Searching Synergistic Drug Combinations to Treat Cancer

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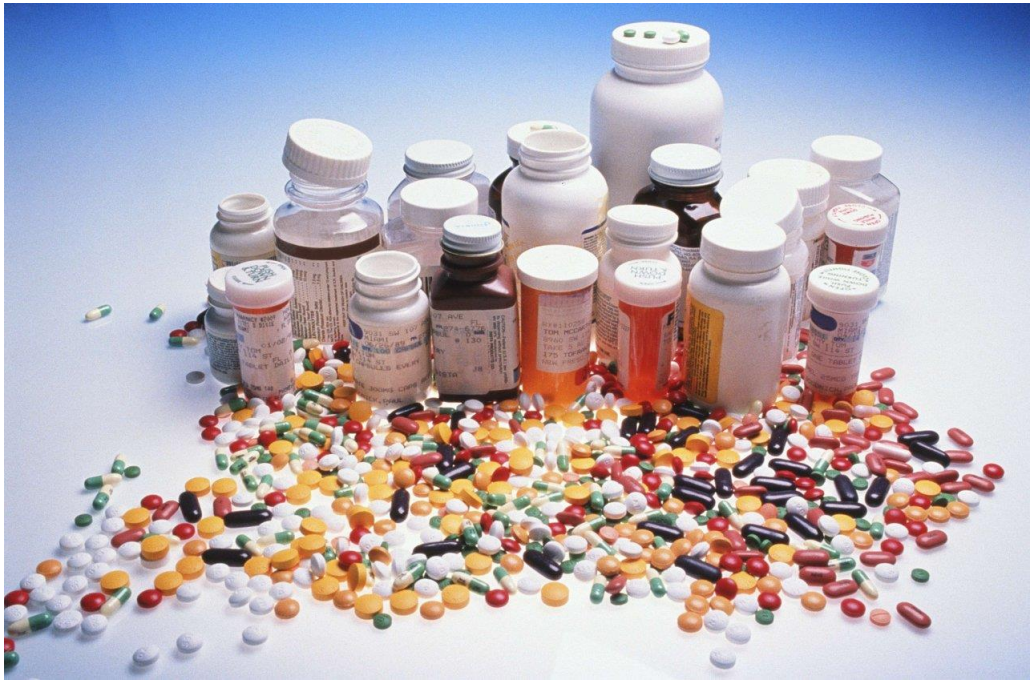
Overview

- MOA of drug synergy
- Model of anti-cancer synergistic drugs: RACS
- Validaton
- Clinical cases

Background

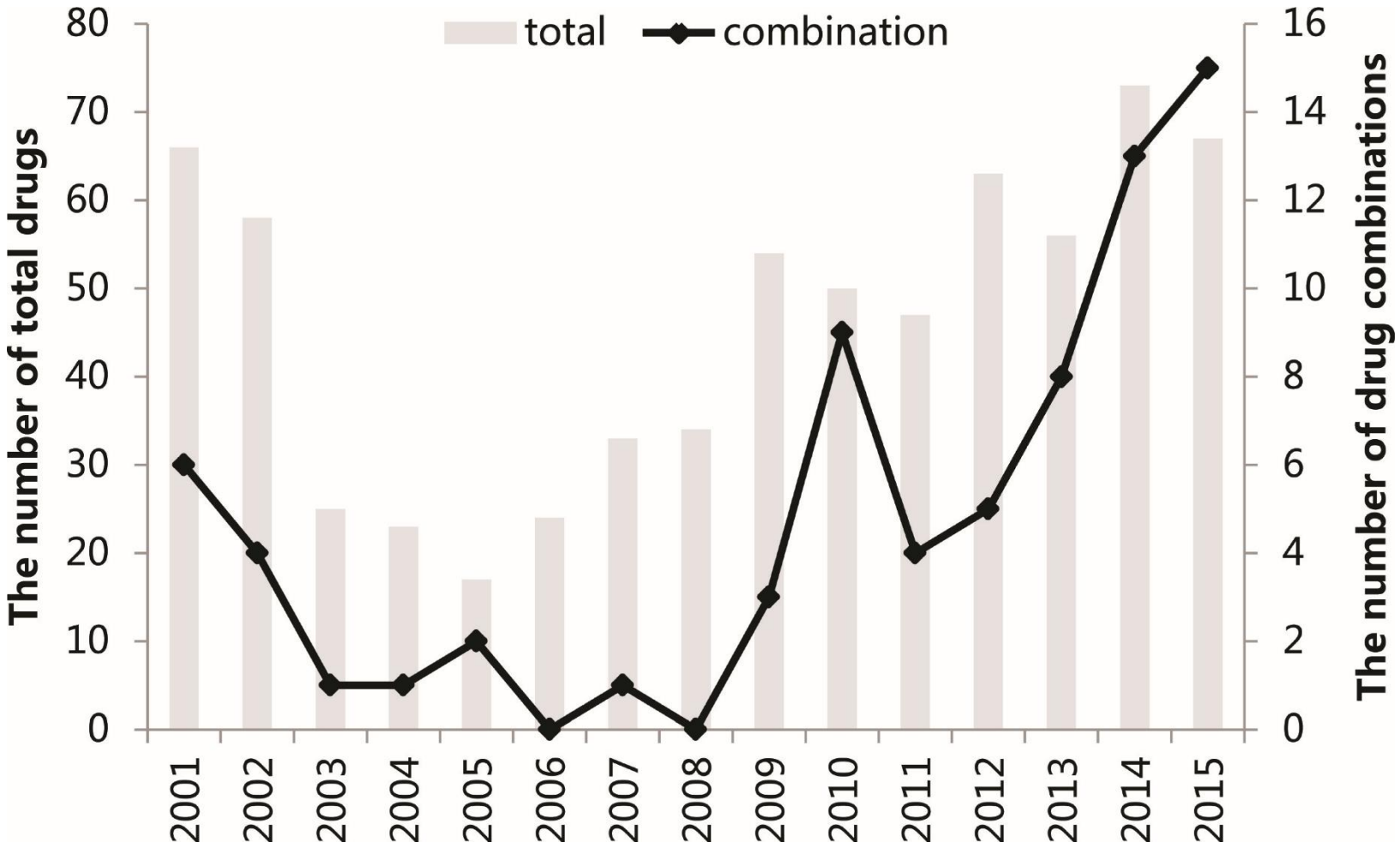
- Single drug therapies:
  - Limited effects
  - Side effects

- Drug combinations:
  - Synergy
  - Low toxicity
  - Challenge: huge amounts of possible combinations

