

The Neuroscience & Magnetic Resonance Research Program
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Discovery of repurposed drug compounds for systems treatment of complex diseases

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Background

- Crisis in new drug discovery
- Side-effect issue of successful drugs
- Repurpose/repositioning of old drugs
- Cancer is a systems disease
- Cells can be reprogrammed

Drug discovery principle

- Multiple cohort gene expression data

多列隊基因表達數據

- Integrate multiple data types

- gene expression 基因表達
- protein interaction 蛋白質相互作用
- gene ontology 基因功能分類

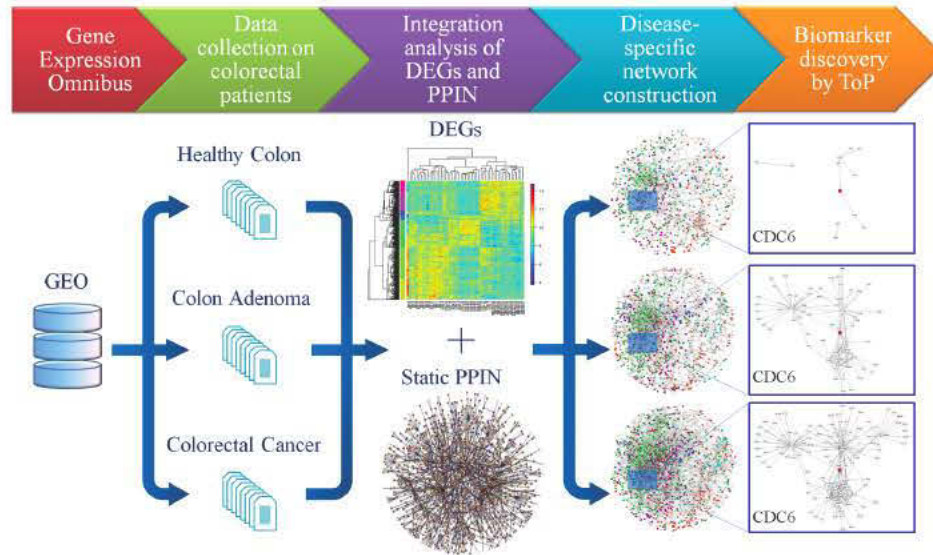
- Drug repurposing 舊藥新用

- Systems treatment 西藥中用*

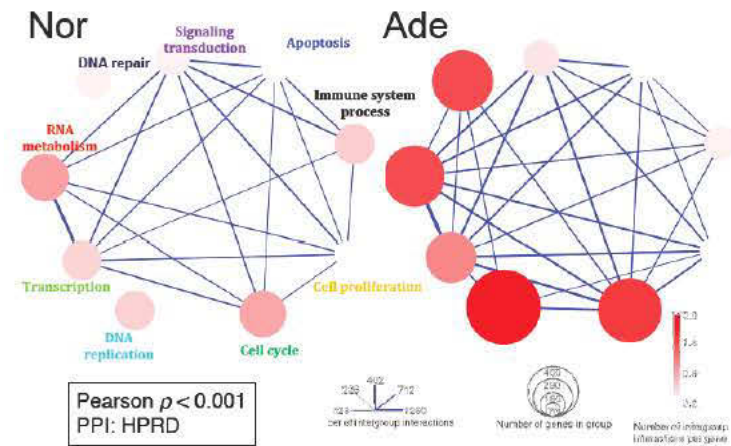
- Multiple network targeting
- No intra-cell side-effects 無胞內不良副作用

Drug discovery protocol

Finding cancer-related genes



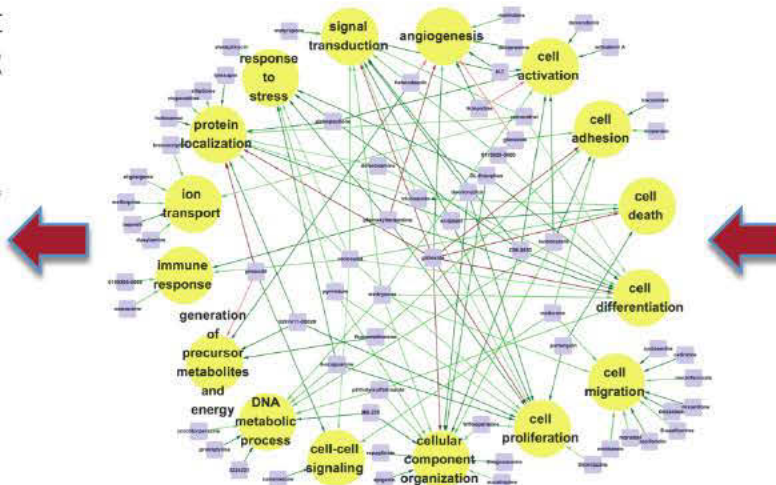
Functional gene modules



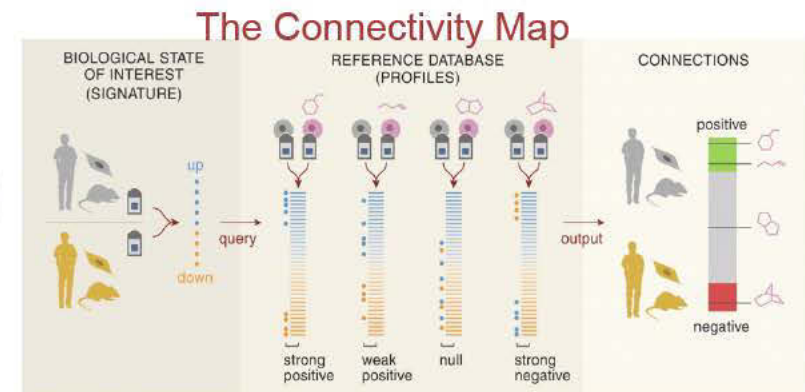
Drug list

Drug	degree	module (ESI)
1. phenylephrine	7	cell cycle (0.967), DNA replication (0.963), apoptosis (0.977), cell proliferation (0.962), transcription (0.960), signal transduction (0.960), RNA metabolic process (0.971)
2. GW4010	7	cell proliferation (0.972), signal transduction (0.956), DNA replication (0.962), apoptosis (0.967), cell cycle (0.934), transcription (0.923), RNA metabolic process (0.971), signal transduction (0.918), signal transduction (0.923), RNA metabolic process (0.967)
3. thapsigargin	5	transcription (0.963), RNA metabolic process (0.974), cell proliferation (0.967), immune system process (0.971), DNA replication (0.970), immune system process (0.969), signal transduction (0.969)
4. phenylbutazone	5	DNA replication (0.961), RNA metabolic process (0.966), transcription (0.963), cell proliferation (0.964), RNA metabolic process (0.963), signal transduction (0.963), cell proliferation (0.963), signal transduction (0.963), RNA metabolic process (0.963)
5. emendate	5	DNA replication (0.961), RNA metabolic process (0.966), transcription (0.963), cell proliferation (0.964), RNA metabolic process (0.963), signal transduction (0.963), cell proliferation (0.963), signal transduction (0.963), RNA metabolic process (0.963)
6. 0197417-00001	4	DNA replication (0.961), RNA metabolic process (0.966), transcription (0.963), cell proliferation (0.964), RNA metabolic process (0.963), signal transduction (0.963), cell proliferation (0.963), signal transduction (0.963), RNA metabolic process (0.963)
7. dexamethasone	4	DNA replication (0.961), RNA metabolic process (0.966), transcription (0.963), cell proliferation (0.964), RNA metabolic process (0.963), signal transduction (0.963), cell proliferation (0.963), signal transduction (0.963), RNA metabolic process (0.963)
8. 0170029-0000	4	DNA replication (0.961), RNA metabolic process (0.966), transcription (0.963), cell proliferation (0.964), RNA metabolic process (0.963), signal transduction (0.963), cell proliferation (0.963), signal transduction (0.963), RNA metabolic process (0.963)
9. aspirin	4	DNA replication (0.961), RNA metabolic process (0.966), transcription (0.963), cell proliferation (0.964), RNA metabolic process (0.963), signal transduction (0.963), cell proliferation (0.963), signal transduction (0.963), RNA metabolic process (0.963)
10. pyruvate	3	cell cycle (0.971), apoptosis (0.964), immune system process (0.971), cell cycle (0.964), DNA replication (0.961), immune system process (0.971)
11. telaprevir	3	apoptosis (0.963), cell proliferation (0.960), signal transduction (0.963), cell proliferation (0.963), RNA metabolic process (0.971), RNA metabolic process (0.971)
12. camptothecin	3	apoptosis (0.963), cell proliferation (0.960), signal transduction (0.963), cell proliferation (0.963), RNA metabolic process (0.971), RNA metabolic process (0.971)
13. metformin	3	apoptosis (0.963), cell proliferation (0.960), signal transduction (0.963), cell proliferation (0.963), RNA metabolic process (0.971), RNA metabolic process (0.971)
14. etoposide	3	apoptosis (0.963), cell proliferation (0.960), signal transduction (0.963), cell proliferation (0.963), RNA metabolic process (0.971), RNA metabolic process (0.971)
15. 0-acetylsalicylic acid	2	apoptosis (0.963), cell proliferation (0.960), signal transduction (0.963), cell proliferation (0.963), RNA metabolic process (0.971), RNA metabolic process (0.971)
16. salicylic acid	2	apoptosis (0.963), cell proliferation (0.960), signal transduction (0.963), cell proliferation (0.963), RNA metabolic process (0.971), RNA metabolic process (0.971)
17. salicylic acid	2	apoptosis (0.963), cell proliferation (0.960), signal transduction (0.963), cell proliferation (0.963), RNA metabolic process (0.971), RNA metabolic process (0.971)
18. salicylic acid	2	apoptosis (0.963), cell proliferation (0.960), signal transduction (0.963), cell proliferation (0.963), RNA metabolic process (0.971), RNA metabolic process (0.971)
19. salicylic acid	2	apoptosis (0.963), cell proliferation (0.960), signal transduction (0.963), cell proliferation (0.963), RNA metabolic process (0.971), RNA metabolic process (0.971)
20. salicylic acid	2	apoptosis (0.963), cell proliferation (0.960), signal transduction (0.963), cell proliferation (0.963), RNA metabolic process (0.971), RNA metabolic process (0.971)
21. salicylic acid	2	apoptosis (0.963), cell proliferation (0.960), signal transduction (0.963), cell proliferation (0.963), RNA metabolic process (0.971), RNA metabolic process (0.971)
22. salicylic acid	2	apoptosis (0.963), cell proliferation (0.960), signal transduction (0.963), cell proliferation (0.963), RNA metabolic process (0.971), RNA metabolic process (0.971)
23. salicylic acid	2	apoptosis (0.963), cell proliferation (0.960), signal transduction (0.963), cell proliferation (0.963), RNA metabolic process (0.971), RNA metabolic process (0.971)

