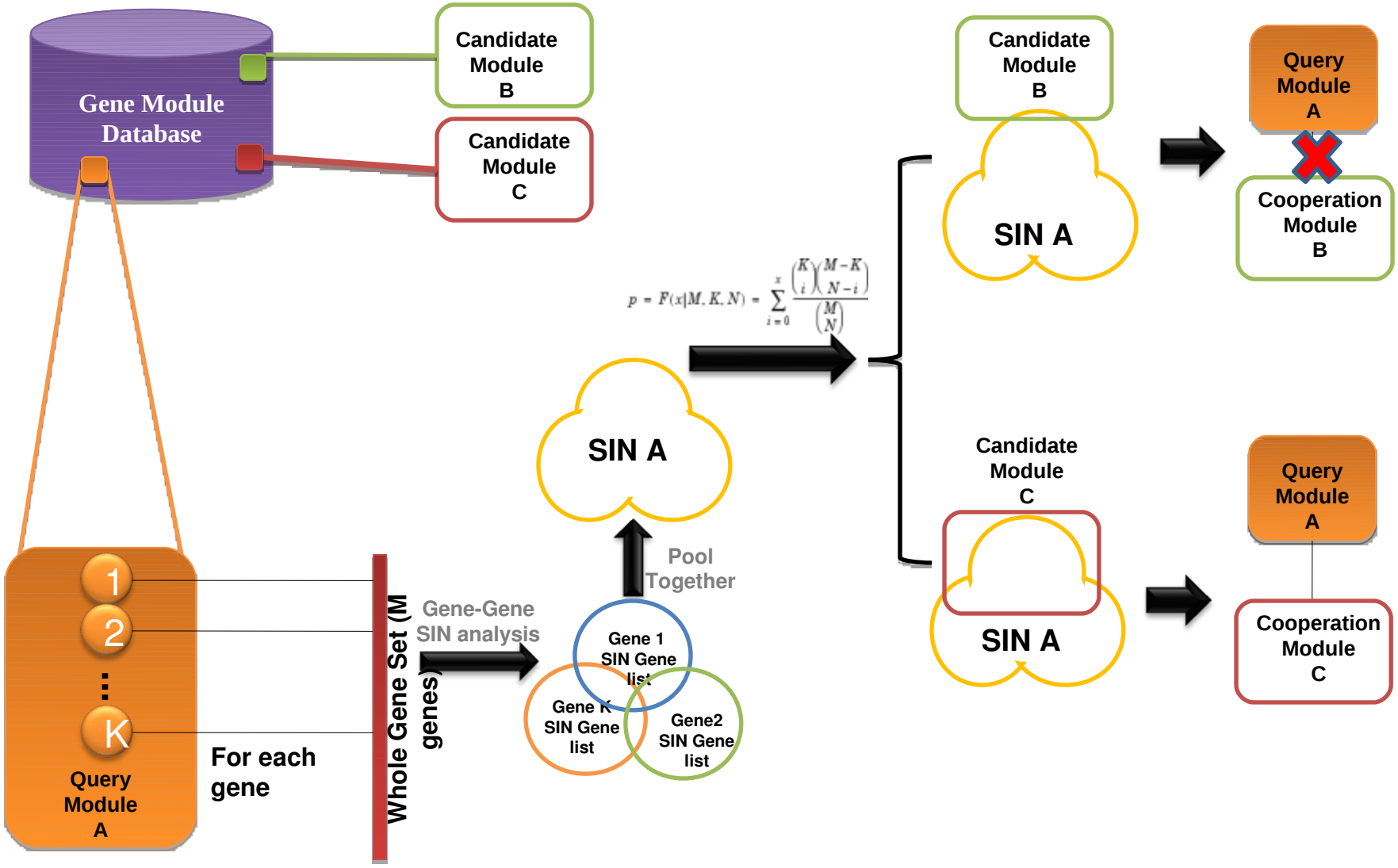


Benefit of Prognosis Data

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

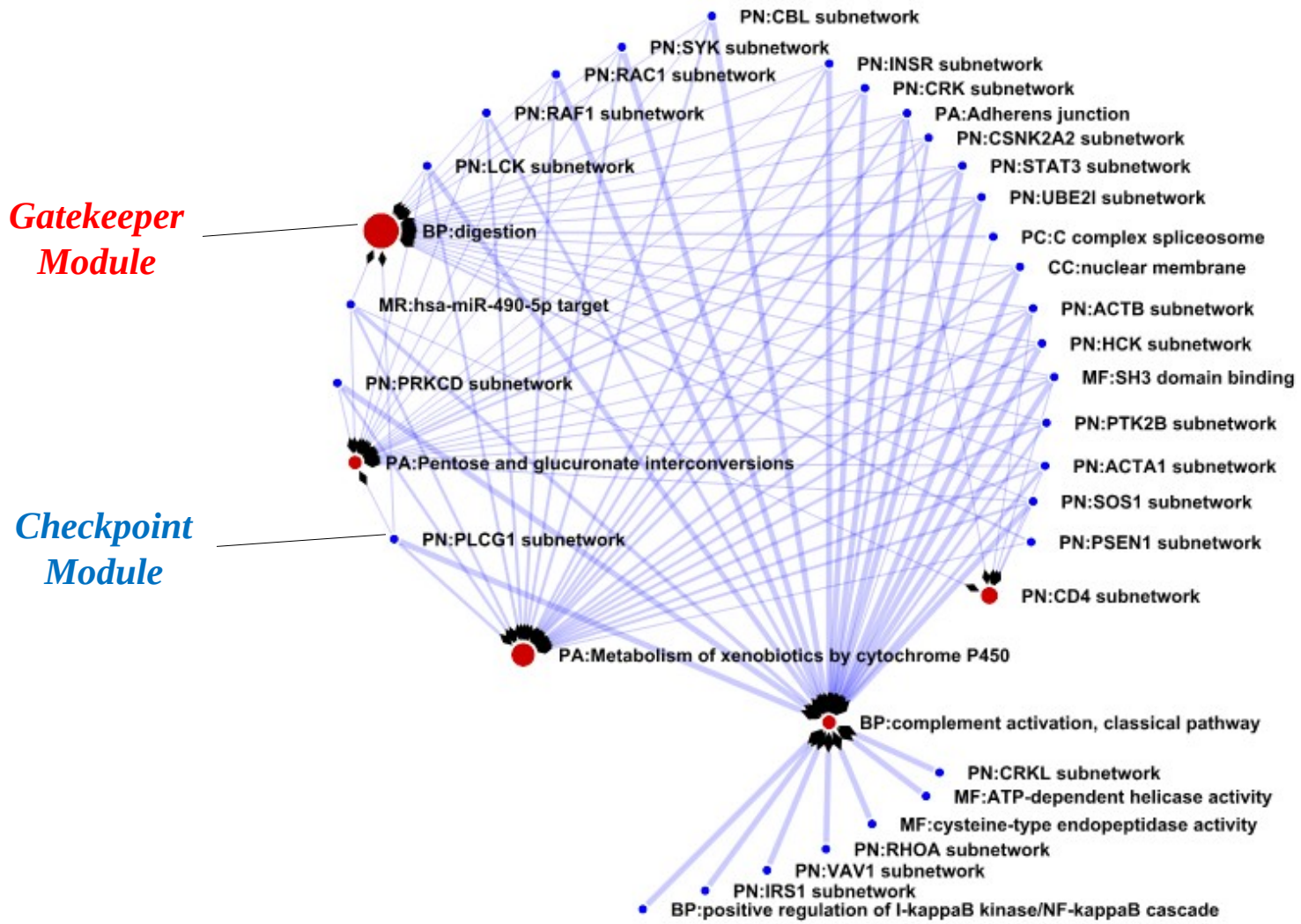
Chang H Y et al. PNAS 2005;102:3738-3743

