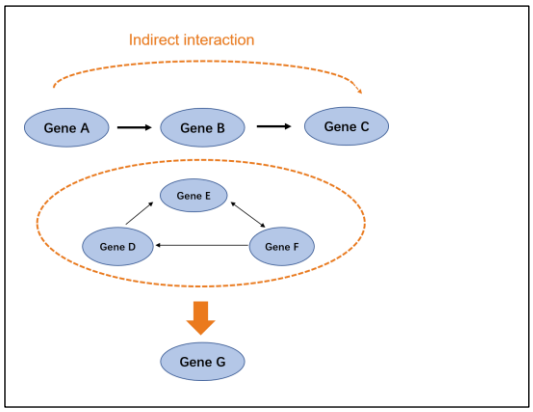
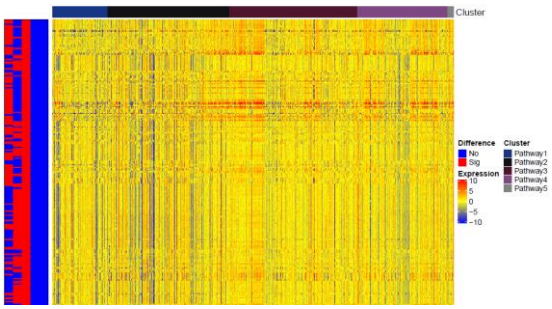
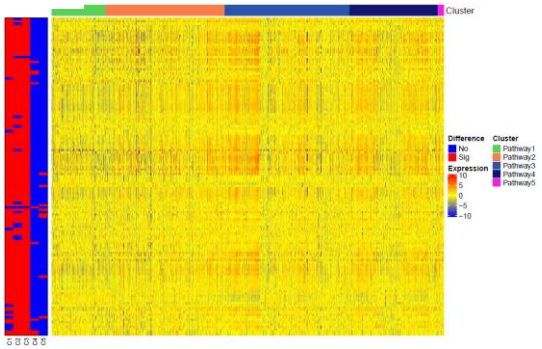


Supplementary Figure 1: . Genes in the same pathway may not just be directly regulated with one another. A: Gene A and Gene C do not have direct interaction; B: Gene D, Gene E and Gene F, etc have group interactions with Gene G, while they do not have direct interactions.