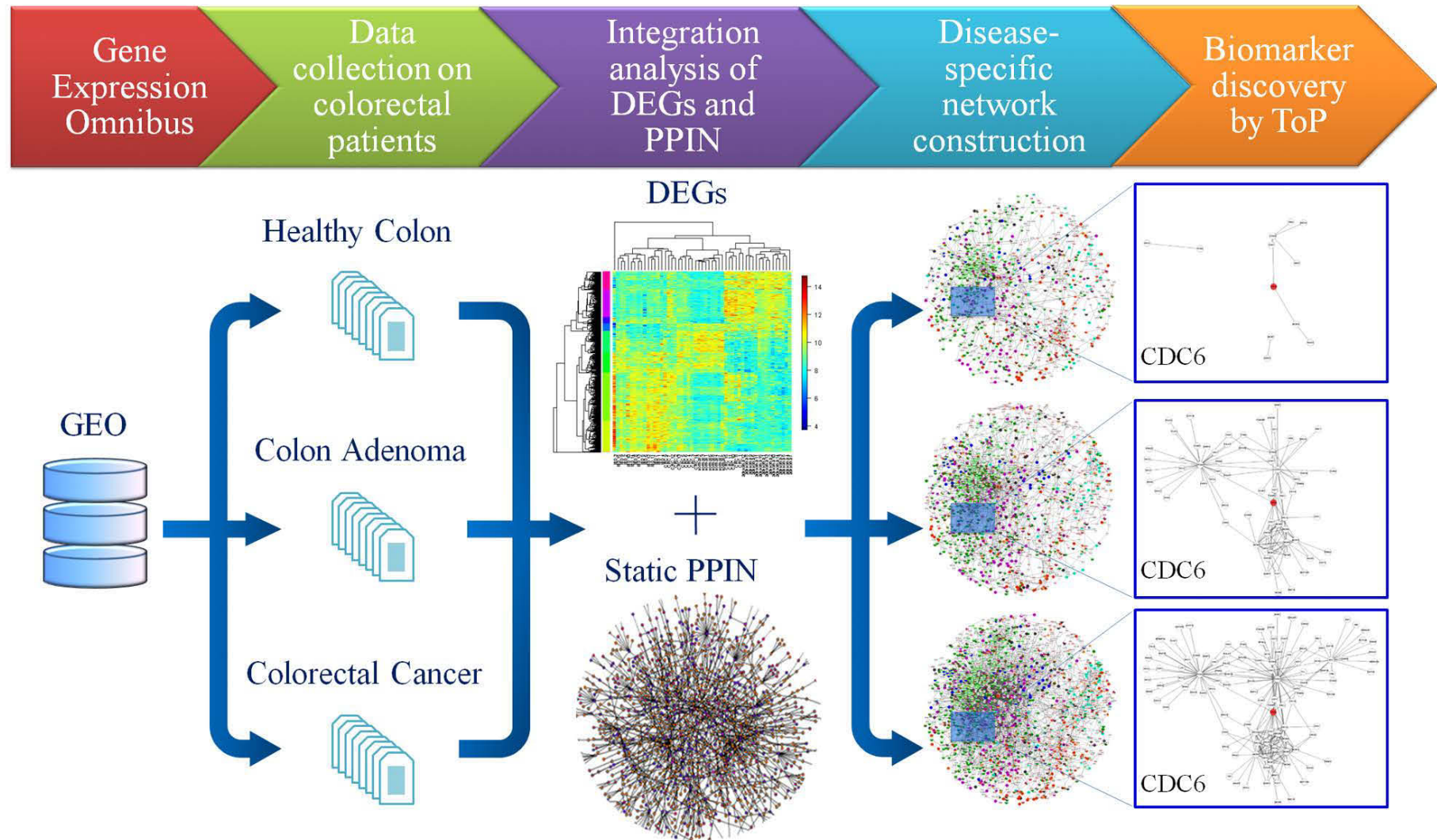
Drug-functional module map



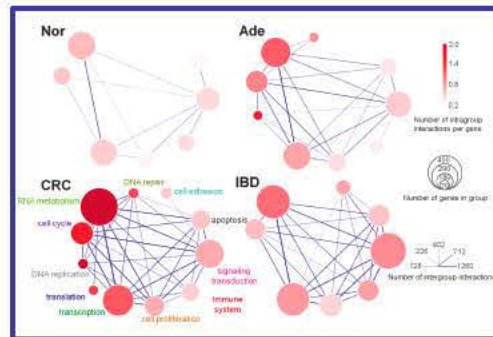
Match drug gene-exp'n profile



Drug prediction flow-chart



ToP procedure for gene selection

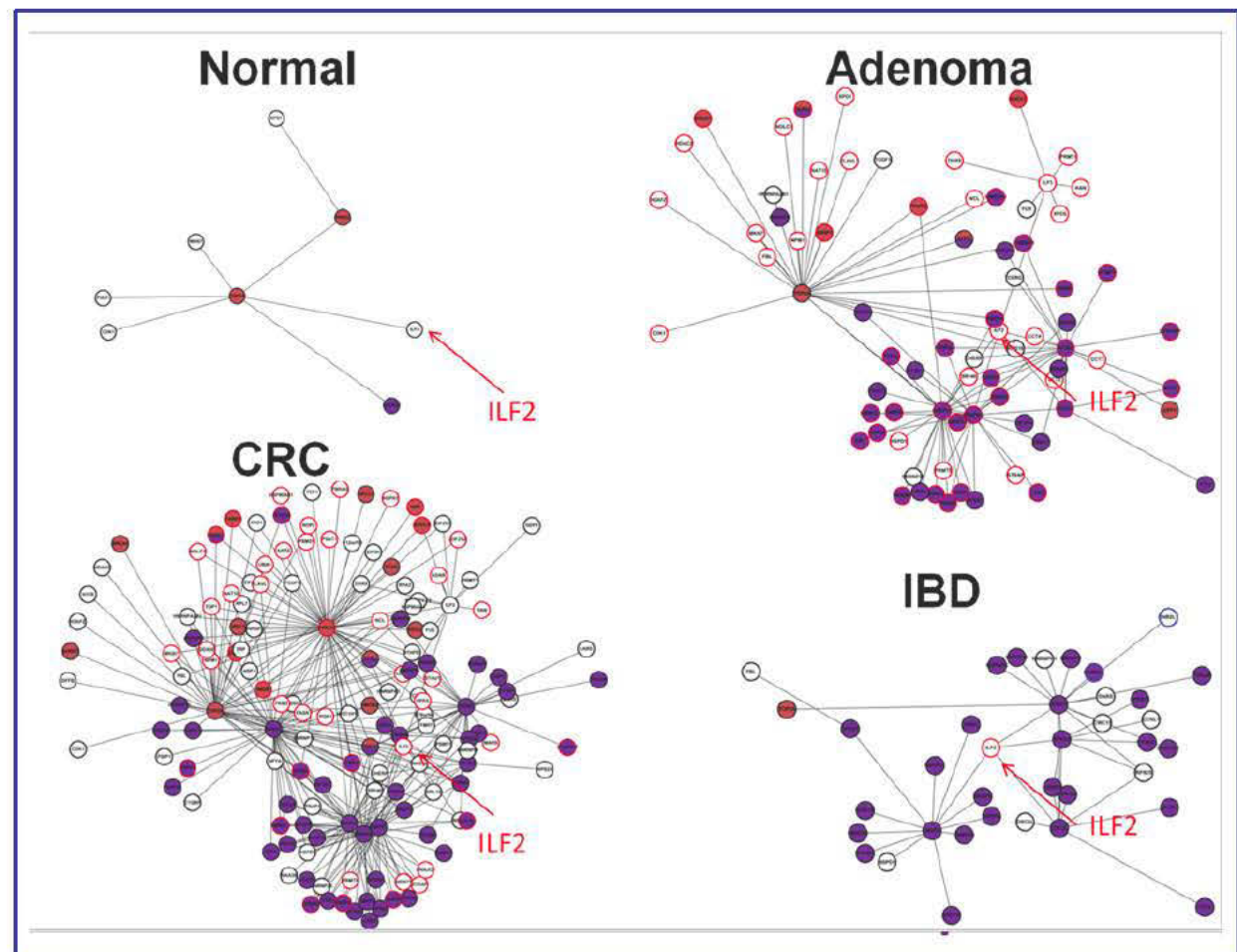


ToP - Trend of (disease) Progression

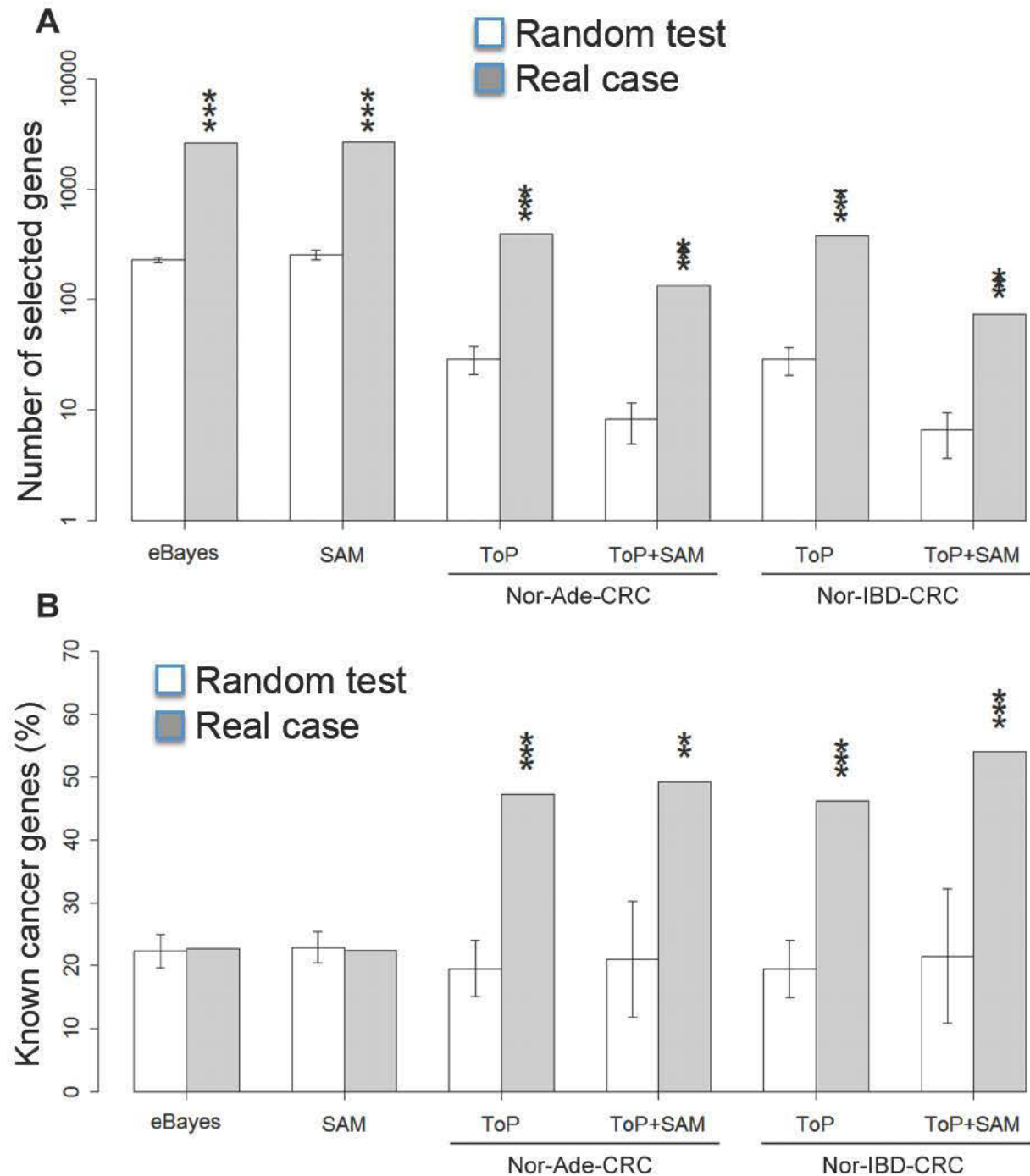
Use a sequence of state specific gene-gene interaction networks to track “growth” of hub genes

