Predicting selective drug targets in cancer through metabolic networks

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Abstract

- **The interest in studying metabolic alterations in cancer and their potential role as novel targets for therapy has been rejuvenated in recent years.**
- **Here, we report the development of the first genome scale network model of cancer metabolism, validated by correctly identifying genes essential for cellular proliferation in cancer cell lines.**

Background

- the development of metabolite profiling technologies and metabolic network databases
- The interest in studying cancer metabolism has recently grown
- cancer cells modify their metabolism to meet the requirements of cellular proliferation, thus facilitating the uptake and conversion of nutrients into biomass
- The observation that many types of cancer cells adapt their metabolism to facilitate biomass formation to enable proliferation suggests that it may be possible to predict characteristic alterations in cancer metabolism via genome-scale computational modeling approaches that have been successfully used in the past to predict the metabolic state of fast growing micro organisms

Method，steps

- Reconstructing a human cancer metabolic model
- Predicting cytostatic anticancer targets
- Predicting synthetic lethal gene targets
- The targeting of both synthetic lethal genes via combination therapy
- The targeting of a gene whose synthetic lethal partner is inactivated in specific cancer types leads to selective treatments

Reconstructing a human cancer metabolic model

- **we integrate the human metabolic model of Duarte et al (2007) with cancer gene expression data, utilizing a variant of our recent computational method for the automatic reconstruction of human tissue metabolic models, termed MBA (Model Building Algorithm)**

1.we begin by assembling an initial core set of 197 metabolic enzyme-coding genes that are highly expressed across 90% of all cancer cell lines in the NCI-60 collection

2.applying MBA, a minimal setof additional reactions from the human metabolic model thatare needed to activate the reactions associated with this initial core set is added, obtaining a cancer metabolism model that is consistent

3.The resulting cancer metabolic model includes 772 reactions and 683 genes

4.To validate the cancer network model generated, we analyzed it via FBA to predict growth-supporting genes whose knockdown would significantly reduce cellular proliferation rate

Overall, we obtain a set of 199 growth-supporting genes, which are reassuringly ranked as highly essential based on shRNA gene silencing data (Luo et al, 2008) (Kolmogorov–Smirnov (KS) P-value0.0045; Supplementary Figure S1). The reference shRNA data set consists of a list of genes, ranked according to the survival rate of 12 cancer cell lines after these genes are knocked down, thus denoting the genes' experimentally measured contribution to cancer growth.

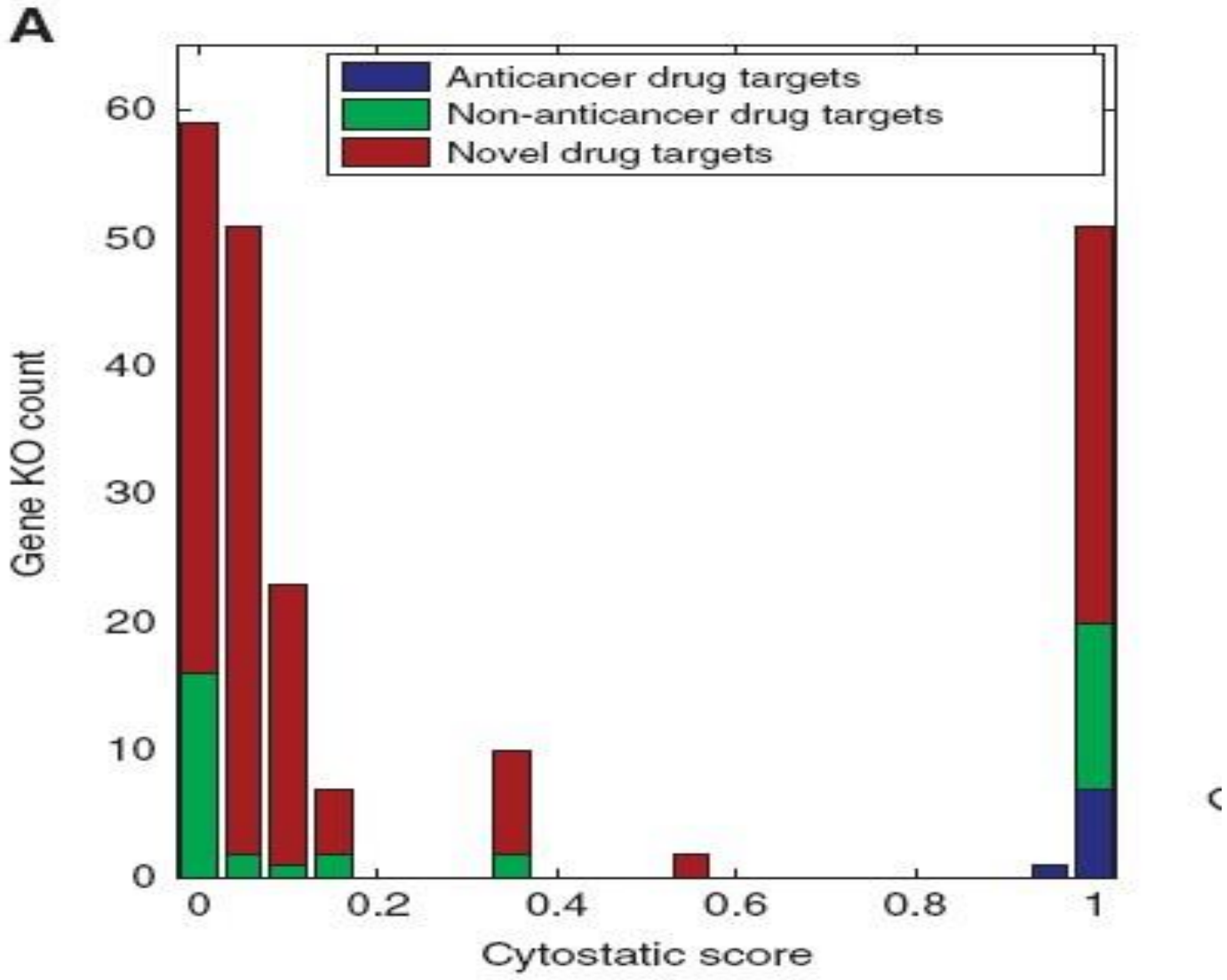
Predicting cytostatic anticancer targets