Module-module cooperation network



Inter-Module Cooperation Network (IMCN)

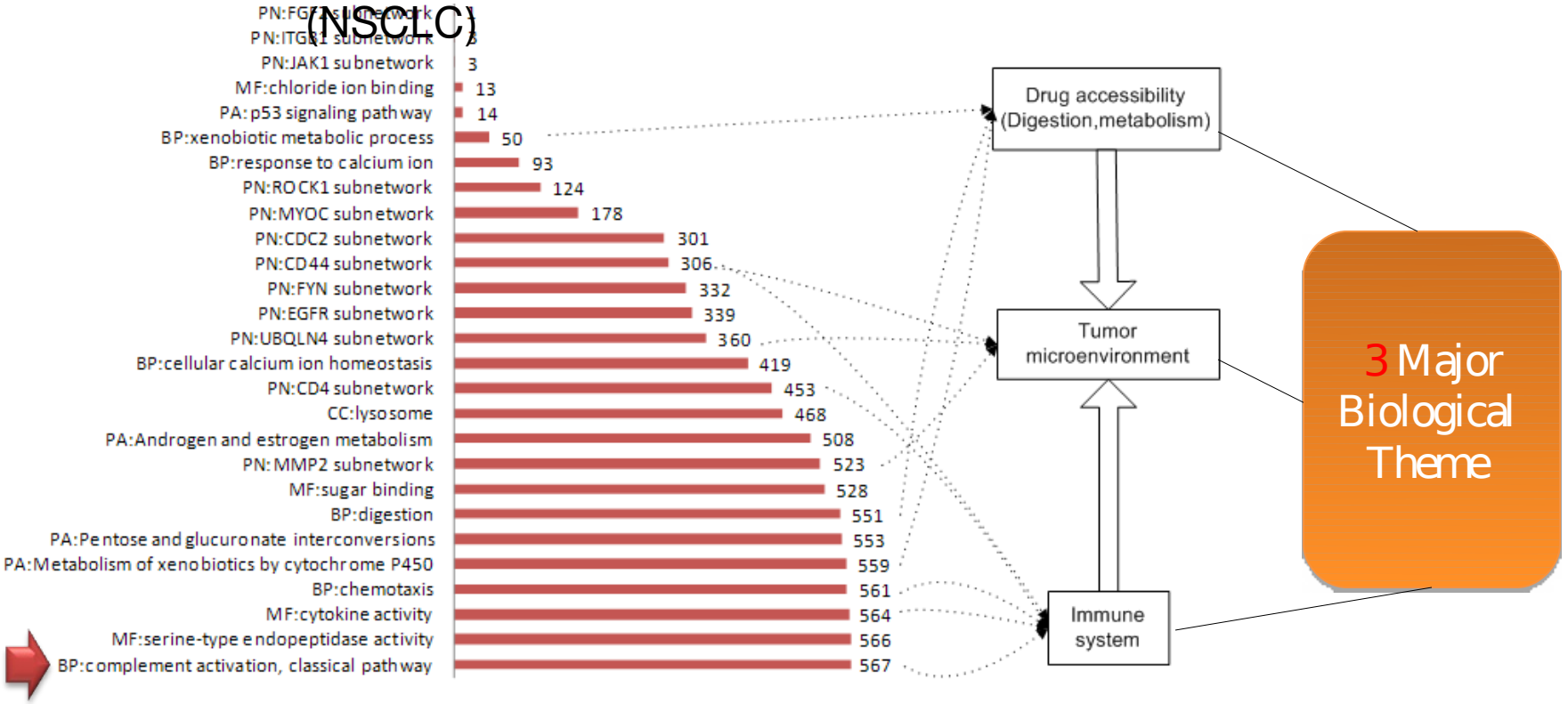
for lung cancer suggests that the network robustness highly dependent on **gatekeeper modules**