Nor-Ade-CRC is a ToP sequence

ILF2 is a ToP gene

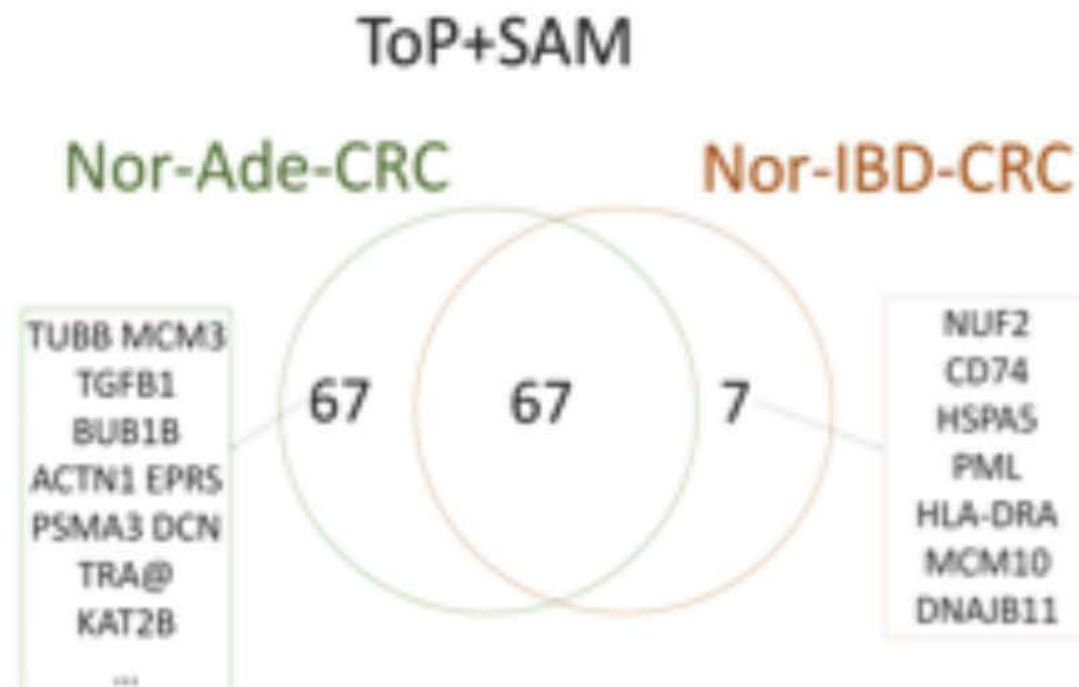


Network based ToP procedure has far higher significant hit rates than standard methods (eg, SAM)



IBD is a weaker CRC precursor than Adenoma

Normal-Adenoma-CRC → Both ToP sequences
Normal-IBD-CRC



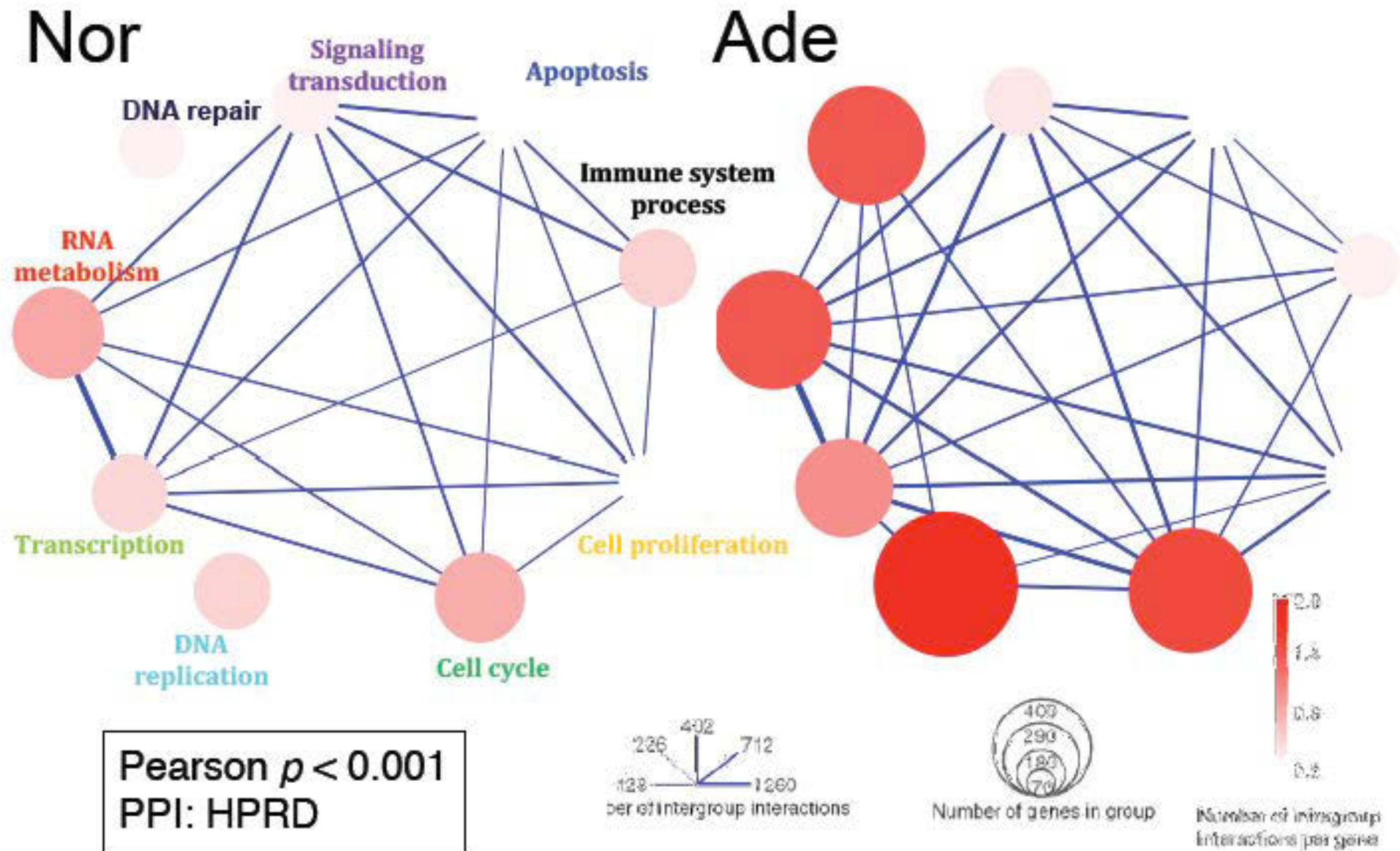
Inflammatory bowel disease is a weaker **CRC precursor**