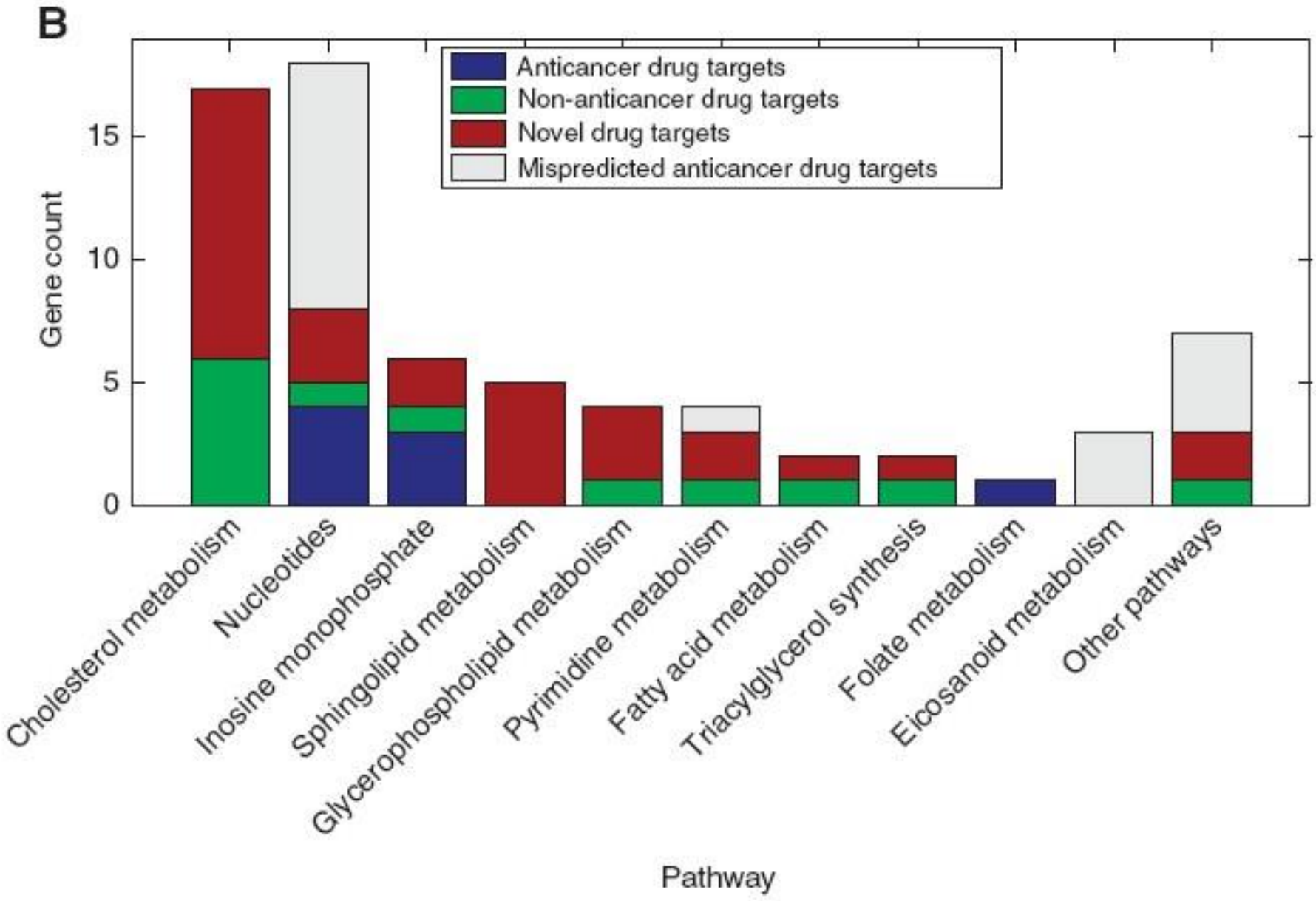
- **To identify which of the above-identified growth-supporting genes may be considered viable anticancer targets, we further aimed to predict whether their knockdown is expected to be toxic to non-dividing cells or damage the proliferation of normal cells.**