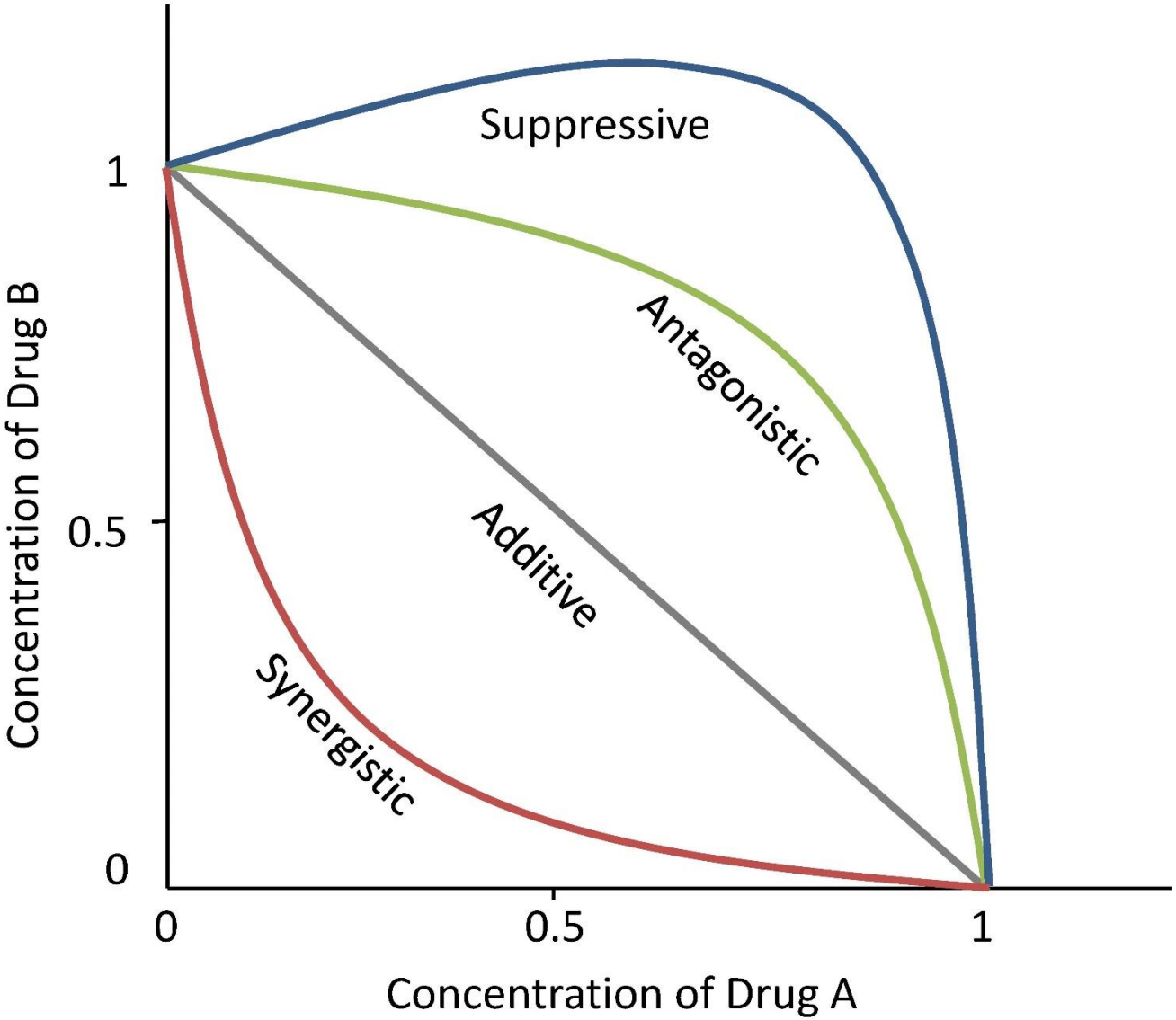


Number of Single drugs	Number of all 2-drug combinations
10	45
100	4,950
1000	499,500
…	…