Markers for early CRC detection - 11 in Adenoma
2 in IBD

Drug discovery for colorectal cancer adenoma

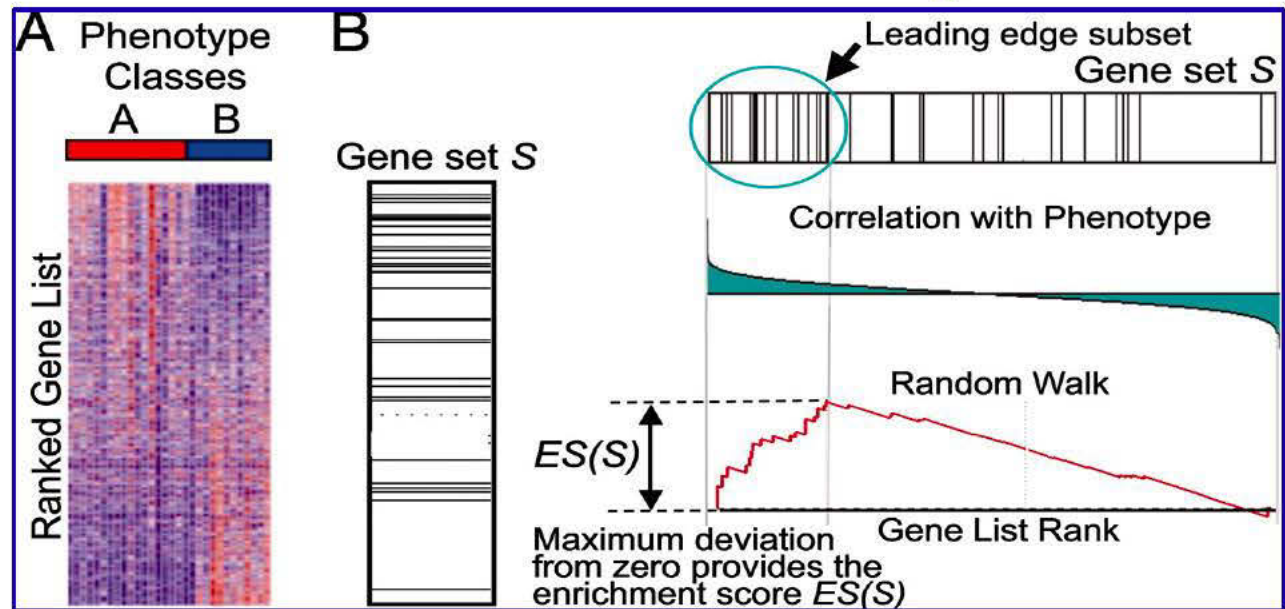
- Microarray data from colorectal cancer and adenomas and from normal mucosa of **32 individuals** (GEO accn. GSE08671)
- Design drug compounds for **multiple network targeting**
 - Select functional group according to “Hallmarks of Cancer”