Cytostatic score

- Cytostatic score=

  (KOatp/WTatp)(1–KOgrowth / WTgrowth)
- The gene knockdown effect on growth rate is computed by applying FBA on the cancer model, denoting by WTgrowth and KOgrowth the growth rate before and after the knockdown


A
Anticancer drug targets
Non-anticancer drug targets
Novel drug targets
Gene KO count
60
50
40
30
20
10
0
0
0.2
0.4
0.6
0.8
1
Cytostatic score


B
Anticancer drug targets
Non-anticancer drug targets
Novel drug targets
Mispredicted anticancer drug targets
Gene count
0
5
10
15
Cholesterol metabolism
Nucleotides
Inosine monophosphate
Sphingolipid metabolism
Glycerophospholipid metabolism
Pyrimidine metabolism
Fatty acid metabolism
Triacylglycerol synthesis
Folate metabolism
Eicosanoid metabolism
Other pathways
Pathway

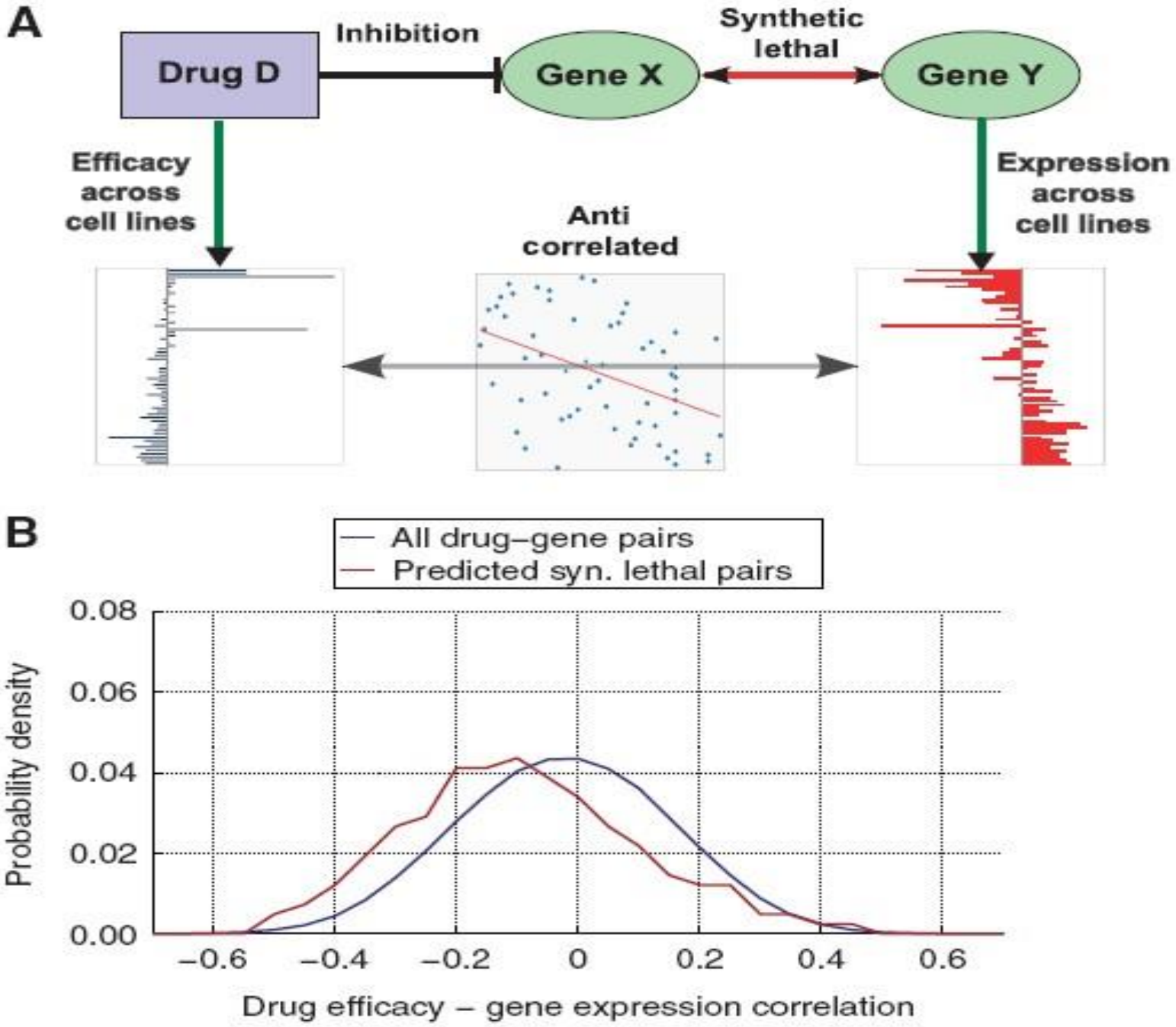
Predicting synthetic lethal gene targets