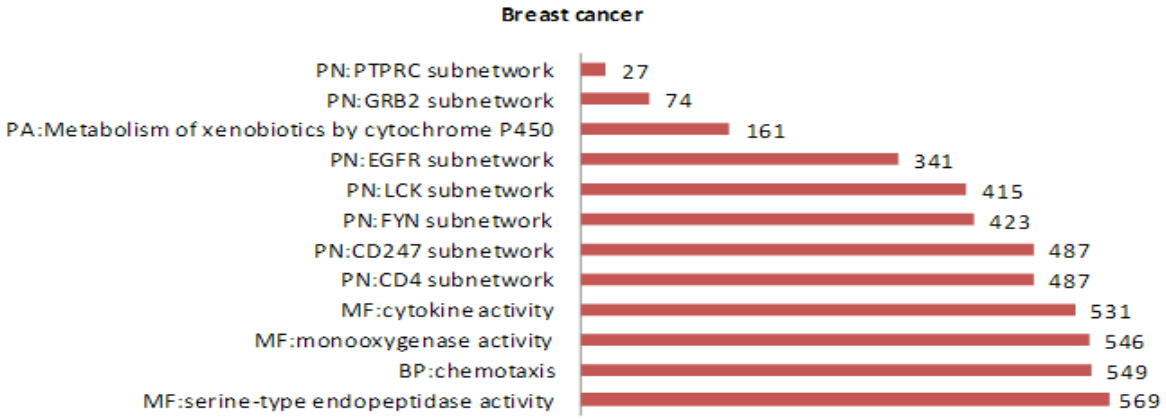


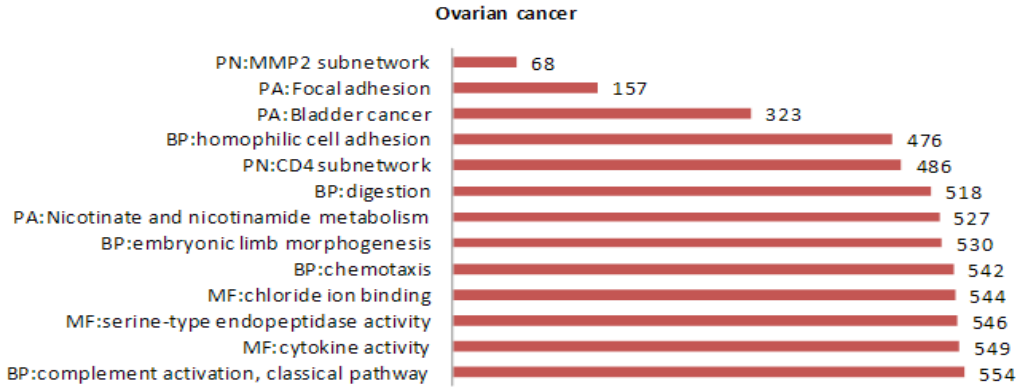
Characterization of the Inter-Module Cooperation Network (IMCN)

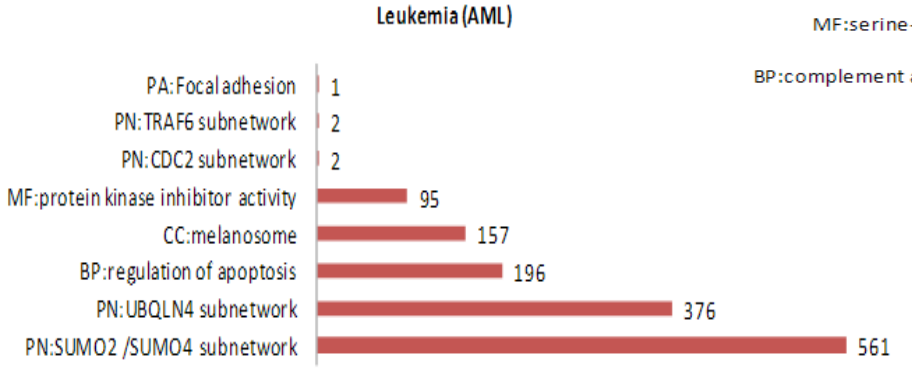
Cancer type	GEO data set
Lung cancer (NSCLC)	GSE3593
Breast cancer	GSE2034
Ovarian cancer	GSE3149
AML	GSE12417

'Gatekeeper' modules for lung cancer (NSCLC)