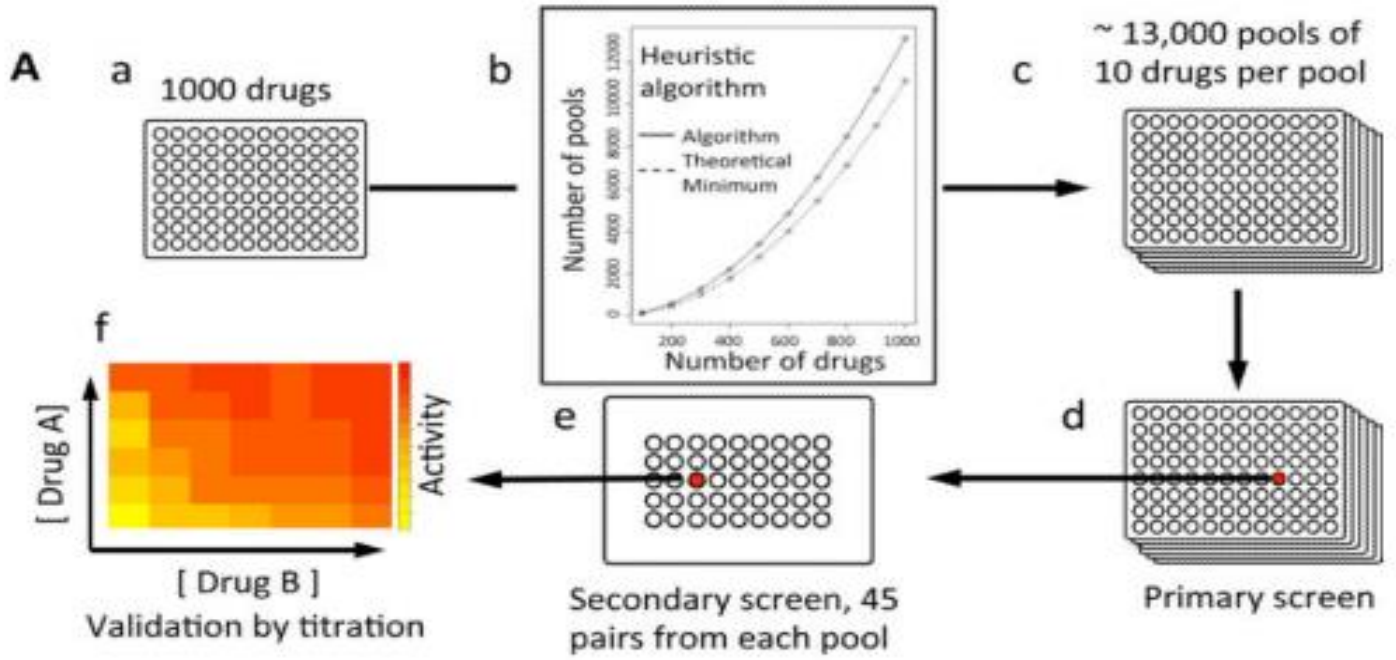
No. of FDA-Approved Drugs



Effects of Drug Combination



HTS: Detecting Mechanism of Synergistic Compounds anti-HIV screening



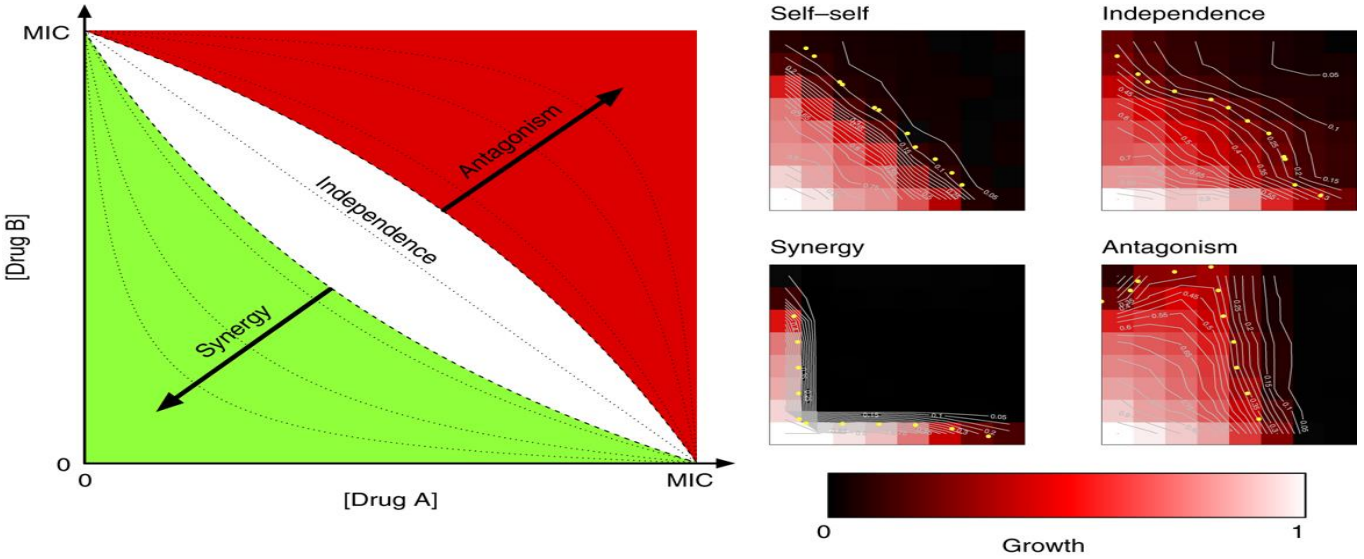
1000 drugs , 500K drug pairs, 46.7% discovery rate.

- **The synergistic combinations were detected to be enriched with anti-inflammatory drugs, and drug pairs targeting different steps in the HIV life cycle.**

Tan, X. and L. Hu, et al. (2012). Nat Biotechnol 30 (11): 1125-1130.

HTS: Detecting Mechanism of Synergistic Compounds

anti-fungal screening on yeast

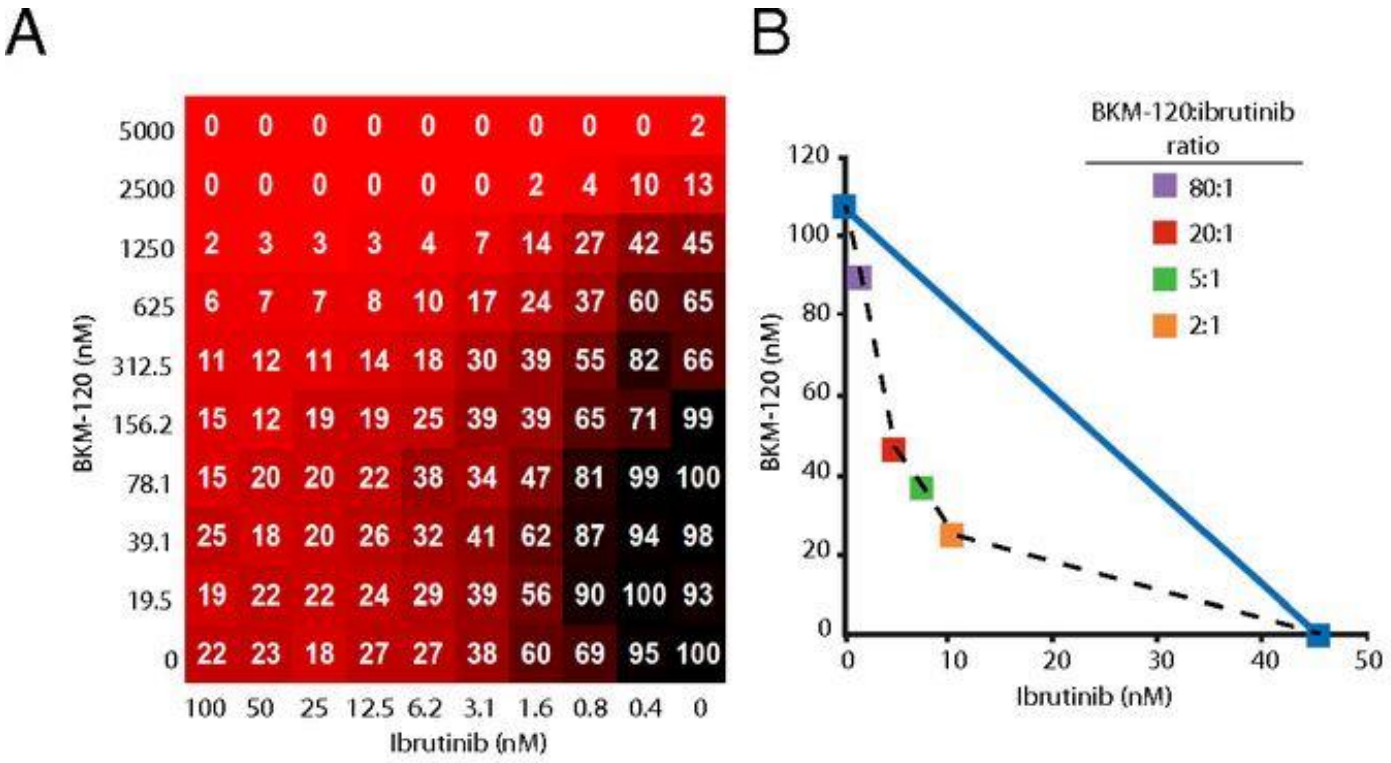


200 pairs, 38 with synergistic activities (discovery rate: 19%)