- To study synthetic lethal drug targets, we systematically simulated all double gene knockdowns in the cancer model. We assigned each gene pair with a synergy score, reflecting the additional drop in proliferation rate below the minimal rate achieved by its individual single knockdowns
- we find that they are significantly enriched with genetic interactions between the corresponding yeast orthologs

Synthetic score

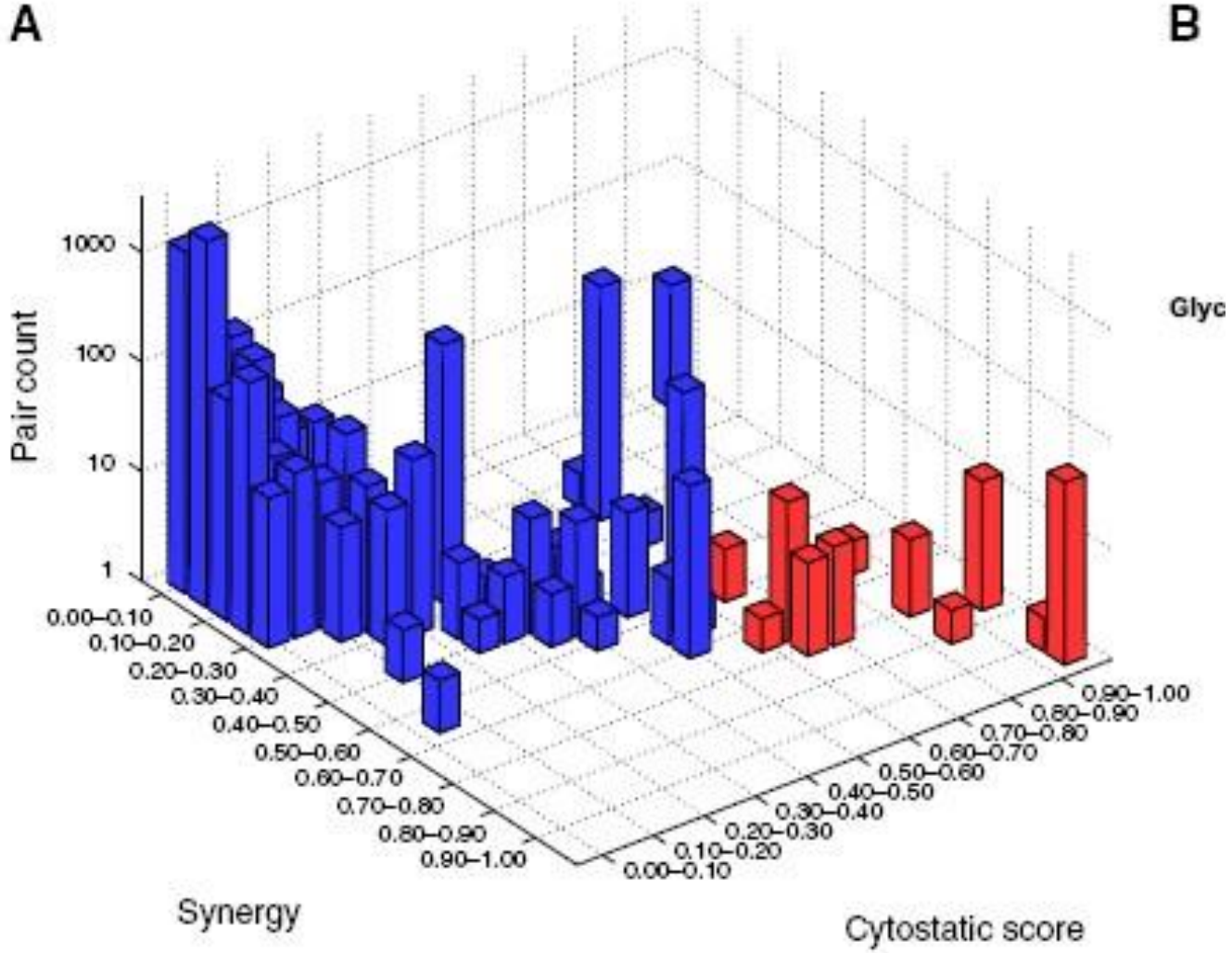
- **Synthetic score=**

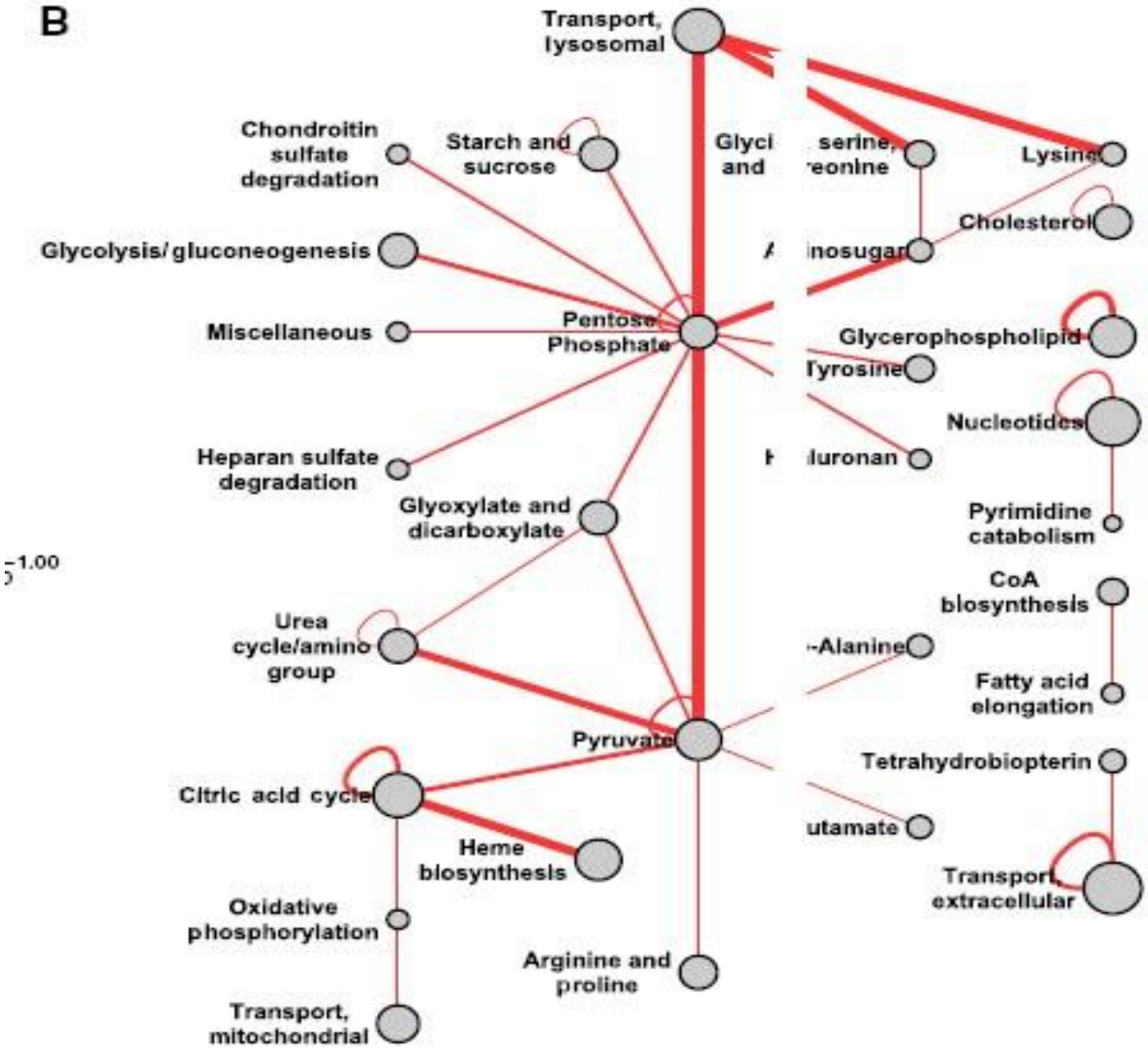
  KOAB/min(KOA, KOB)
- **Specifically, denoting by KOA, KOB and KOAB, the growth rates following the knockout of gene A, gene B and the joint knockout of genes A and B**