Interaction map for functional modules

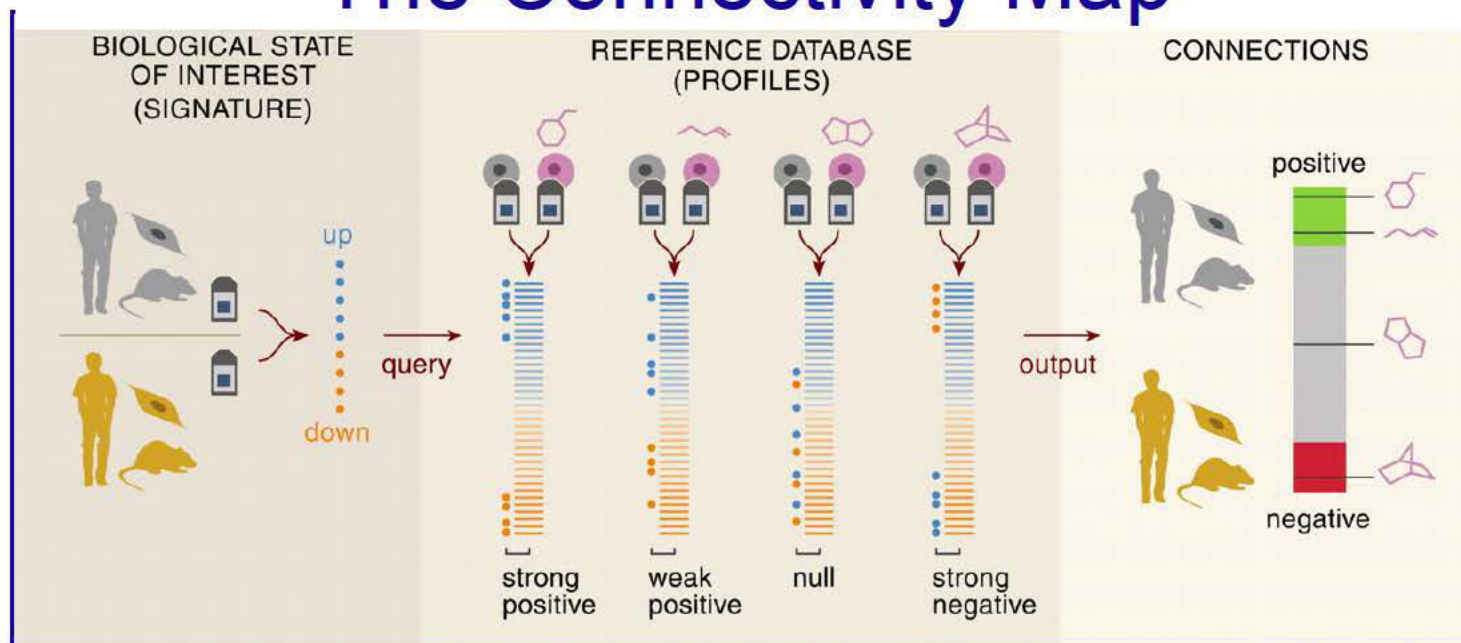


GSEA - Gene set enrichment analysis

Subramanian A
et al. PNAS 2005;
102:15545-15550

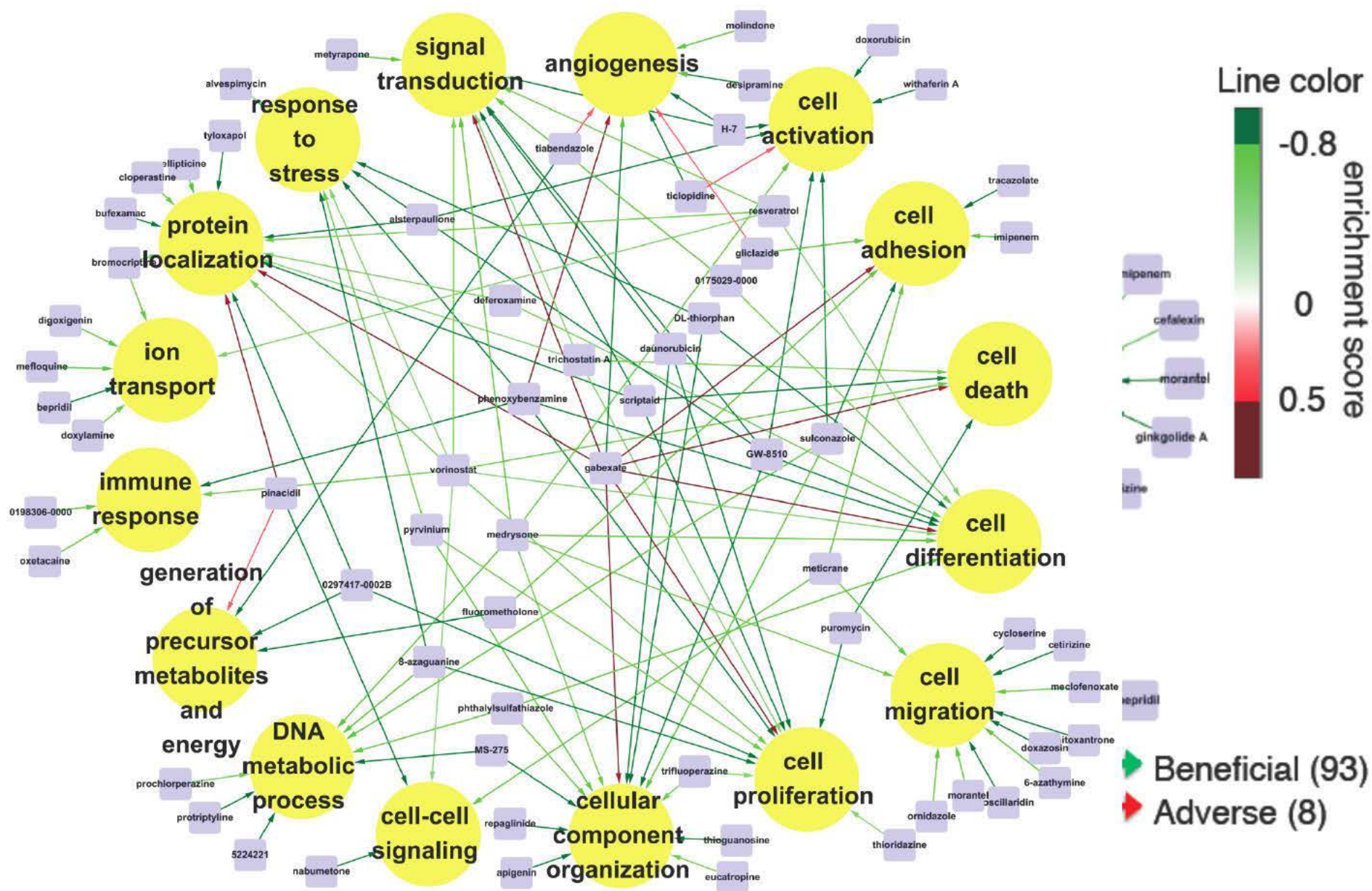


The Connectivity Map



J Lamb et al.
Science 2006;
313:1929-1935

Drug-function module association map for 16 Hallmark functions for adenoma



Predicted functional specific drugs and carcinogen/mutagen or antitumor agents

drug	degree	module (ES)	function	藥理	carcinogen/ mutagen	anticancer agents
1 phenoxybenzamine	7	cell cycle(-0.987), DNA replication(-0.983), apoptosis(-0.977), cell proliferation(-0.962), transcription(-0.905), signal transduction(-0.886), RNA metabolic process(-0.81)	an α -adrenergic-antagonist	神經系統用藥/抗腎上腺素藥	[1, 2]	
2 GW-8510	7	cell proliferation(-0.972), signal transduction(-0.936), DNA replication(-0.882), apoptosis(-0.867), cell cycle(-0.834), transcription(-0.822), RNA metabolic process(-0.791)	a CDK2 inhibitor that protects hair-loss in chemotherapy	防化療脫髮藥, CDK2抑制劑		[3]
3 thapsigargin	5	apoptosis(-0.918), signal transduction(0.4), transcription(0.521), cell proliferation(0.526), RNA metabolic process(0.887)	a nonselective inhibitor of endoplasmic reticulum Ca^{2+} -ATPase	內質網 Ca^{2+} -ATPase選擇性抑制劑	[4-7]	[8-11]
4 phthalylsulfathiazole	5	transcription(-0.882), RNA metabolic process(-0.874), cell proliferation(-0.767), immune system process(-0.771), DNA replication(-0.705)	antimicrobial	磺胺類藥, 用於細菌性病疾, 細菌性潰瘍性腸炎		
5 medrysone	5	DNA replication(-0.755), transcription(-0.698), cell proliferation(-0.675), immune system process(-0.686), signal transduction(-0.658)	Adrenocorticotrophic hormone drugs	腎上腺皮質激素類藥		
6 0297417-0002B	4	DNA replication(-0.981), RNA metabolic process(-0.966), transcription(-0.943), immune system process(0.668)	unknown	未知		
7 daunorubicin	4	cell cycle(-0.867), cell proliferation(-0.844), RNA metabolic process(-0.8), signal transduction(-0.786)	a chemotherapeutic antibiotic	抗生素類抗腫瘤藥		[12-14]
8 0175029-0000	4	transcription(-0.771), cell proliferation(-0.766), signal transduction(-0.698), RNA metabolic process(-0.69)	unknown	未知		
9 apigenin	4	DNA replication(-0.896), cell proliferation(-0.837), transcription(-0.796), RNA metabolic process(-0.784)	a flavone that have the chemopreventive action in vegetables	芹菜素, 黃酮類		[15-18]
10 pyrvinium	3	cell cycle(-0.75), apoptosis(-0.694), immune system process(0.314)	anthelmintic	其它抗寄生蟲病藥	[19, 20]	[21, 22]
11 trifluoperazine	3	cell cycle(-0.604), DNA replication(-0.501), immune system process(0.415)	a typical antipsychotic of the phenothiazine chemical class.	phenothiazines類抗精神病藥物	[23]	[24, 25]
12 camptothecin	3	apoptosis(-0.953), cell proliferation(-0.935), signal transduction(-0.878)	a cytotoxic quinoline alkaloid which inhibits the DNA enzyme topoisomerase I (TOP1)	TOP1抑制劑, 生物鹼, 抗癌藥物		[26-28]
13 meticrane	3	transcription(-0.726), apoptosis(-0.72), RNA metabolic process(-0.713)	Diuretics	利尿劑		
14 ellipticine	2	apoptosis(-0.827), immune system process(0.422)	an antineoplastic agent which inhibits the DNA enzyme topoisomerase II (TOP2)	TOP2抑制劑, 玫瑰樹鹼, 抗癌藥物	[29-31]	[29-31]
15 8-azaguanine	2	apoptosis(-0.87), cell proliferation(-0.83)	a purine analog that shows antineoplastic activity	鳥嘌呤類似物抑制嘌呤的生物合成, 抗腫瘤藥		[32, 33]
16 etacrynic acid	2	apoptosis(-0.891), cell cycle(-0.875)	GST Inhibitor-2, diuretics	利尿酸, GST Inhibitor-2		[34]
17 alsterpaullone	2	signal transduction(-0.874), apoptosis(-0.866)	CDK inhibitor	CDK抑制劑		[35]
18 vorinostat	2	cell proliferation(-0.592), signal transduction(-0.503)	HDAC inhibitor, antineoplastic agent	HDAC抑制劑, 抗癌藥物		
19 thioguanosine	2	DNA replication(-0.935), transcription(-0.811)	antineoplastic agent	抗癌化合物		[39, 40]
20 sulconazole	2	DNA replication(-0.869), transcription(-0.814)		外用抗生素		
21 chrysin	2	transcription(-0.934), DNA replication(-0.913)	a naturally occurring flavone, antineoplastic agent	白楊素, 類黃酮素, 抗腫瘤		[41, 42]
22 thiostrepton	2	DNA replication(-0.837), transcription(-0.816)	a natural cyclic oligopeptide antibiotic	多肽類抗生素		[43-45]
23 luteolin	2	transcription(-0.856), DNA replication(-0.811)	a flavonoid, antioxidant, anti-inflammatory, and an antineoplastic agent	植物類黃酮, 抗菌, 抗炎, 抗癌		[46-48]

Some predicted side-effect free drug compound for colorectal adenoma

Abbreviation

ISP: immune system process - trifusal or morantel or gingolide or cetirizine or imipenem

APO: apoptosis – irinotecan or doxazosin or cycloserine or repaglinide

CC: cell cycle – doxorubicin or withaferin A

ST: signal transduction – 6-azathymine or tyloxapol

TR: transcription – sanguinarine

DR: DNA replication – piperlongumine

CP: Cell proliferation – bepridil

RM: RNA metabolic process

TDNA: transcription and DNA replication –chrysin or thioguanosine or luteolin or thiostrepton or sulconazole

Code	No. components	Components	Ratio
1	2	phenoxybenzamine + ISP	7:1
2	2	GW-8510 + ISP	7:1
3	3*	phthalylsulfathiazole + etacrynic acid + ST	5:2:1
4	4	daunorubicin + TDNA + APO + ISP	4:2:1:1
5	4	apigenin + etacrynic acid + ST + ISP	4:2:1:1
6	4	apigenin + alsterpaullone + CC + ISP	4:2:1:1
7	5	camptothecin + ifenprodil + DR + CC + ISP	3:2:1:1:1
8	5	vorinostat + etacrynic acid + TDNA + RM + ISP	2:2:2:1:1
9	6	ifenprodil + 8-azaguanine + DR + CC + ST + ISP	2:2:1:1:1:1
10	6	ifenprodil + etacrynic acid + DR + CP + CC + ISP	2:2:1:1:1:1
11	6	ifenprodil + alsterpaullone + DR + CP + ST + ISP	2:2:1:1:1:1
12	6	TDNA + 8-azaguanine + RM + CC + ST + ISP	2:2:1:1:1:1
13	6	TDNA + etacrynic acid + RM + CP + ST + ISP	2:2:1:1:1:1
14	6	TDNA + alsterpaullone + RM + CC + CP + ISP	2:2:1:1:1:1

Drug discovery for breast Cancer

- NCBI GEO, access. # **GSE25066**

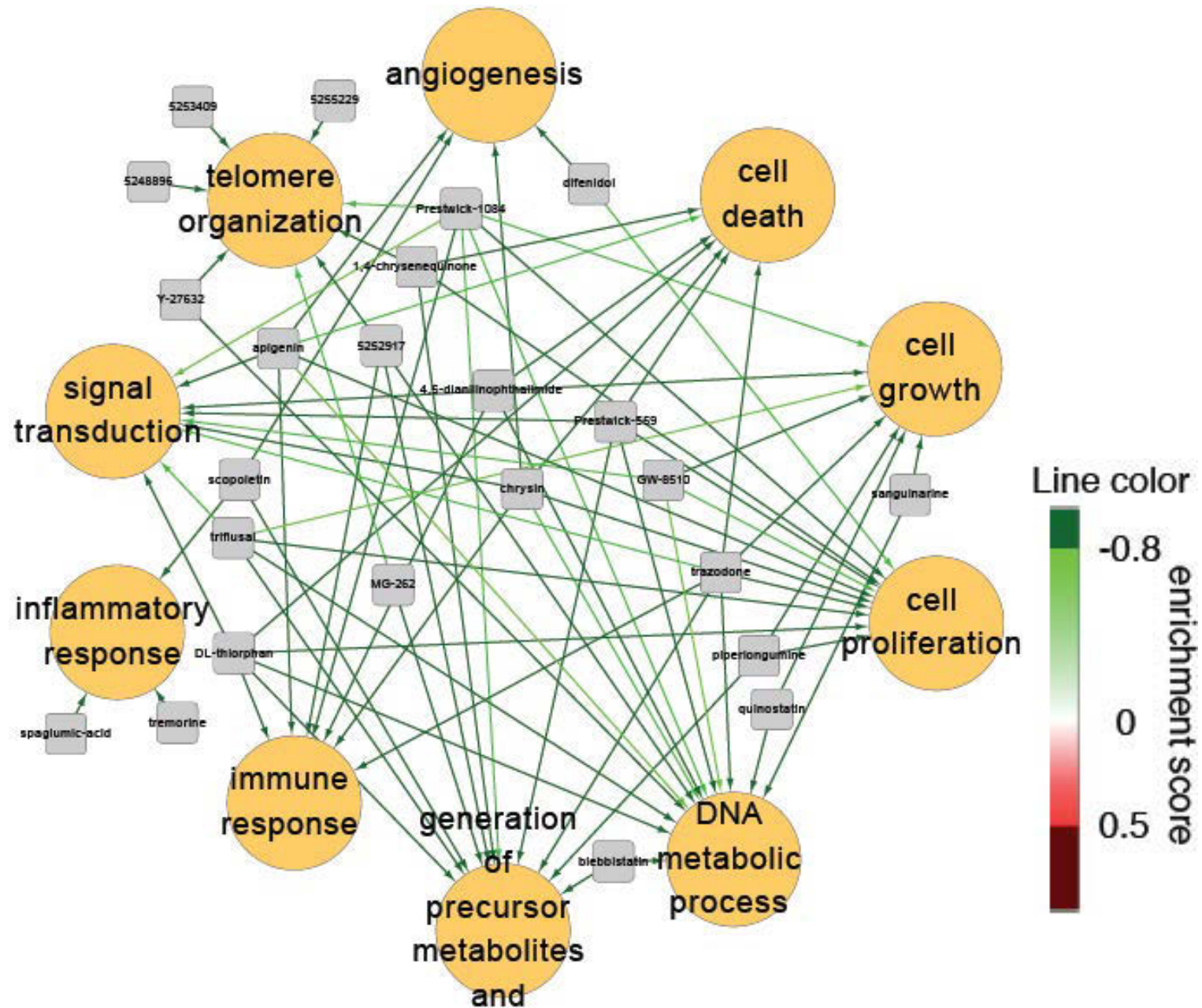
C. Hatzis, *et al.*, (2011) A genomic predictor of response and survival following taxane-anthracycline chemotherapy for invasive breast cancer. *JAMA* 305 (18), 1873-1881.