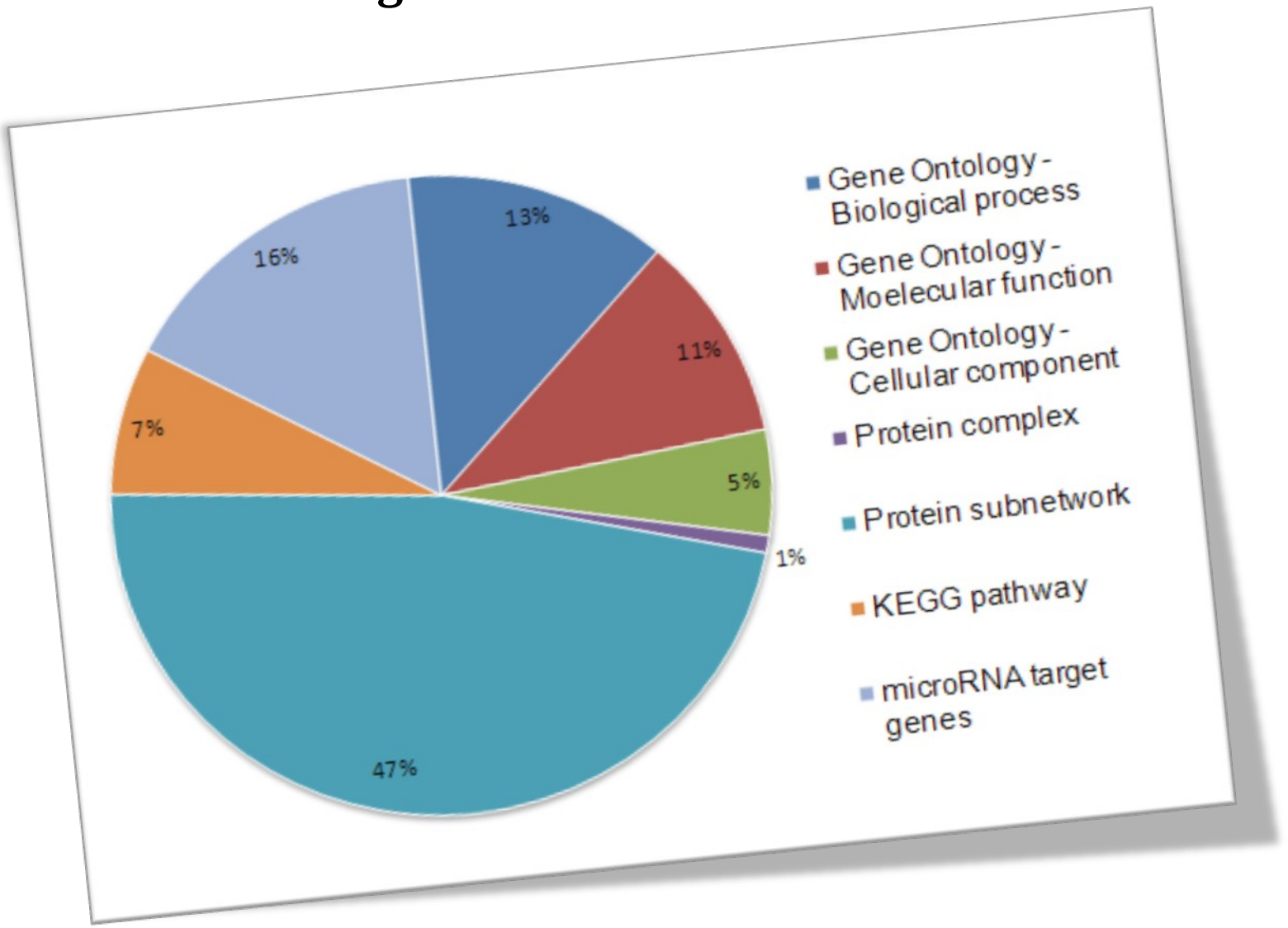




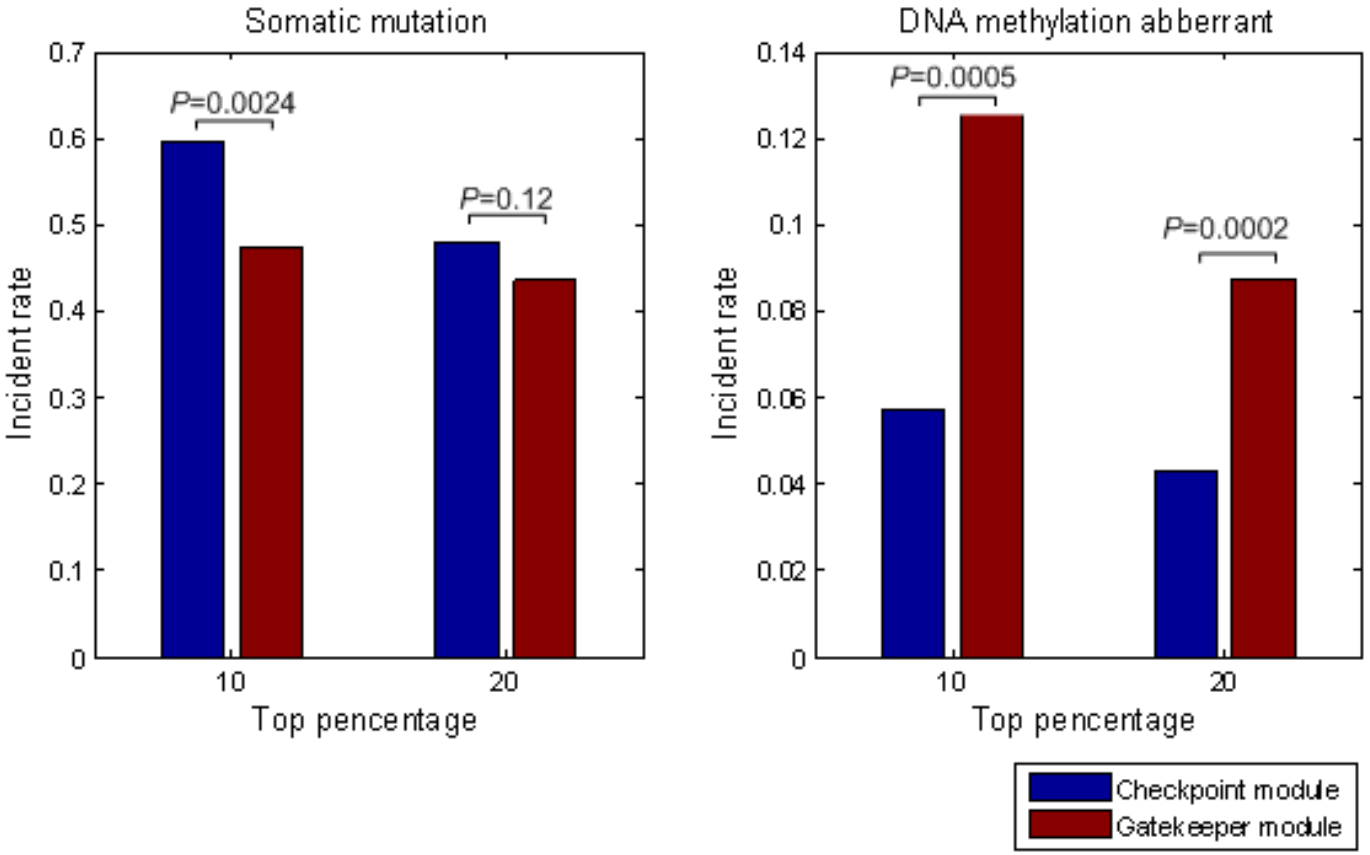




Contribution of various evidence sources for gene module definition



Comparing genetic (somatic mutation) and epigenetic (DNA methylation) aberration rate (in tumor vs. normal) of two types of modules