A
Drug D
Inhibition
Gene X
Synthetic lethal
Gene Y
Efficacy across cell lines
Anti correlated
Expression across cell lines
B
All drug–gene pairs
Predicted syn. lethal pairs
Probability density
0.08
0.06
0.04
0.02
0.00
−0.6
−0.4
−0.2
0
0.2
0.4
0.6
Drug efficacy – gene expression correlation

The targeting of both synthetic lethal genes via combination therapy

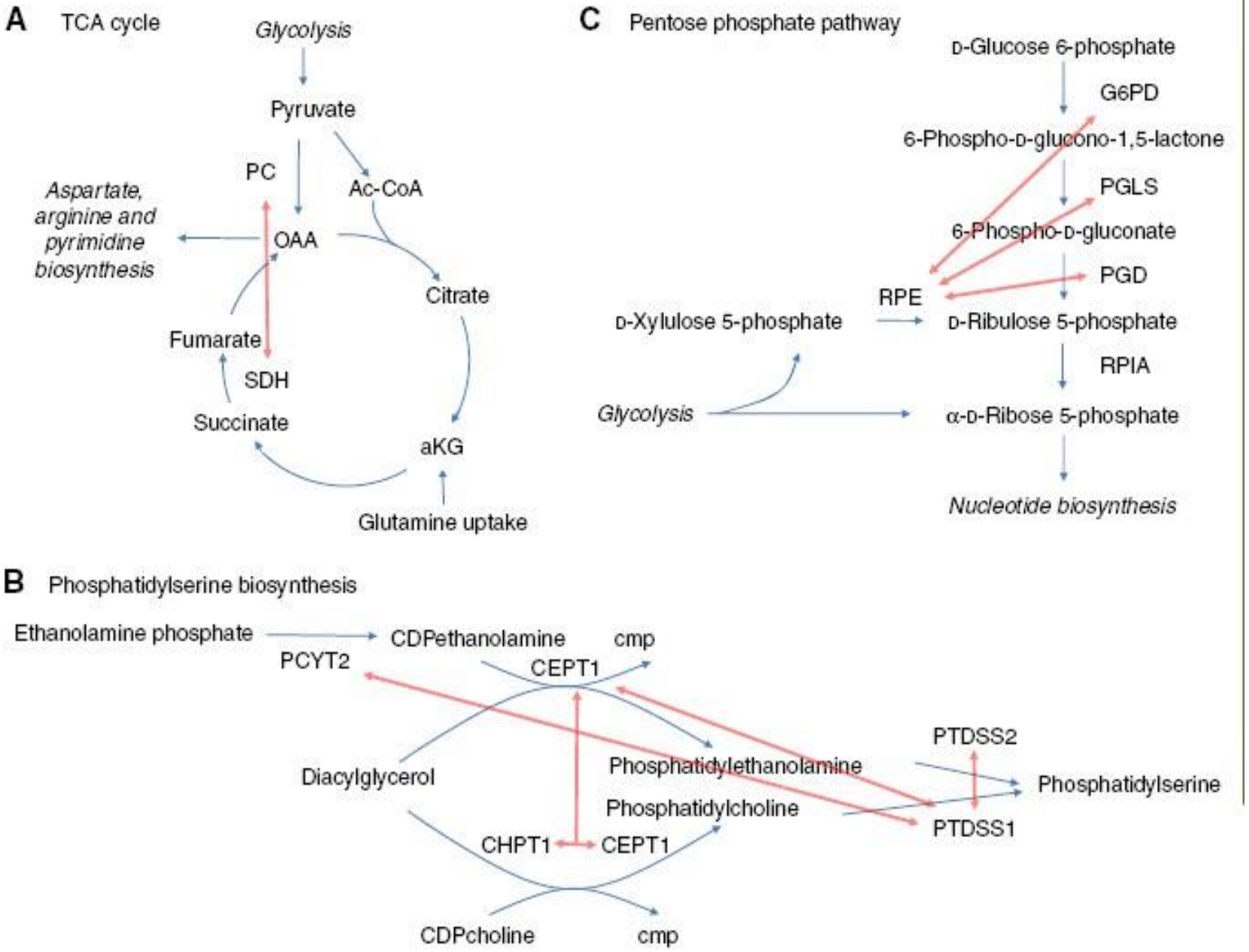
- To identify which of the synthetic lethal genes may be further considered for combinatorial drug therapies, we further predicted whether their joint knockdown is expected to be toxic for non-dividing cells or damage the proliferation of normal cells