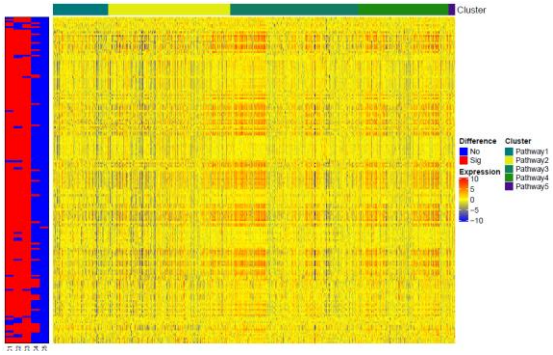
A



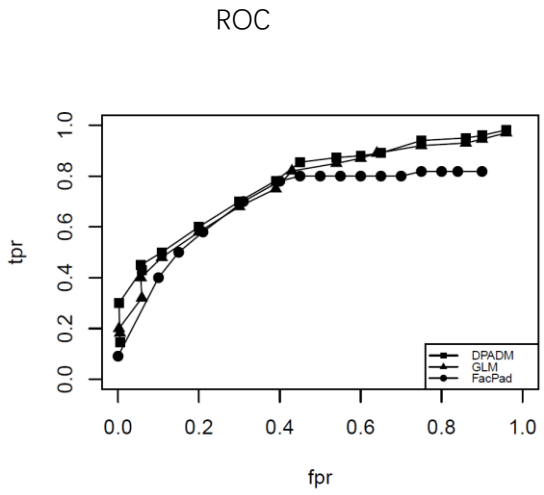
B



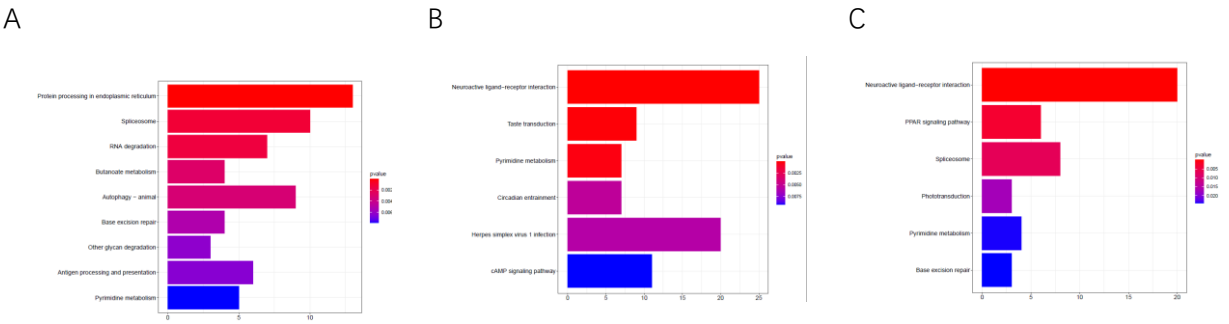
C



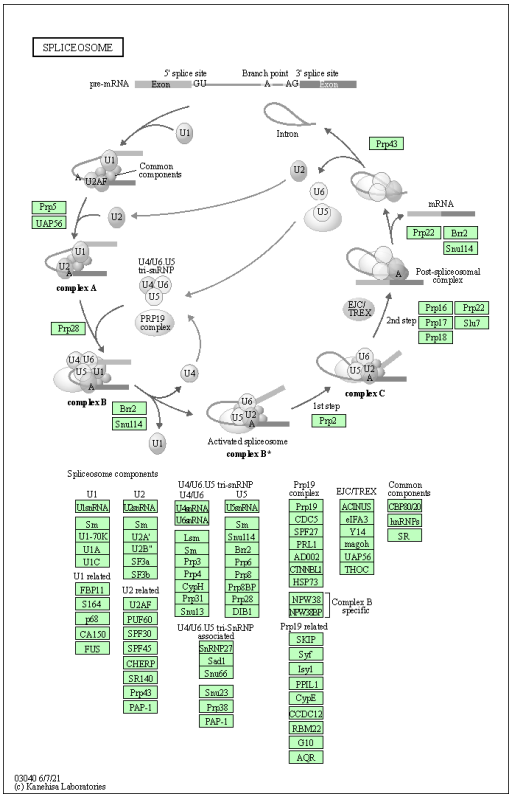
Supplementary Figure 2: The heatmaps of gene expression response to drug treatments for three cell-line panels, where genes clustered by the five known KEGG pathways. Row name of heatmap is the drug treatment, and column name is gene name. Differentially expressed genes were determined by Wilcoxon rank sum test with $q <= 0.05$ as the significance threshold. A: the Breast cancer dataset (MCF7); B: the liver cancer dataset (HCC); C: the non-small cell lung cancer (A549).



Supplementary Figure 3: ROC curves of three compared methods.

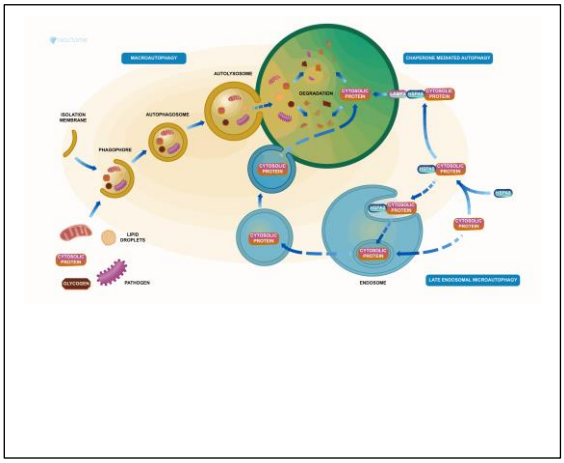


Supplementary Figure 4: Enrichment heatmaps with KEGG pathways with the three cell lines. A: the Breast cancer dataset (MCF7); B: the liver cancer dataset (HCC); C: the non-small cell lung cancer (A549).