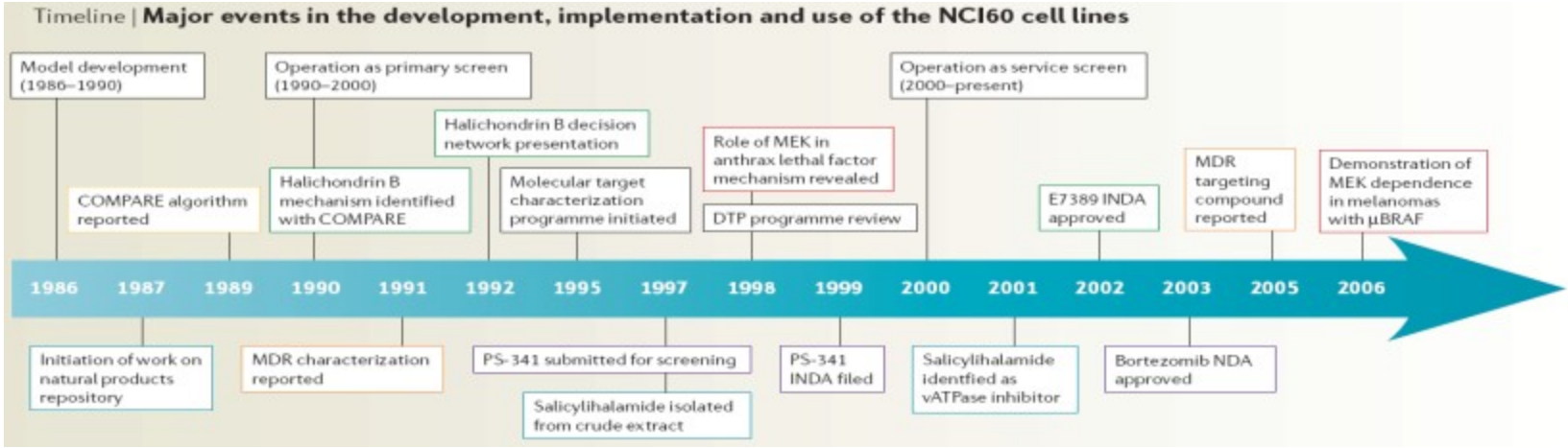
Top 10% or 20% of genes which highly used (i.e. one gene involved in multiple gene modules) as representative of each types of modules

Compound action on cells

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



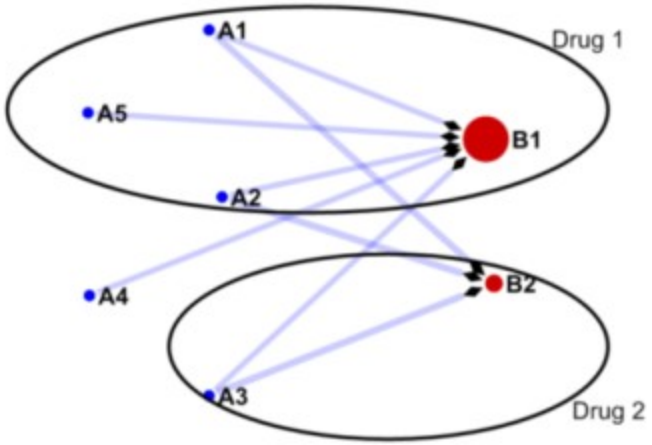
Use Perturbation Index (PI) to quantify Drug action

Hypothesis

- **To disrupt/perturb cancer network, the key to success is to simultaneously perturbs the corresponding gatekeeper modules with the checkpoint modules**

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

- *Hi* -- the number of hits by compound *c*
- *Li* -- 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