- **The majority displays promiscuous synergy.**
- **The minority with specific synergy resulted from targeting genetic interactions, eg. genes acting in parallel.**

Murat Cokol et al. Mol Syst Biol 2011;7:544

HTS: Detecting Mechanism of Synergistic Compounds anti-cancer screening on DLBCL



459 agents with ibrutinib **(discovery rate： nearly 27%)**

- **Ibrutinib was identified to interact favorably with PI3K pathway inhibitors or the components that are standard in caring for DLBCL.**

Lesley A. Mathews Griner et al. PNAS 2014;111:2349-2354

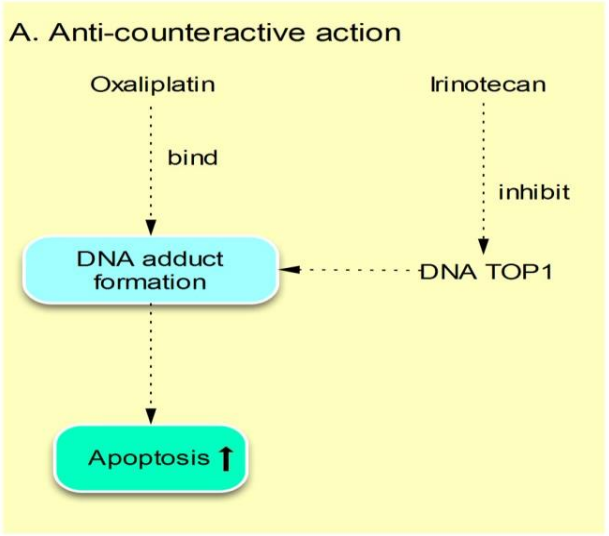
MOA of Drug Synergy:
PK（药效协同）and PD(药代增效）

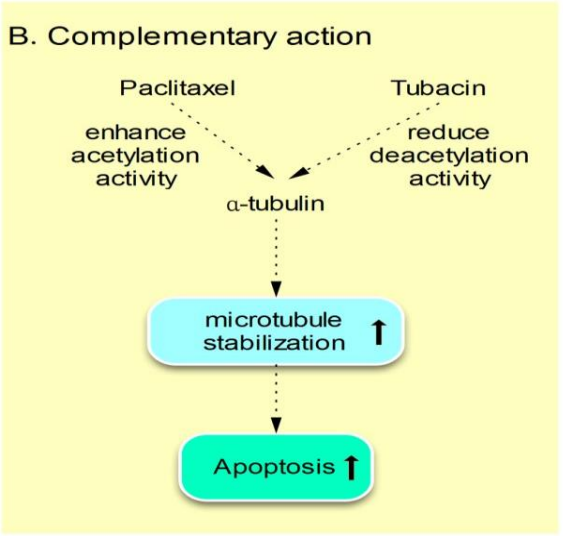
A.抗抵抗作用
(anti-counteractive action）

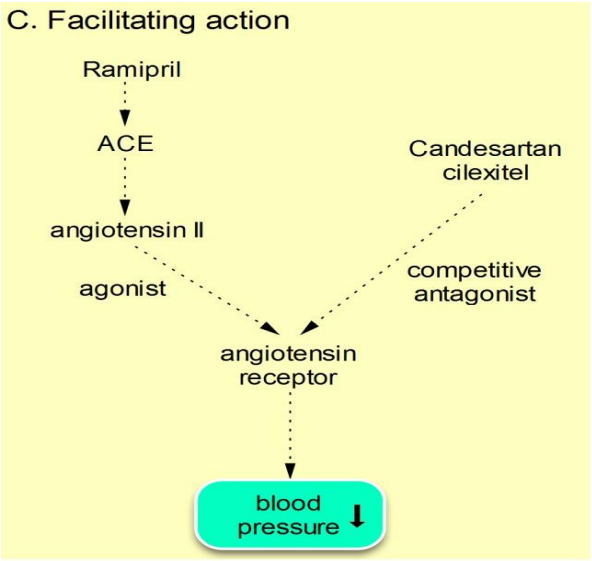
B.互补作用
(complementary action）

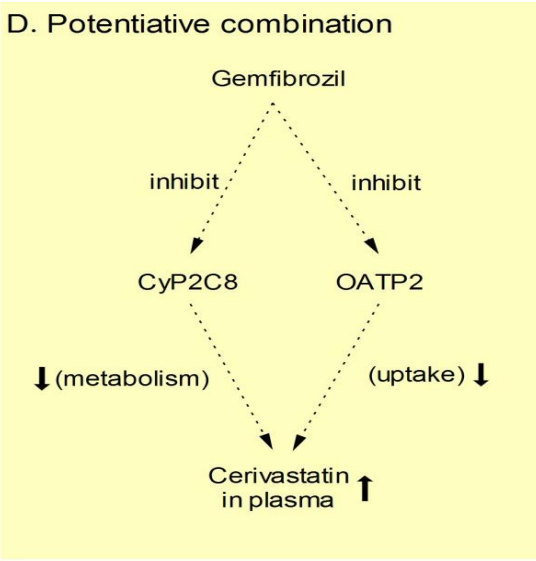
C.辅助作用
(facilitating action)

D.增效作用
(potentiative action)