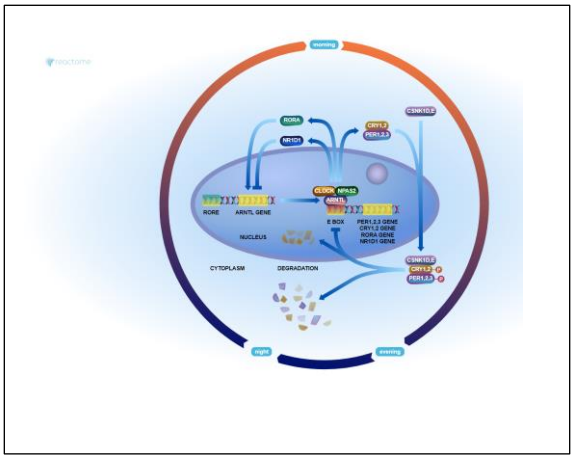


Supplementary Figure 5: The KEGG pathway diagram: Spliceosome

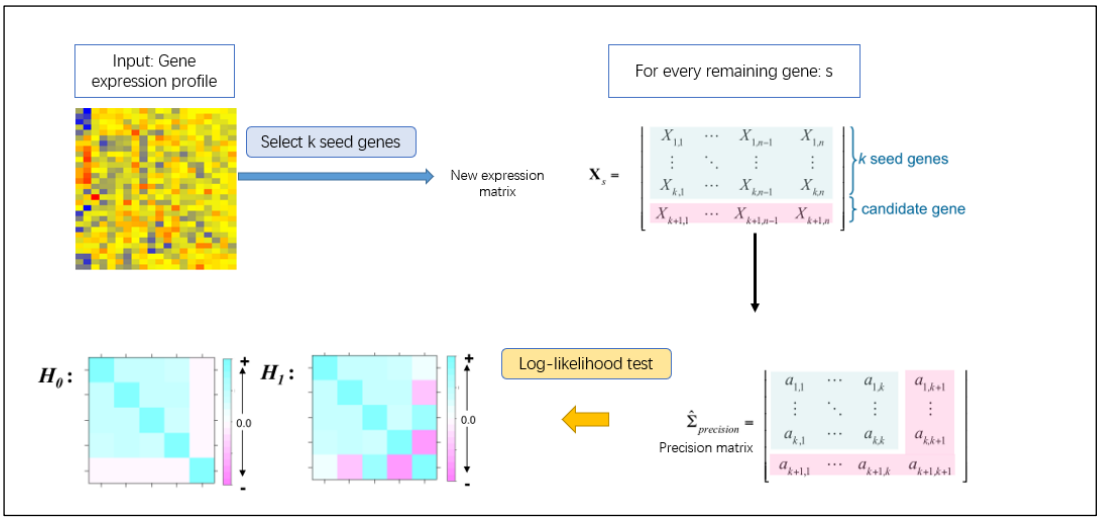
A



B



Supplementary Figure 6: schematic diagrams downloaded from Reactome. A: Autophagy, B: Circadian



Supplementary Figure 7: Description of DPADM method.