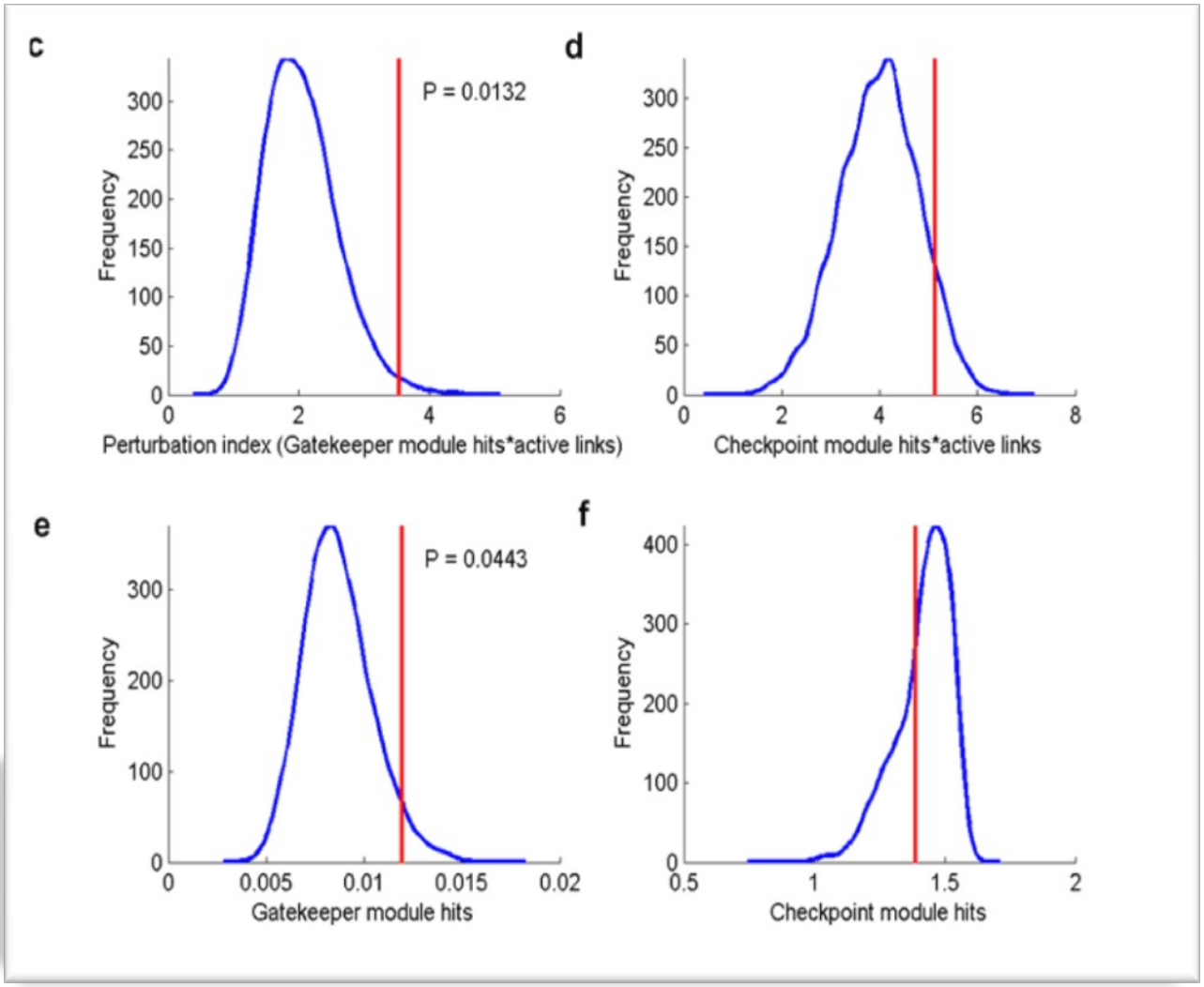


Benchmarking for pre-clinical drug prioritizing

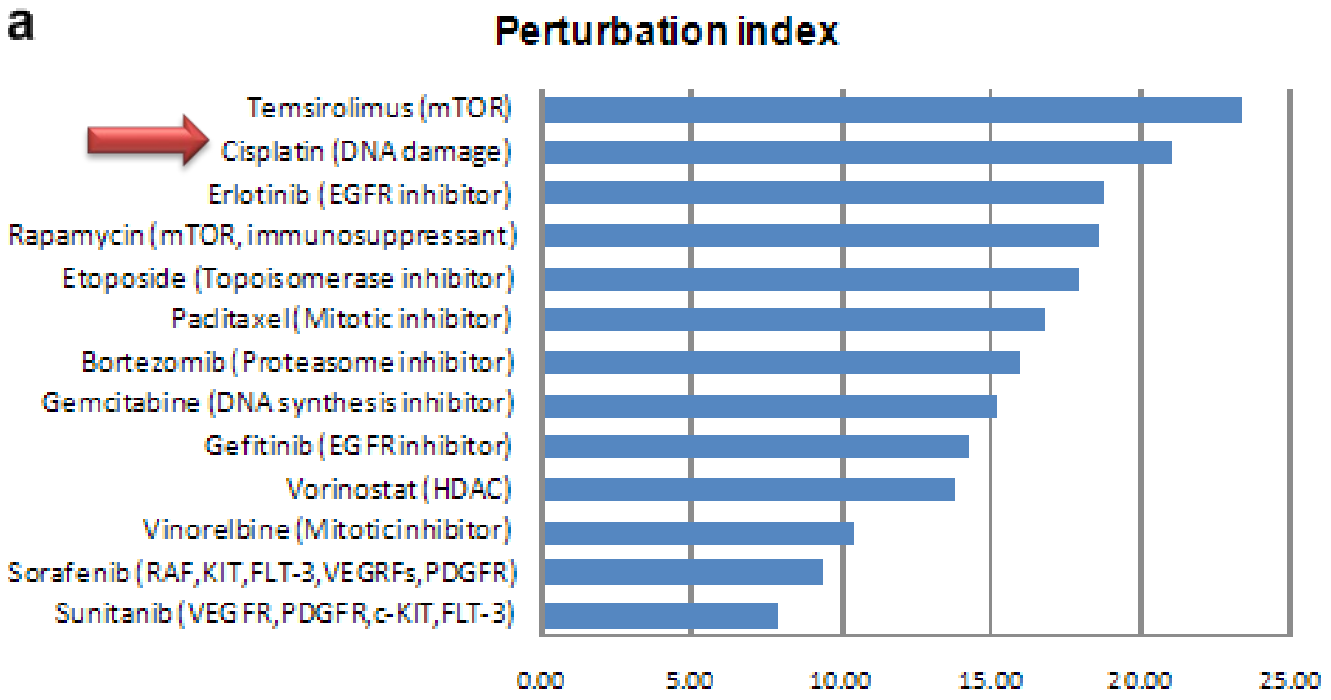
- **Why test?**
  - Assess the potential application for prioritizing compounds for clinical trials, based on the information available in pre-clinical stage
- ***'Standard Agent Database'***
  - Originally created by Boyd [29] and ultimately finalized by the NCI
  - Compounds which have been submitted 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

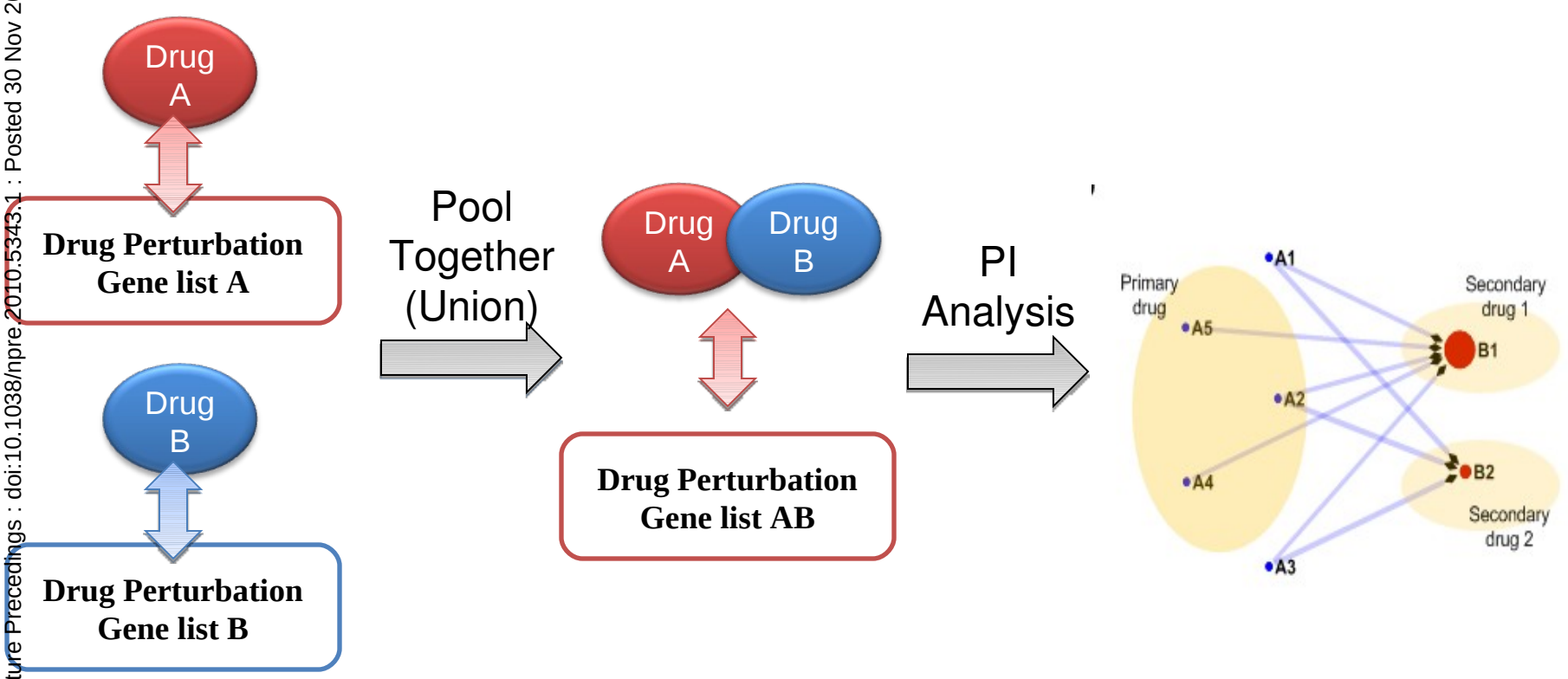
$$PI(c) = \frac{\sum_{i=1}^{N}(H_i \times L_i)}{G(c)}$$