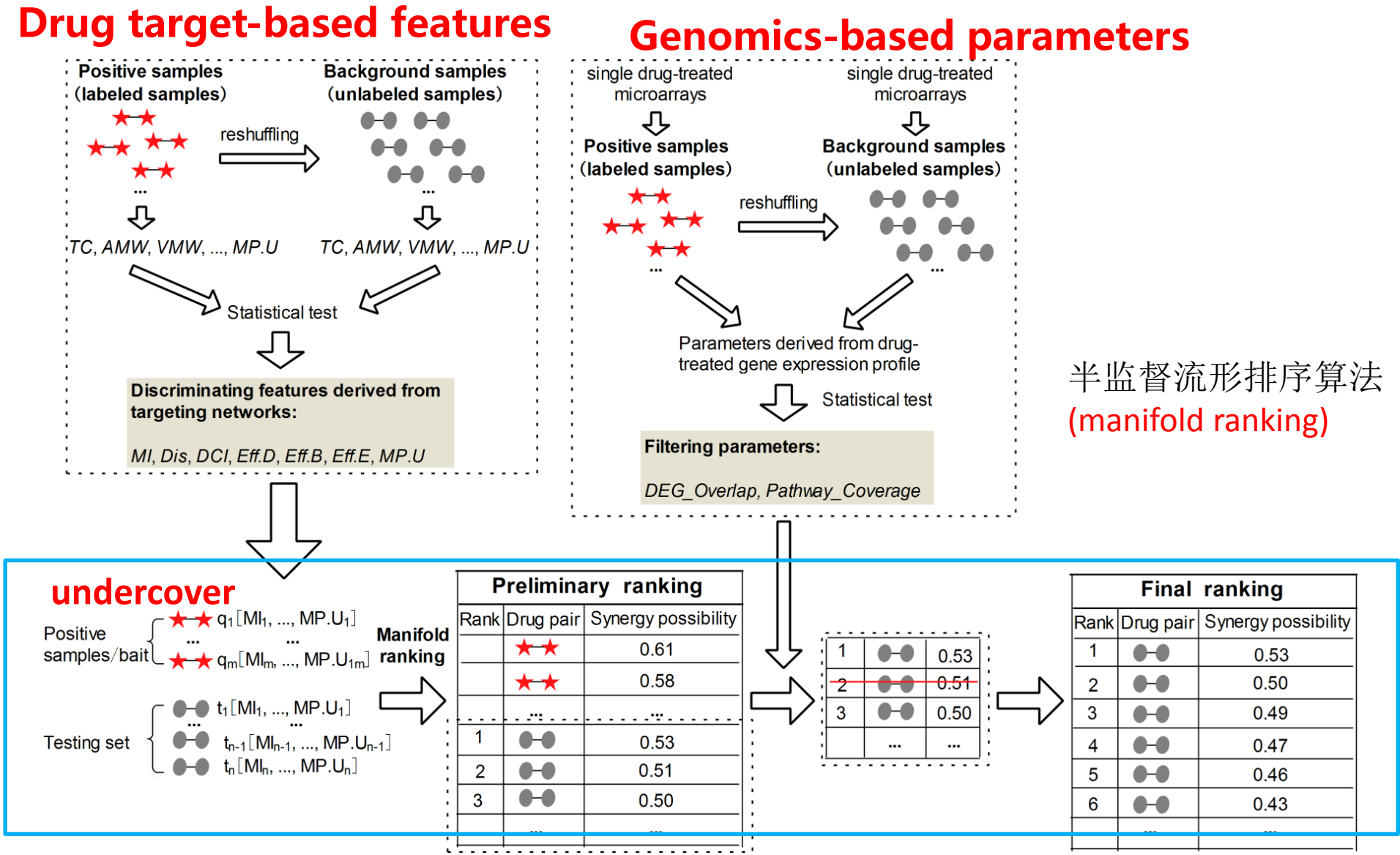




Jia J, et al. Nat Rev Drug Discov, 2009, 8(2):111-128.

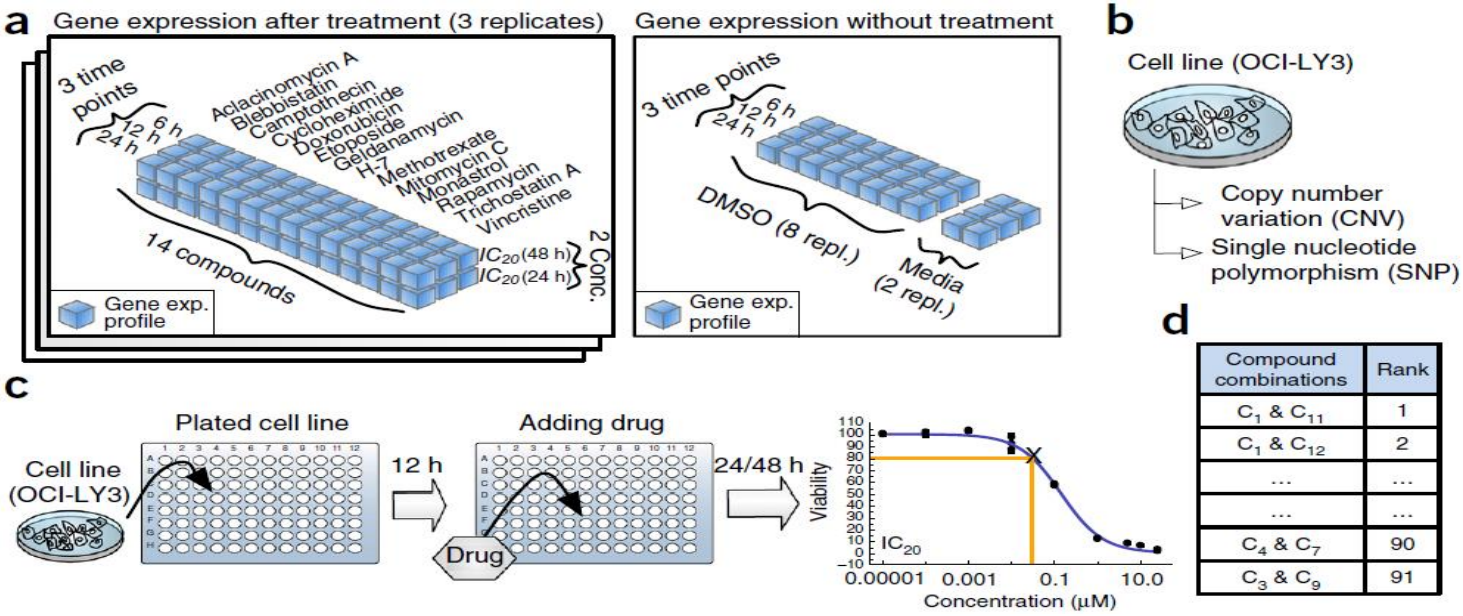
RACS:

a Ranking-system of Anti-Cancer Synergy (RACS) that combines features of targeting networks and transcriptomic profiles



NCI-DREAM challenge： Best 0.61

Predicting 91 cooperative effects between 14 distinct drugs/compounds on a human β-cell lymphoma cell line lymphoma cell line (DLBCL)



Compound combinations	Rank
C_1 & C_{11}	1
C_1 & C_{12}	2
…	…
…	…
C_4 & C_7	90
C_3 & C_9	91