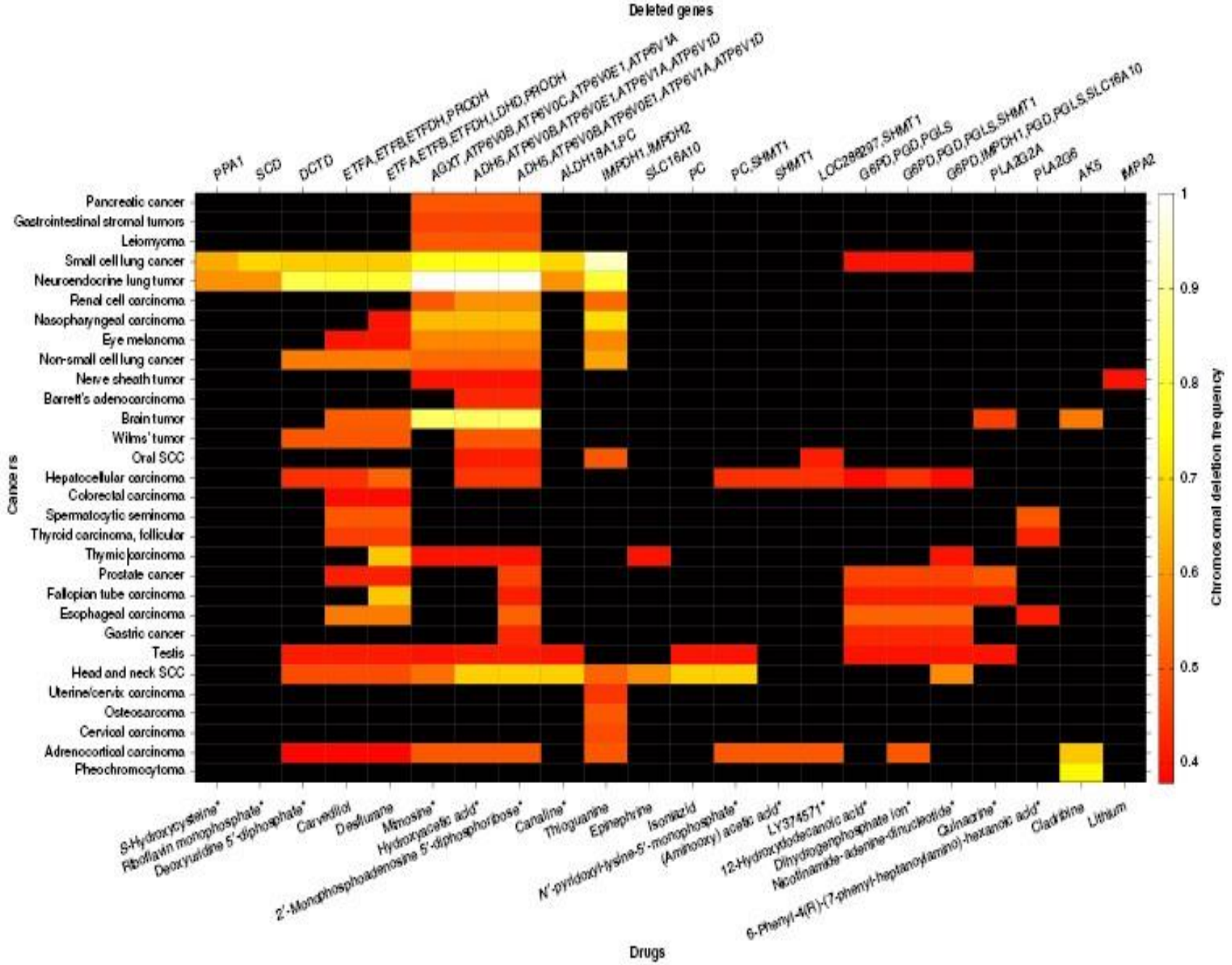

A
B
Glyc
Pair count
1000
100
10
1
0.00–0.10
0.10–0.20
0.20–0.30
0.30–0.40
0.40–0.50
0.50–0.60
0.60–0.70
0.70–0.80
0.80–0.90
0.90–1.00
Synergy
Cytostatic score


B
Transport, lysosomal
Chondroitin sulfate degradation
Starch and sucrose
Glycolysis/gluconeogenesis
Miscellaneous
Pentose Phosphate
Heparan sulfate degradation
Glyoxylate and dicarboxylate
Urea cycle/amino group
Pyruvate
Citric acid cycle
Heme biosynthesis
Oxidative phosphorylation
Arginine and proline
Transport, mitochondrial
Lysine
Cholesterol
Glycerophospholipid
Tyrosine
Nucleotides
Pyrimidine catabolism
CoA biosynthesis
Fatty acid elongation
Tetrahydrobiopterin
Transport, extracellular

The targeting of a gene whose synthetic lethal partner is inactivated in specific cancer types leads to selective treatments

- The specific targeting of a gene participating in a synergistic pair is especially appealing in tumors in which its interacting gene is specifically inactivated.
- We utilized genomic and transcriptomic data to infer gene inactivation across an array of cancers, which leads to the identification of cancer type-specific targets based on the predicted synergistic gene pairs.