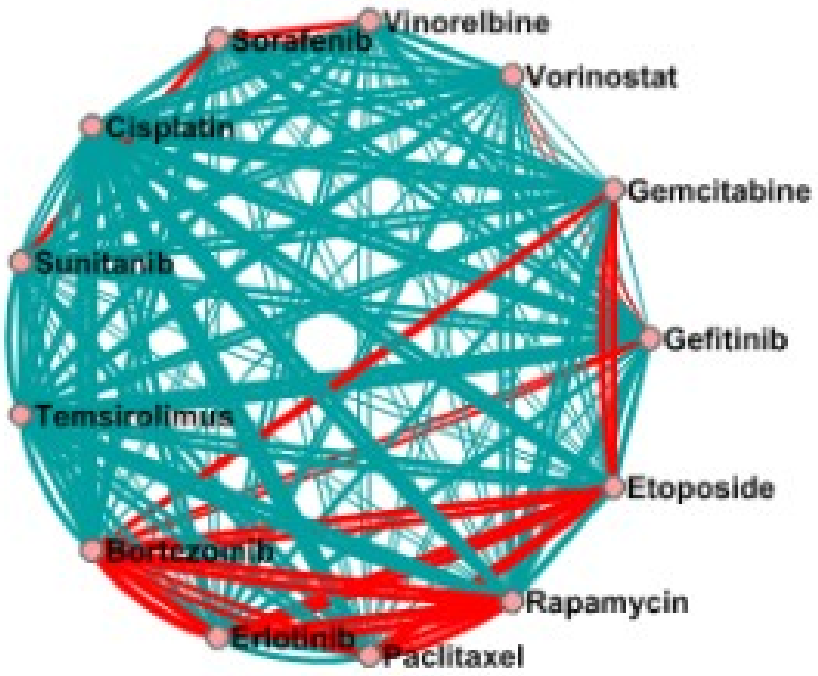
Rank of drugs and agents in clinical development for lung cancer according to their Perturbation Index



How to quantify synergistic effect of Drug Combination?



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

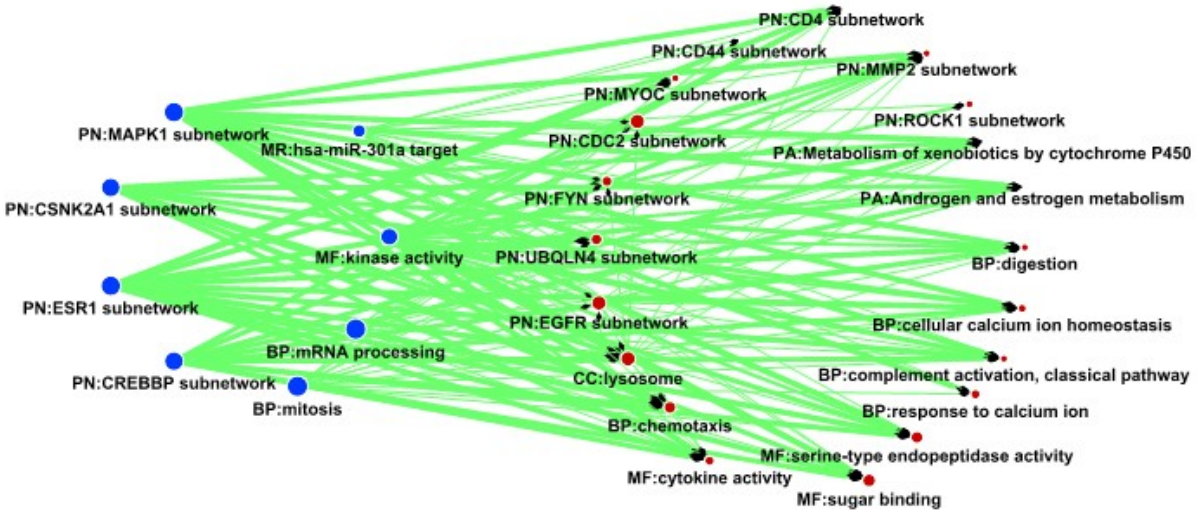


- Validity of Bortezomib-Gemcitabine
  - Notable survival benefits in lung cancer patients using a Bortezomib + gemcitabine/carboplatin combination as first-line treatment (phase II clinical trial reported)
    - Davies, A.M. et al. ***J Thorac Oncol*** 4, 87-92 (2009)
- Validity of Bortezomib-Paclitaxel
  - 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