- Composed of two series, GSE25055 (untreated) and GSE 25065 (treated).

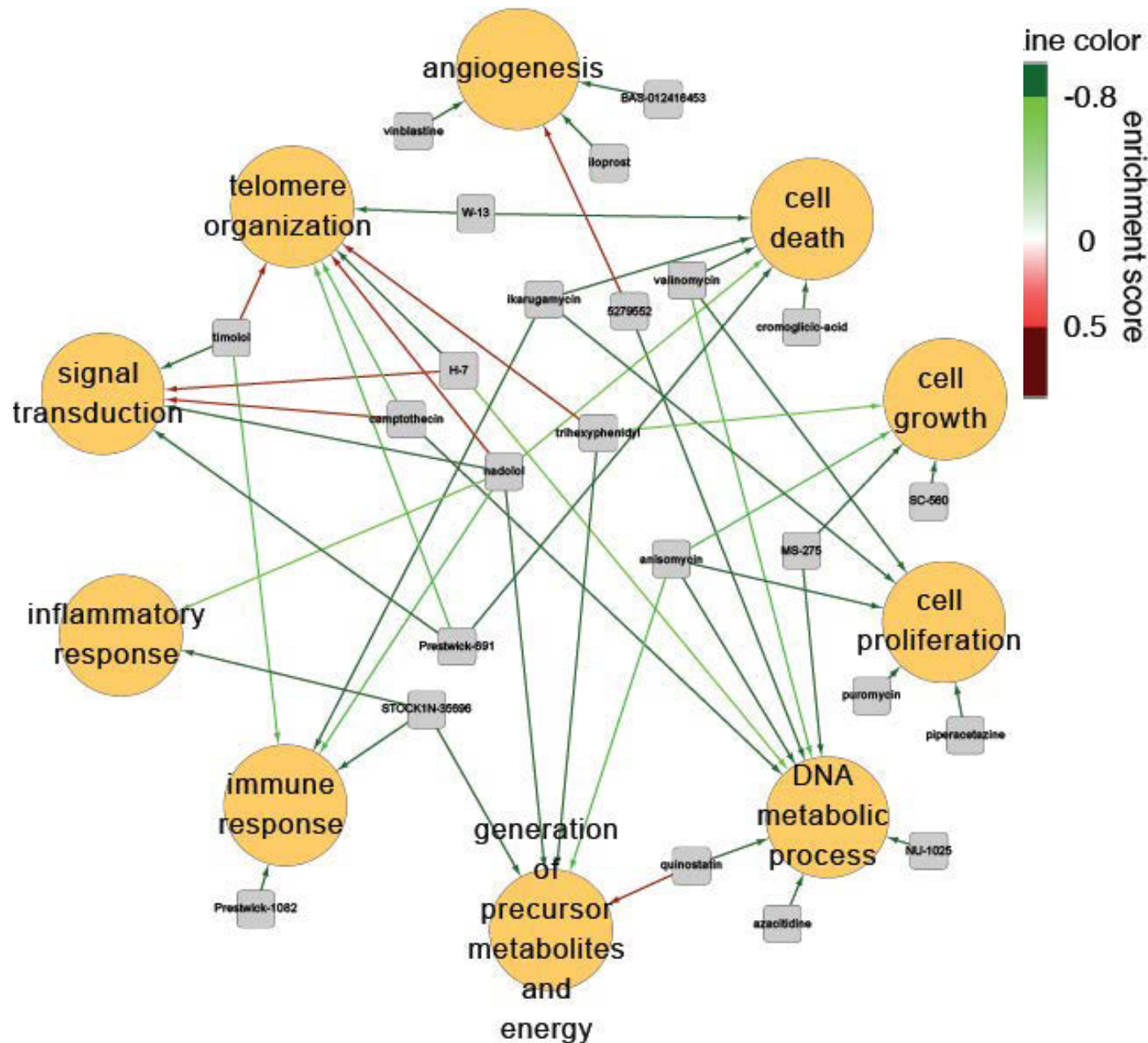
GEO No.	Grade 1	Grade 2	Grade 3	Other	Total
GSE250 55	19*	117	151	23	310
GSE250 65	13	64	107	14	198

Breast cancer drug-function association map

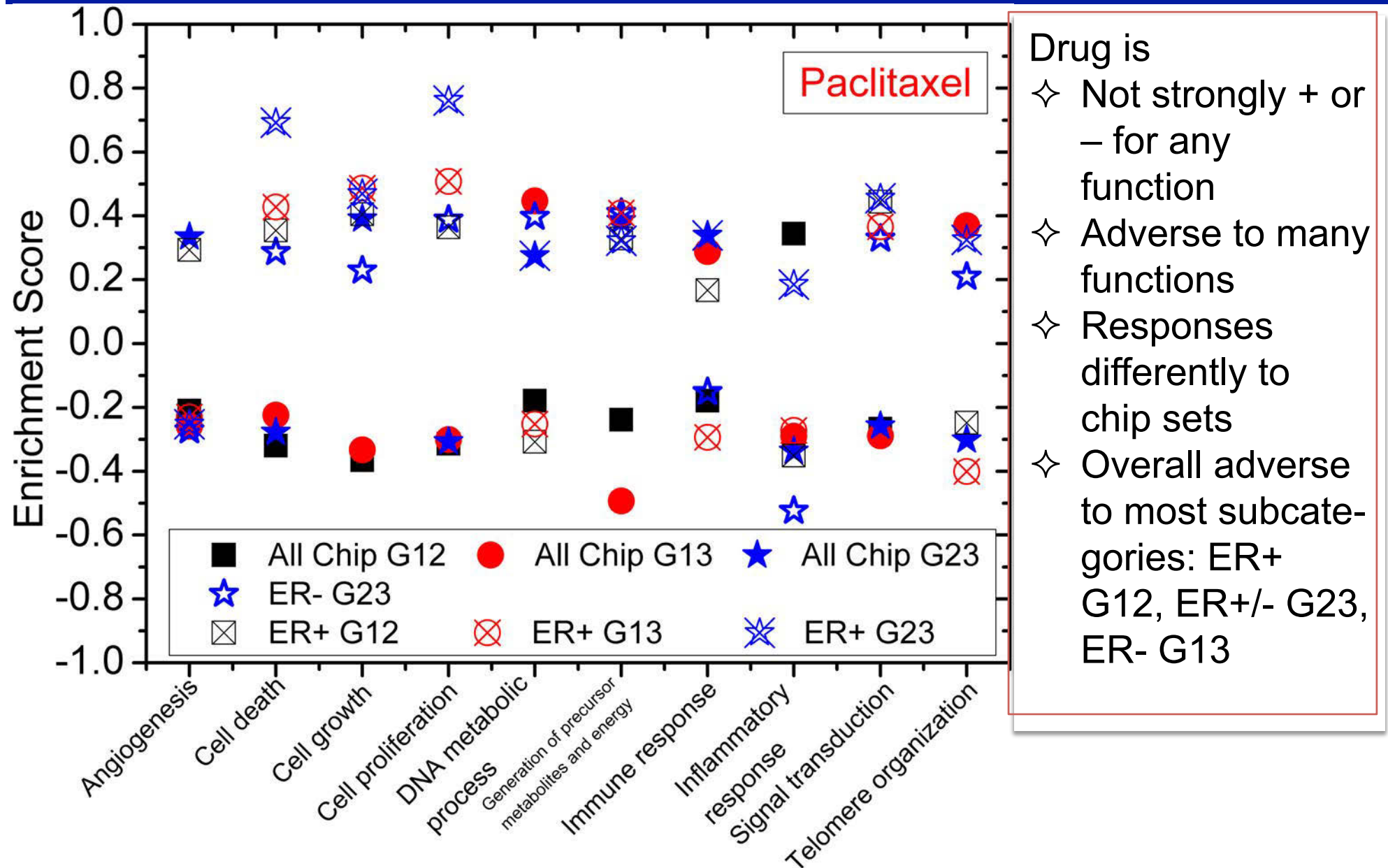
Grade 2 versus grade 3, **Estrogen response NEGATIVE**