Supplementary Table 1. Transcriptional response profiles from CMAP

Tumor cell line	MCF7	HCC	A549
Number of treatment response profiles	13476	1900	2082
Number of different detection plates	115	15	25
Number of different compounds represented	1818	270	307
Number of genes	12328	12328	12328

Supplementary Table 2. Information of three cell line panels from CMAP

Cell line panel	No. of treatments	No. of drugs Corresponding to treatments	No. of KEGG pathways **a**fter filtering
MCF7	13476	1761	300
HCC	1900	270	275
A549	2082	307	274

Supplementary Table 3. Number of KEGG pathways after filtering, and number of new genes in the known 5 pathways from the top 100, 500, and 1000 genes in the list detected by DPADM algorithm for the cell line panels MCF7, HCC, and A549, respectively

A: Cell line MCF7

Pathway	Top 100	Top 500	Top 1000
Number of KEGG pathways after filtering	6	15	30
Number of genes in G2/M DNA damage Checkpoints	10	20	23
Number of genes in Cell cycle	31	82	90

Number of genes in PI3K/AKT signaling pathway	20	37	40
Number of genes in Transcriptional Regulation by TP53	23	58	61
Number of genes in Signaling by EGFR	9	23	25

B: Cell line HCC

Pathway	Top 100	Top 500	Top 1000
Number of KEGG pathways after filtering	6	8	13
Number of genes in G2/M DNA damage Checkpoints	7	16	20
Number of genes in Cell cycle	30	64	71
Number of genes in PI3K/AKT signaling pathway	18	32	38
Number of genes in Transcriptional Regulation by TP53	12	29	32
Number of genes in Signaling by EGFR	13	25	29

C: Cell line A549

Pathway	Top 100	Top 500	Top 1000
Number of KEGG pathways after filtering	5	6	29
Number of genes in G2/M DNA damage Checkpoints	10	20	23
Number of genes in Cell cycle	29	56	70
Number of genes in PI3K/AKT signaling pathway	19	31	37
Number of genes in Transcriptional Regulation by TP53	11	29	32
Number of genes in Signaling by EGFR	8	19	22

Supplementary Table 4. List of specific drugs related with pathways that differ with the five known ones for each of three cell line panels

Pathway	**Pathway-specific drugs**
MCF7 cell line panel	
Protein processing in endoplasmic reticulum	LDN-193189, withaferin-a, linagliptin, flutamide, midostaurin, bortezomib, MG-132, melperone
Spliceosome	PHA-848125
RNA degradation	ZD-7114, AT-9283, ganetespib, altrenogest, Gemifloxacin, PD-184352
Butanoate metabolism	Nicotine, homoharringtonine, digoxin
Autophagy - animal	CGP-60474, rebastinib, OTS-167, vorinostat,

	alvespimycin
Base excision repair	belinostat
Other glycan degradation	bruceantin
Antigen processing and presentation	XMD-16144, MG-132, PF-03758309, PF-03814735, linifanib
Pyrimidine metabolism	Staurosporine, vorinostat, bropirimine, camptothecin, BIIB-021, alvocidib
HCC cell line panel	
Neuroactive ligand−receptor interaction	PD-0325901
Taste transduction	Dacomitinib, TGX-221, LY-2603618
Pyrimidine metabolism	None
Circadian entrainment	dasatinib
Herpes simplex virus 1 infection	Linifanib, doramapimod, dasatinib, buparlisib, entinostat, belinostat, ruxolitinib, geldanamycin, CP-466722
cAMP signaling pathway	alpelisib
A549 cell line panel	
Neuroactive ligand−receptor interaction	DMSO, GSK-J4, celastrol, lapatinib, ruxolitinib, radicicol, PD-0325901, saracatinib
PPAR signaling pathway	PD-0325901, SU-11274, AS-601245, I-BET-151, NVP-BHG712
Spliceosome	Belinostat, methylstat, AKT-inhibitor-1-2, AZD-8330, erlotinib, sorafenib, saracatinib, calpain inhibitor ii
Phototransduction	unc-0646, zebularine, AKT-inhibitor-1-2
Pyrimidine metabolism	PD-0325901, XMD-1150, bosutinib, afatinib, pelitinib, calpain inhibitor ii
Base excision repair	BX-912, brivanib, calpain inhibitor ii, withaferin-a, RGFP-966, niclosamide