14
compounds

91
binary pairs

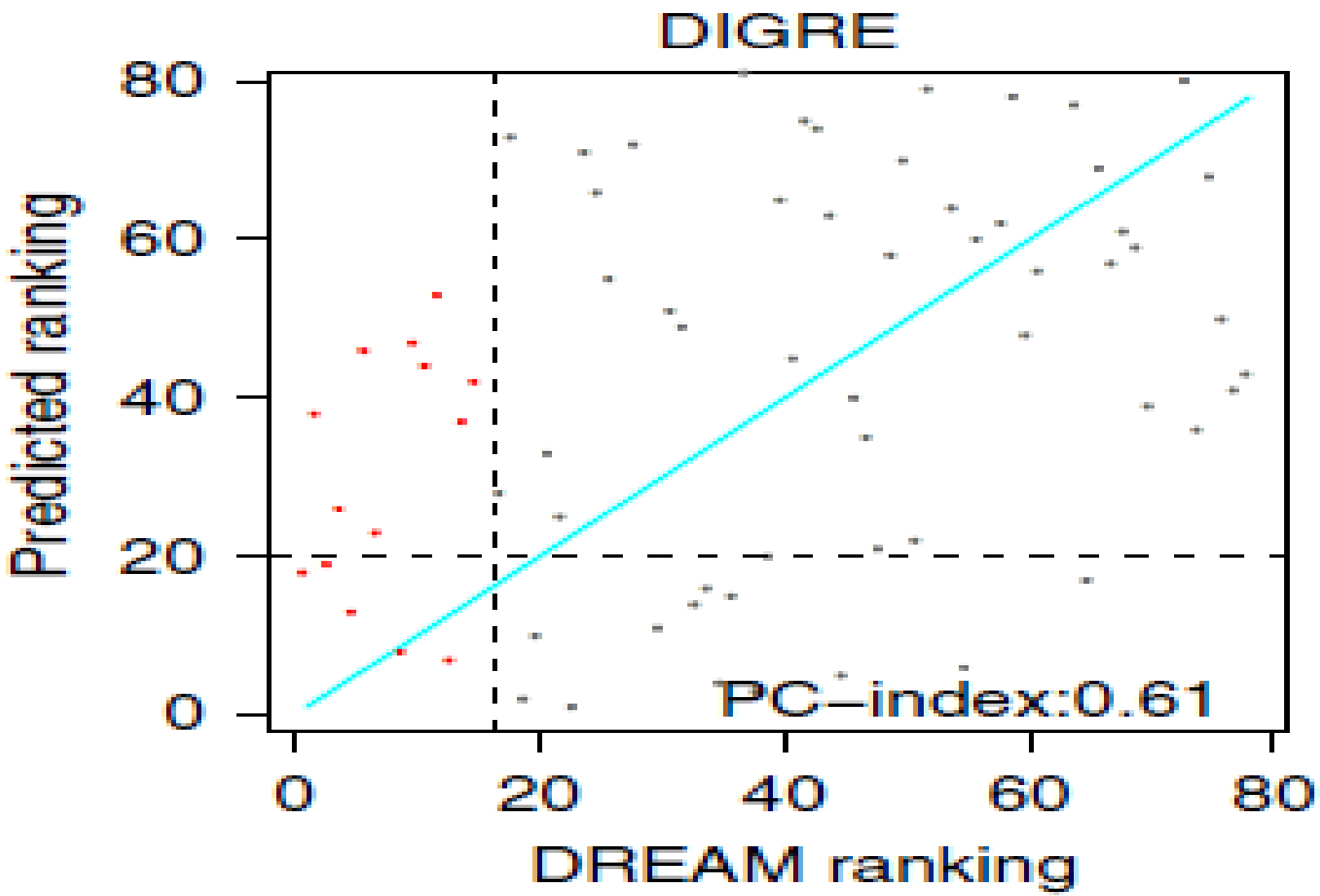
31
teams

Random guessing： PC-index of 0.50
Ground truth: PC-index of 0.90

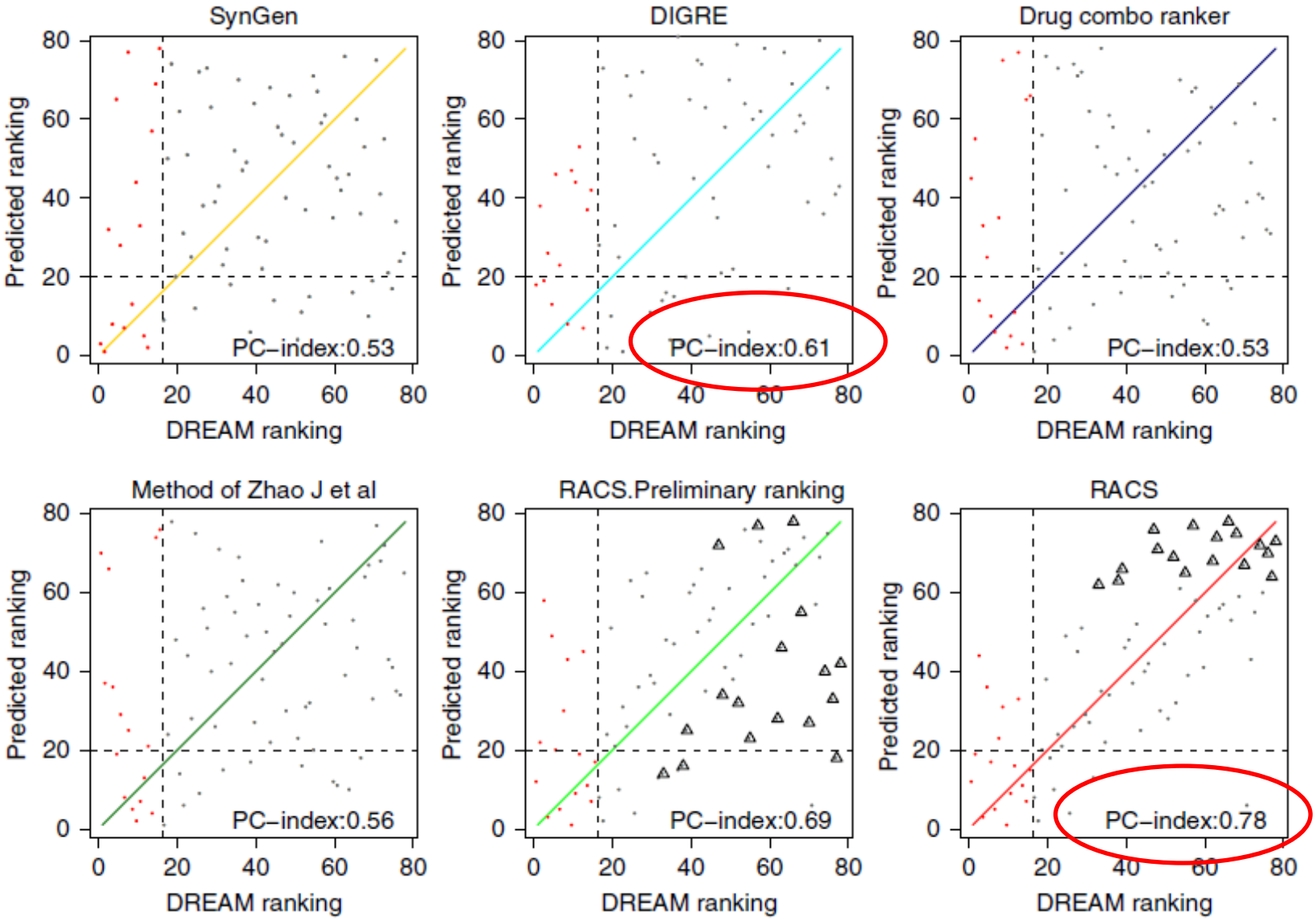
0.61: Merely better than random guess

Bansal M, et al. Nature biotechnology, 2014, 32(12):1213-1222.