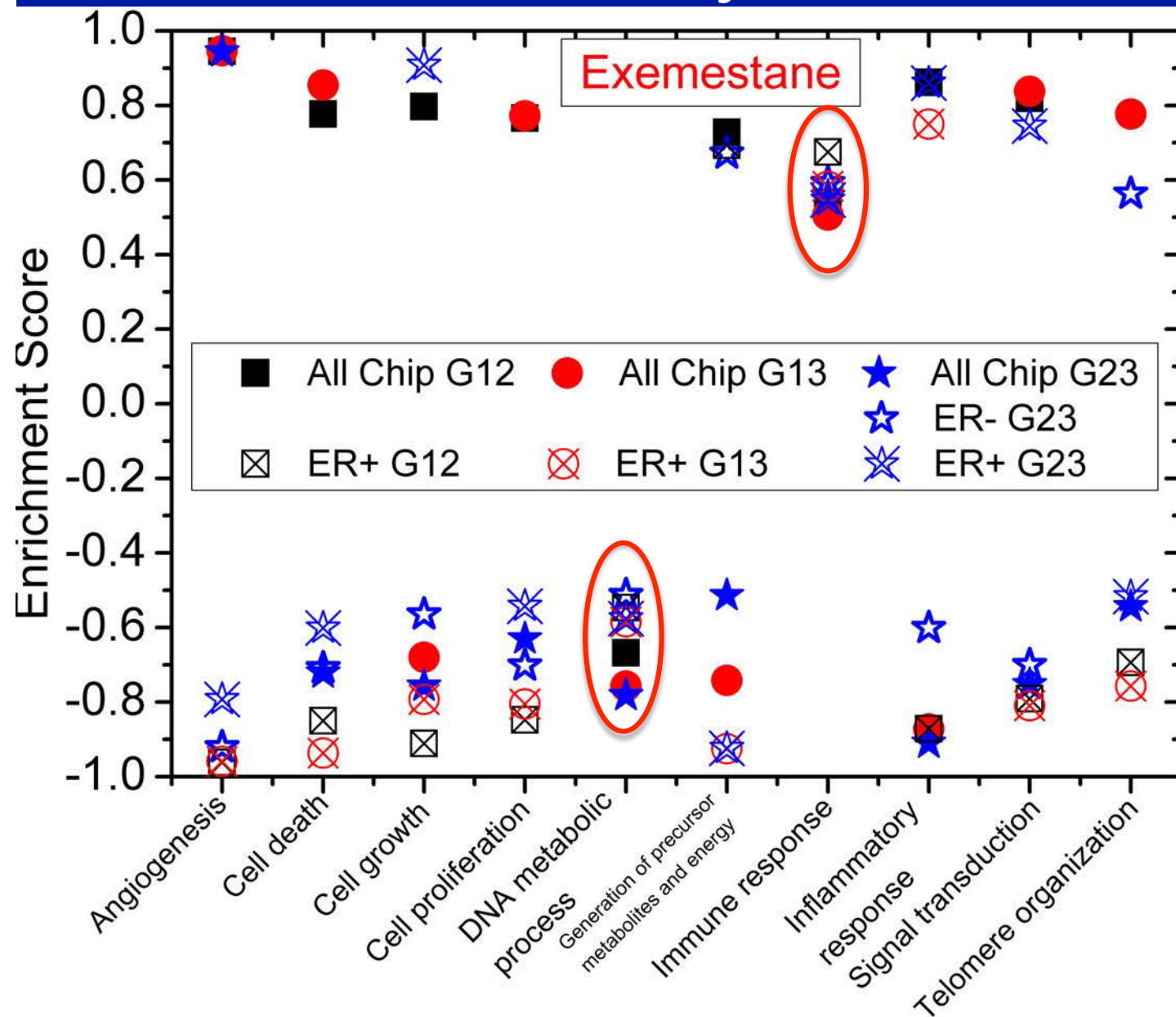
Breast cancer drug-function association map
Grade 2 versus grade 3, Estrogen response POSITIVE



Paclitaxel is detrimental to many functions



Exemestane is detrimental to many functions



- Drug is
- ✧ Highly adverse to immune response and beneficial to DNA metabolic process in all cases
 - ✧ Good for ER+ G12 except for immune response
 - ✧ Good for ER+ G12 except for immune & inflammatory response

Drug discovery for Astrocytoma

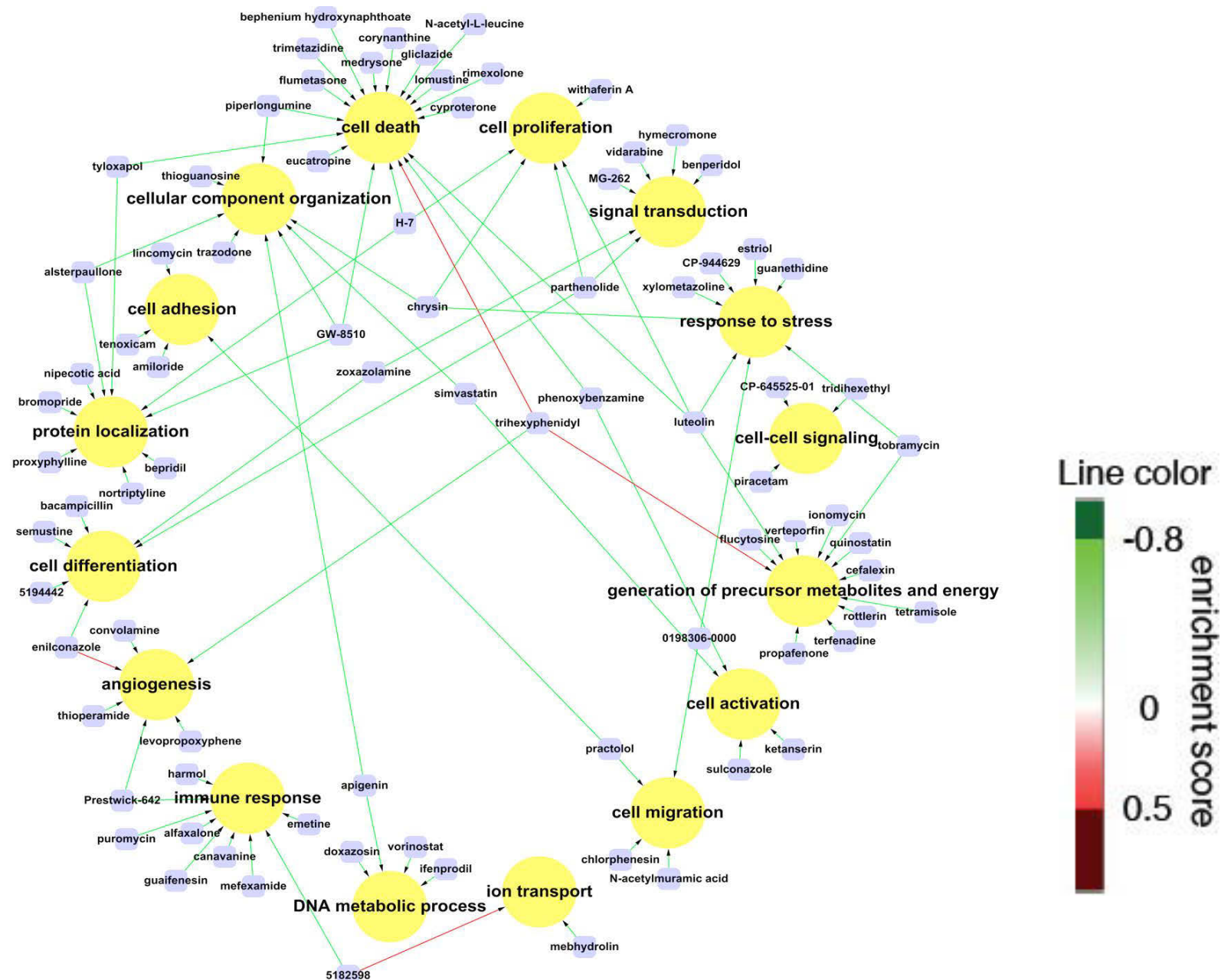
- WHO-grading of astrocytoma – based on appearance of features: *atypia*, *mitosis*, *endothelial proliferation*, and *necrosis*

WHO Grade	Astrocytomas	Description	%
Grade 1	Pilocytic astrocytoma	None of the features	2%
Grade 2	Low-grade astrocytoma	One feature (usually atypia)	8%
Grade 3	Anaplastic astrocytoma (AA)	Two features	20%
Grade 4	Glioblastoma multiforme (GBM)	Three or four features	70%

- We used: GSE4290
 - Grade 1 (non-tumor) (23 arrays)
 - Grade 2 (7)
 - Grade 3 (19)
 - Grade 4 (77)

Astrocytoma drug-function association map (preliminary)

Grade 3 versus non-tumor



Summary

- ToP - trend of disease progression applied to multistate gene-interaction networks led to powerful tool for cancer gene prediction
- Use of multiple functional modules (gene sets) instead of whole genome expression profile to screen drugs with Connectivity Map yielded drug compounds that were predicted:
 - To be free of intra-cellular adverse side effects
 - Good for systems treatment of diseases

Genomic functional signatures of psychiatric disorders

- Are there functional characteristics in the genomic profiles of patients of psychiatric disorders
- Bipolar disorder, schizophrenia, depression
- Cohort gene expression microarrays

Validation Underway

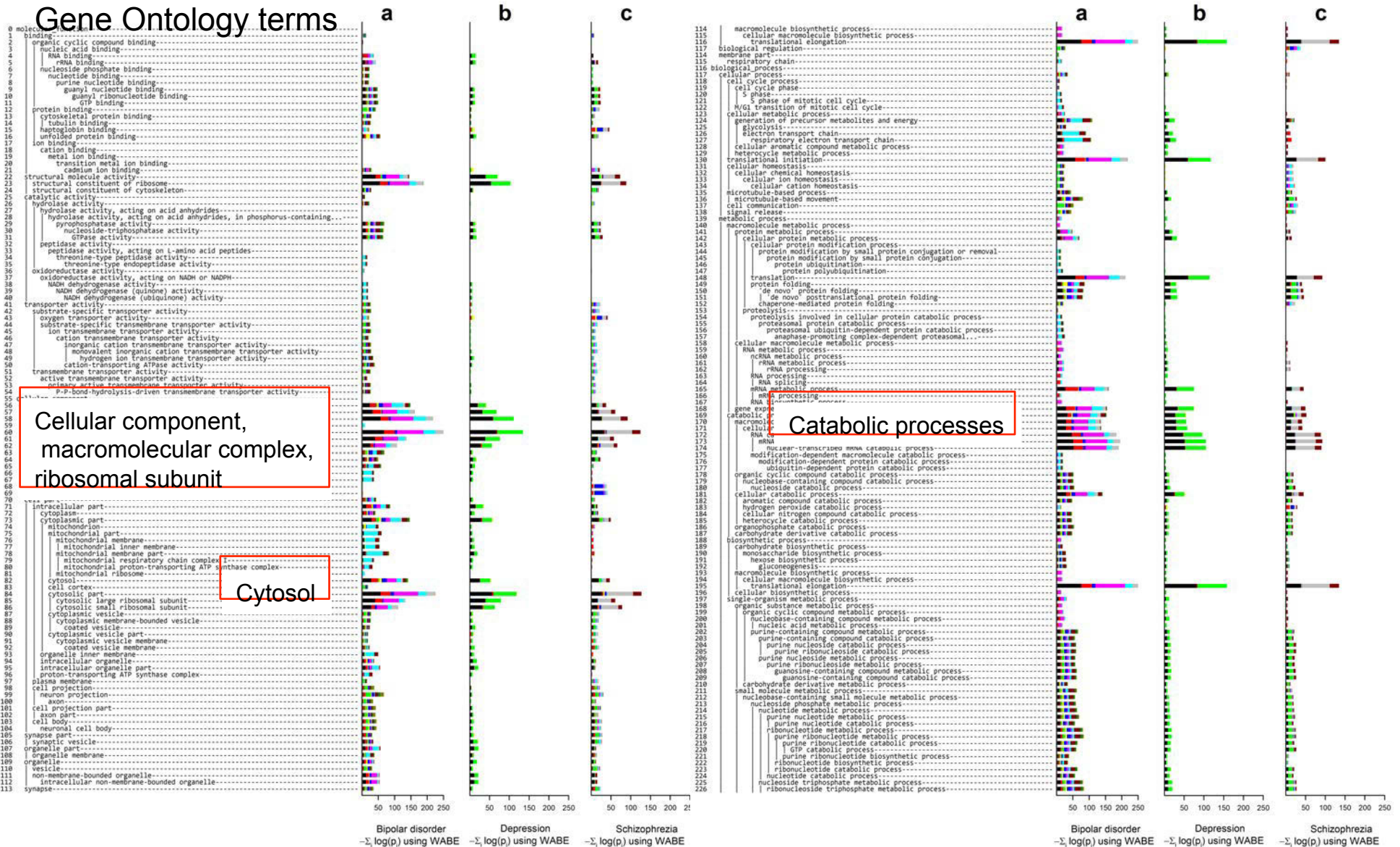
- **Cell model validation** - Predicted drug compound now under validation in cell model
- **Mouse model validation** planned for future