Gemcitabine

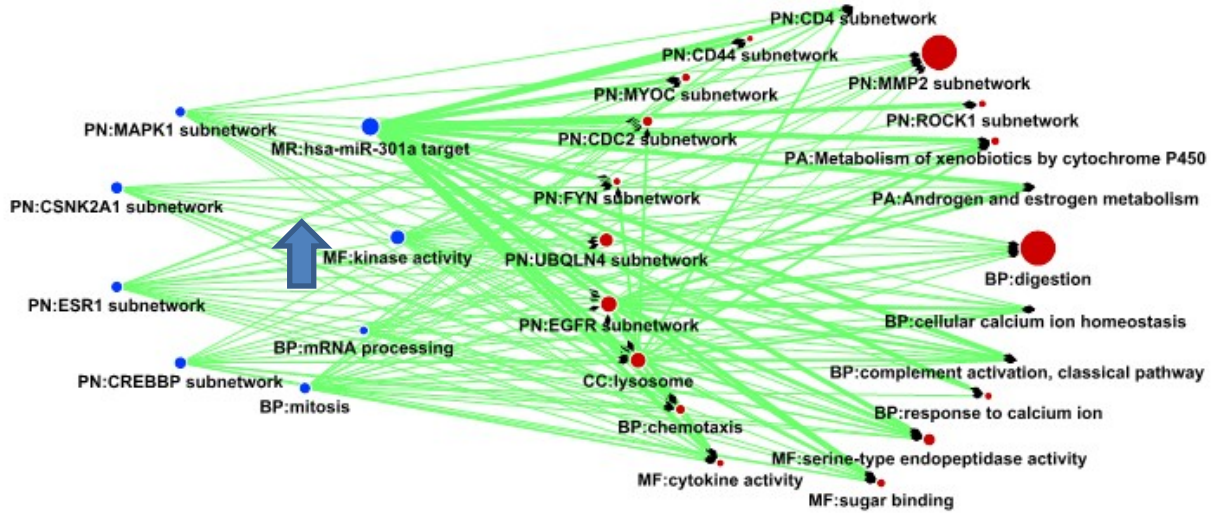
baseline perturbation



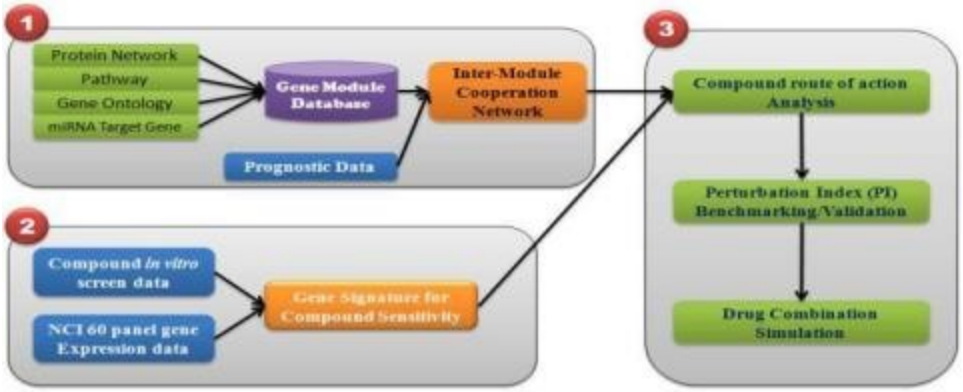
Gemcitabine

Bortezomib

add a focused perturbation on key gatekeeper modules



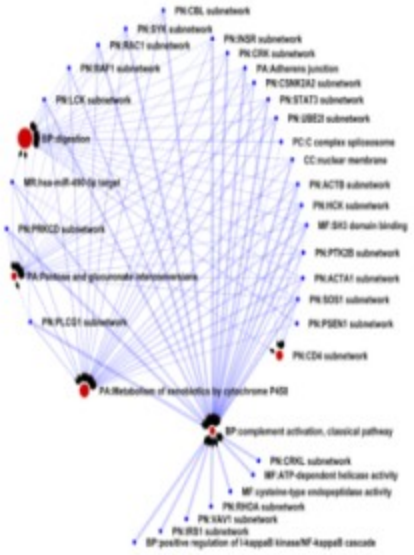
Discussion (1)
As a preclinical *in silico* modeling tool



- Mirroring drug behavior on natural populations
- Cost-effectiveness
- Easy to integrate drug action mechanisms/patterns

Discussion (2)
Strategy against cancer

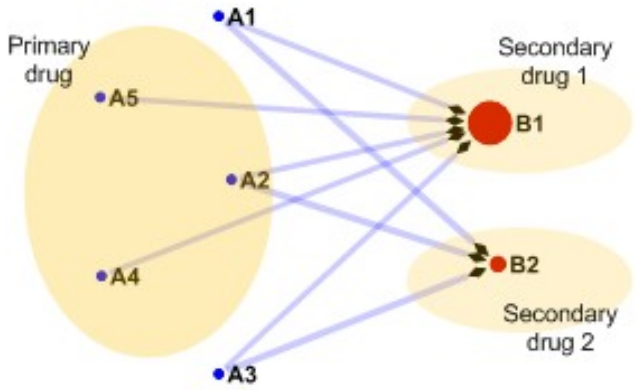
Etiology-based strategy → Prediction-based strategy



- **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**
  - **Drug accessibility <- Multi Drug Resistance**
  - **Microenvironment <- Inflammatory**
  - **Immune modulation <- Complement activation**
- **Battle against cancer**
- **know the history of tumorigenesis <etiology>**
- **know future survival strategy of tumor under therapeutic interventions**
- **Systems biology modeling could provide prediction of the tumor survival strategy**

A new perspective to understand principle of drug combination in Traditional Chinese Medicine ?

The Inter-Module Network



Different Roles of the Gene Modules & their cooperation effects

- - King
- - Minister
- - Assistant
- - Ambassador

Acknowledgements

- Simon Rayner
  (State Key Lab of Virology, CAS)
- Ze Tian
  (Harvard Medical School, USA)