Detailed Ranking of DIGRE



Significant improvement on DREAM data of DLBCL cells



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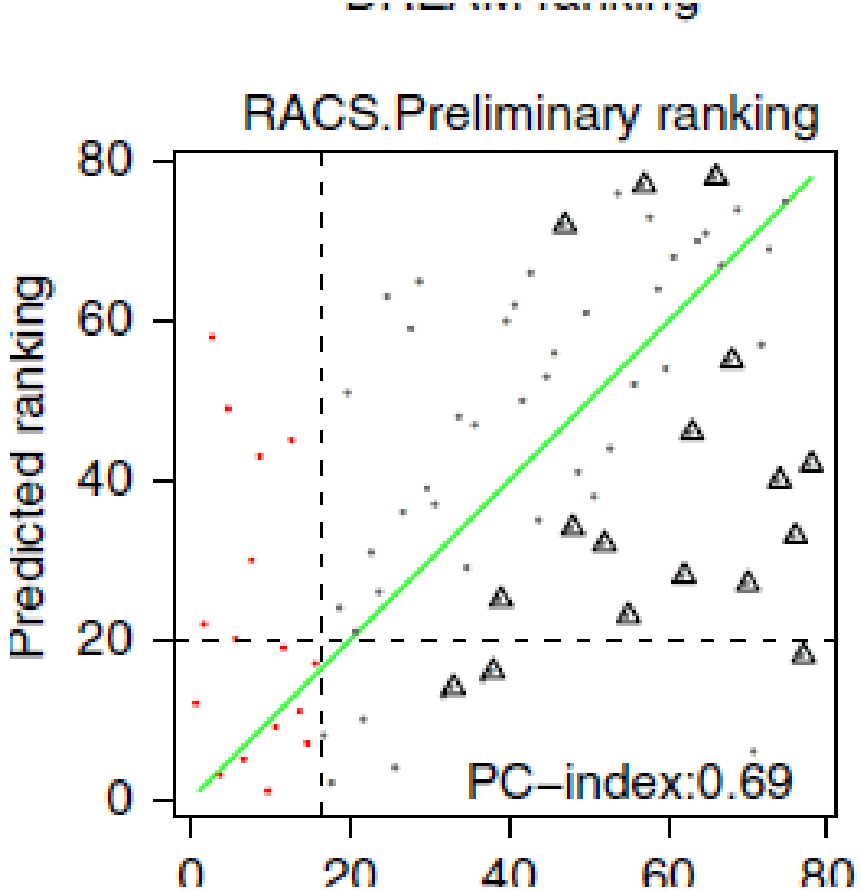
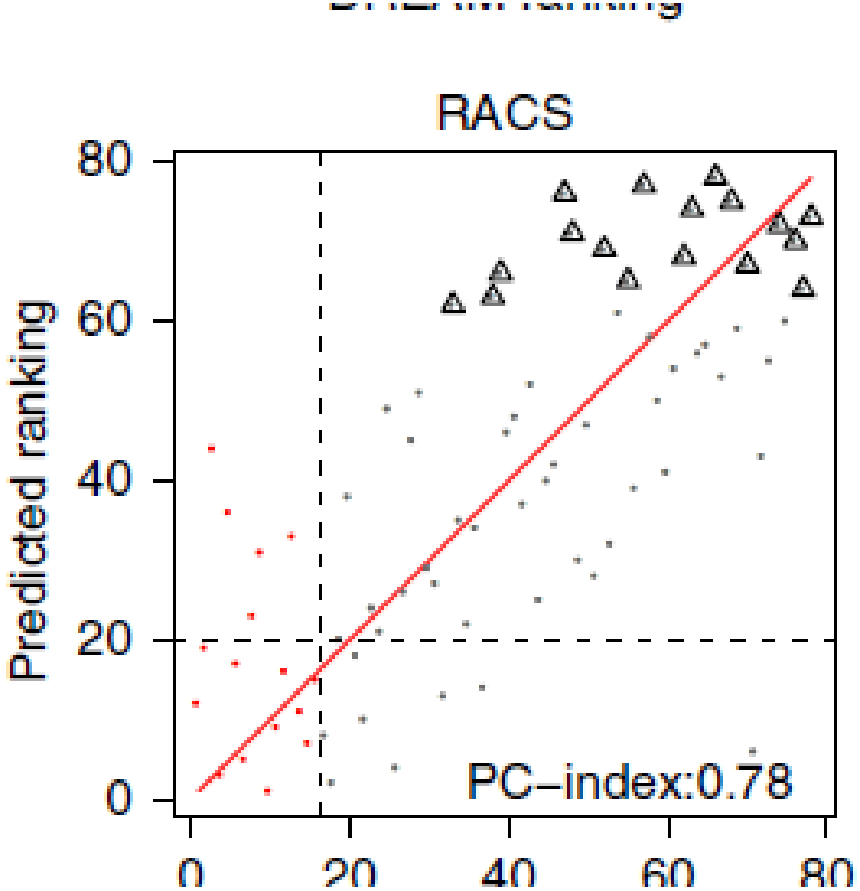
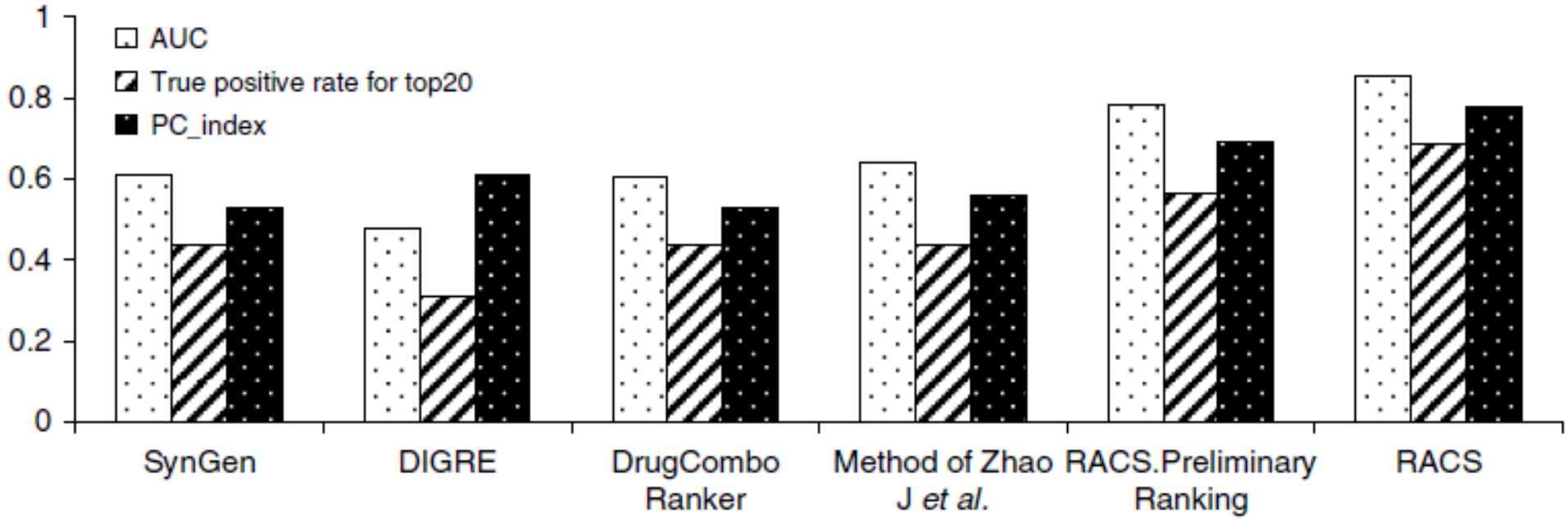