Functional genomic profiles of the psychiatric disorders: Bipolar disorder, Schizophrenia, Depression

Condition	Data sets	Patient cases	Control cases
Bipolar Disorder	12	253	240
Schizophrenia	9	185	193
Depression	4	48	51

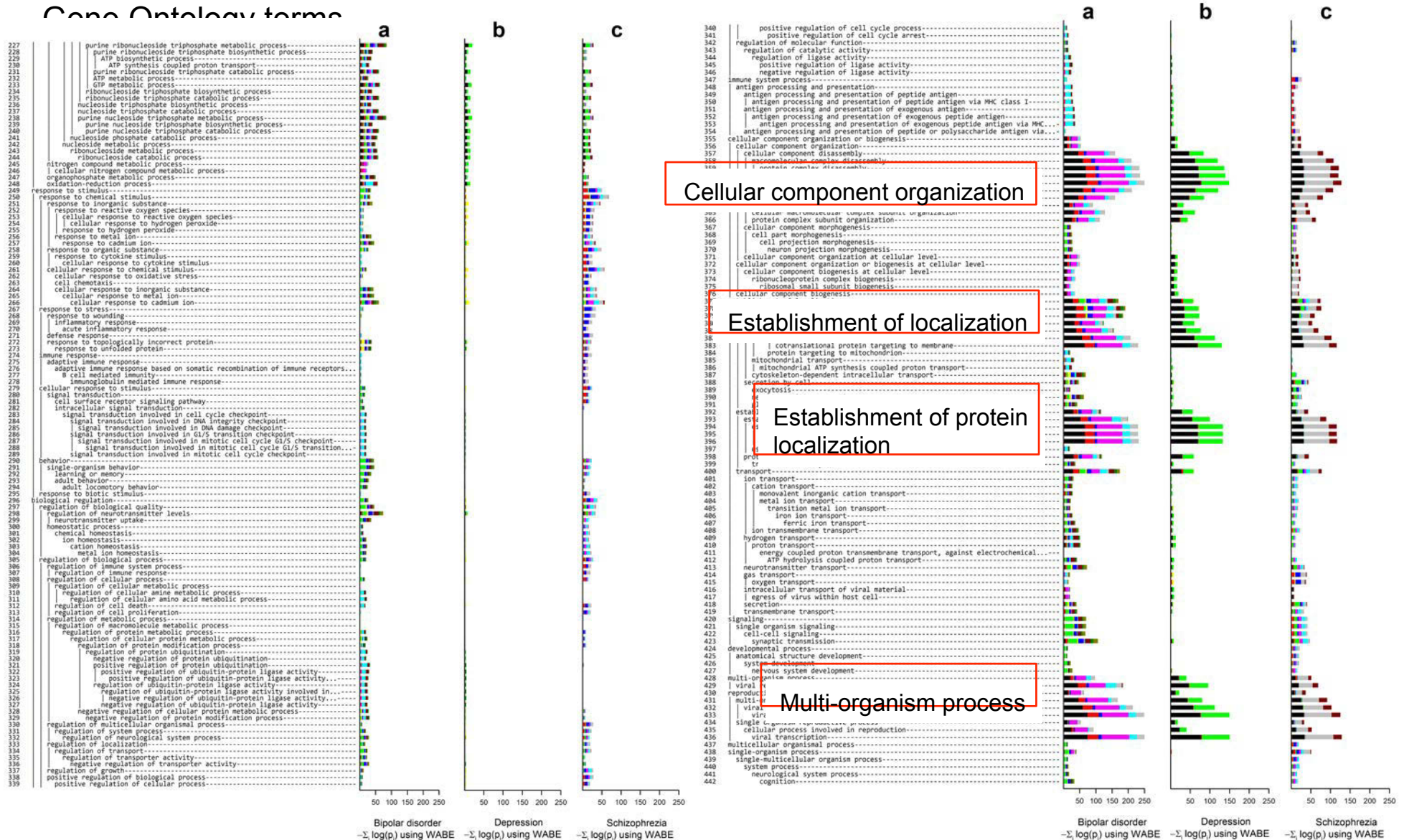
Functional analysis of genomic profile of patients of three psychiatric disorders I

There are many differentially overrepresented functions (compared with normal cohorts)

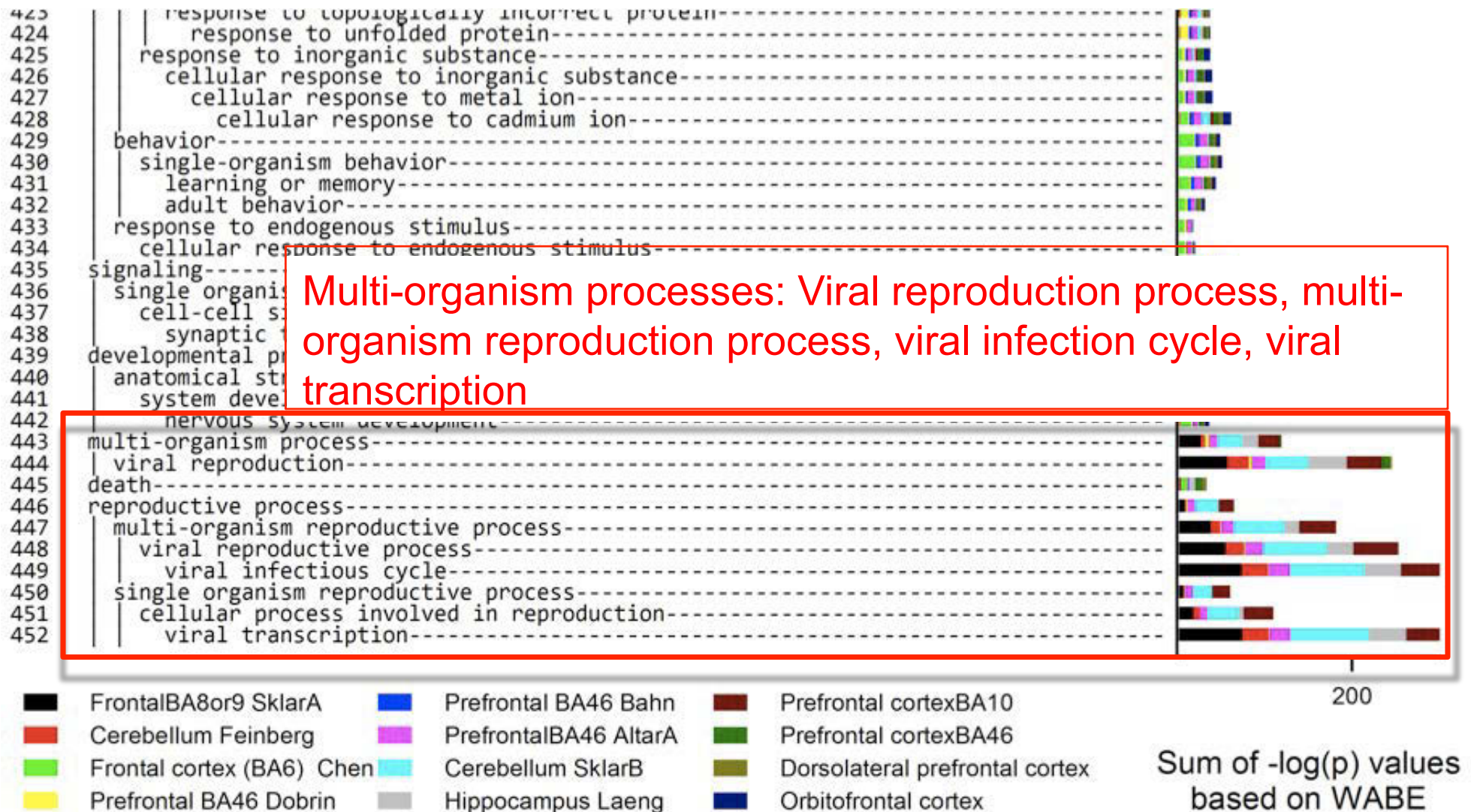


Functional analysis of genomic profile of patients of three psychiatric disorders II

There are many differentially overrepresented functions (compared with normal cohorts)



Functional analysis of genomic profile of psychiatric disorder patients (detail)



- Acknowledgement
 - National Science Council
 - Ministry of Education
 - National Central University – Cathay General Hospital Collaborative Research Program
- Analysis
 - Colorectal cancer FH Chung, Dr. SG Kong
 - Breast cancer Dr. SG Kong, Dr. CH Chen
 - Brain cancer TT Hsu, Dr. CH Chen
 - Breast cancer stem cell CL Hsu, FH Chung
 - Psychiatric disorders Dr. CH Chen, YS Peng
- Validation
 - Cell model (Prof. NH) Ma Lab
 - Mouse model (Prof. SL) Su Lab

Thank you for your attention