A
TCA cycle
Glycolysis
Pyruvate
PC
Ac-CoA
Aspartate, arginine and pyrimidine biosynthesis
OAA
Citrate
Fumarate
SDH
Succinate
aKG
Glutamine uptake
C
Pentose phosphate pathway
D-Glucose 6-phosphate
G6PD
6-Phospho-D-glucono-1,5-lactone
PGLS
6-Phospho-D-gluconate
PGD
RPE
D-Xylulose 5-phosphate
D-Ribulose 5-phosphate
RPIA
Glycolysis
α-D-Ribose 5-phosphate
Nucleotide biosynthesis
B
Phosphatidylserine biosynthesis
Ethanolamine phosphate
CDPethanolamine
cmp
PCYT2
CEPT1
PTDSS2
Diacylglycerol
Phosphatidylethanolamine
Phosphatidylserine
Phosphatidylcholine
PTDSS1
CHPT1
CEPT1
CDPcholine
cmp


Deleted genes
PPA1
SCD
DCTD
ETFA,ETFB,ETFDH,PRODH
ETFA,ETFB,ETFDH,LDHD,PRODH
AGXT,ATP6V0B,ATP6V0C,ATP6V0E1,ATP6V1A
ADH5,ATP6V0B,ATP6V0E1,ATP6V1A,ATP6V1D
ADH5,ATP6V0B,ATP6V0E1,ATP6V1A,ATP6V1D
ALDH18A1,PC
IMPDH1,IMPDH2
SLC16A10
PC
PC,SHMT1
SHMT1
LOC286297,SHMT1
G6PD,PGD,PGLS
G6PD,PGD,PGLS,SHMT1
G6PD,IMPDH1,PGD,PGLS,SLC16A10
PLA2G2A
PLA2G6
AK5
IMPA2
Pancreatic cancer
Gastrointestinal stromal tumors
Leiomyoma
Small cell lung cancer
Neuroendocrine lung tumor
Renal cell carcinoma
Nasopharyngeal carcinoma
Eye melanoma
Non-small cell lung cancer
Nerve sheath tumor
Barrett's adenocarcinoma
Brain tumor
Wilms' tumor
Oral SCC
Hepatocellular carcinoma
Colorectal carcinoma
Spermatocytic seminoma
Thyroid carcinoma, follicular
Thymic carcinoma
Prostate cancer
Fallopian tube carcinoma
Esophageal carcinoma
Gastric cancer
Testis
Head and neck SCC
Uterine/cervix carcinoma
Osteosarcoma
Cervical carcinoma
Adrenocortical carcinoma
Pheochromocytoma
Cancers
1
0.9
0.8
0.7
0.6
0.5
0.4
Chromosomal deletion frequency
S-Hydroxycysteine*
Riboflavin monophosphate*
Deoxyuridine 5'-diphosphate*
Carvedilol
Desflurane
Mimosine*
Hydroxyacetic acid*
2'-Monophosphoadenosine 5'-diphosphoribose*
Canaline*
Thioguanine
Ephedrine
Isoniazid
N'-pyridoxyl-lysine-5'-monophosphate*
(Aminooxy) acetic acid*
LY374571*
12-Hydroxydodecanoic acid*
Dihydrogenphosphate ion*
Nicotinamide-adenine-dinucleotide*
Guinacrine*
6-Phenyl-4(R)-(7-phenyl-heptanoylamino)-hexanoic acid*
Cladribine
Lithium
Drugs

Discussion

- **studied the predicted synergy between the TCA cycle enzyme FH and the heme metabolism pathway.**
- **Beyond the prediction of new potential drug treatments, the modeling approach presented here is expected to open up many additional exciting possibilities in the near future.**

Conclusion

- **In summary, the model presented here lays down a fundamental computational counterpart for interpreting the rapidly accumulating proteomics and metabolomics data characterizing cancer metabolic alterations, and paves the way both for obtaining a systems level understanding of cancer metabolism and for designing new therapeutic means that selectively target them.**


Thanks!