Overall performance of RACS



- Racs AUC： 0.85，
- Positive rate of top 20: 68.75%,
- PC Index 0.78.

Significant ranking ability on breast cancer cells

乳腺癌（MCF7）

118 anti-cancer drugs ↔ **6877** drug pairs

positive rate in top1%

63.64% VS random **13.33%**

强协同的药物组合
Erlotinib+Sorafenib

a

17 Agent pairs tested by experiment on MCF7 cell line

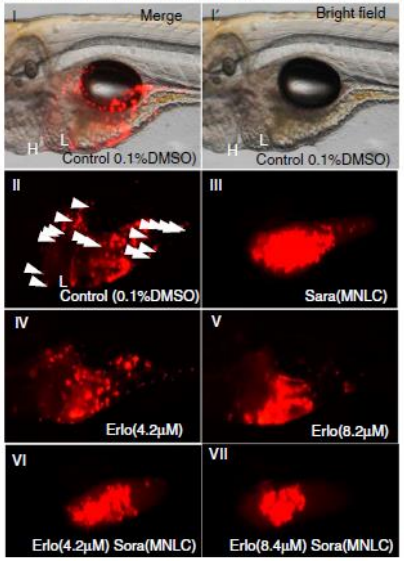
Rank	Drug1#	Drug2#	CI (1#+2#) 4+1	3+2	2+3	1+4	Result
1	Gefitinib	Everolimus	0.67±0.03	0.73±0.02	0.74±0.05	0.66±0.04	
2	Gefitinib	Thalidomide	0.82±0.01	0.89±0.03	0.77±0.05	0.86±0.02	
3	Gefitinib	Tamoxifen	0.68±0.03	0.22±0.05	0.25±0.03	0.86±0.01	
5[a]	Erlotinib	Tamoxifen	0.36±0.08	0.23±0.06	0.45±0.04	0.63±0.02	
7	Sorafenib	Tamoxifen	0.71±0.04	0.67±0.04	0.3±0.07	0.22±0.04	
8	Gefitinib	Toremifene	0.89±0.01	0.55±0.12	0.75±0.07	0.76±0.02	
10[a]	Erlotinib	Sorafenib	0.61±0.09	0.55±0.05	0.28±0.01	0.21±0.03	
13	Sorafenib	Dasatinib	0.62±0.04	0.54±0.02	0.76±0.06	0.75±0.01	
16	Gefitinib	PD98059	0.61±0.05	0.73±0.01	0.8±0.04	0.89±0.02	
6	Gefitinib	Sorafenib	1.09±0.05	0.44±0.14	0.85±0.08	0.65±0.06	
12[a]	Gefitinib	BIBW-2992	1.04±0.02	0.76±0.01	0.89±0.05	0.93±0.03	
14	Sorafenib	Everolimus	0.82±0.02	1.05±0.10	0.98±0.04	1.23±0.09	
18[a]	Everolimus	BIBW-2992	3.47±0.07	0.78±0.07	1.31±0.02	0.94±0.04	
19[a]	Tamoxifen	Flavopiridol	3.32±0.15	0.86±0.02	2.6±0.05	0.92±0.01	
20[a]	Erlotinib	Flavopiridol	0.95±0.02	0.93±0.04	0.84±0.06	1.46±0.02	
21[a]	Gefitinib	Erlotinib	1.18±0.04	0.97±0.02	0.96±0.05	0.96±0.02	
22[a]	Erlotinib	Sunitinib	0.54±0.02	0.77±0.05	1.09±0.16	0.73±0.08	

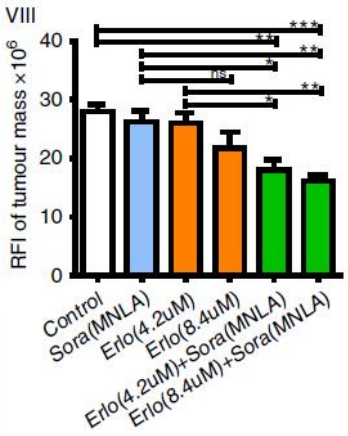
b

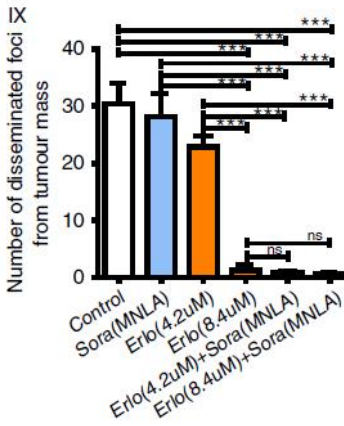
Literature-reported 5 synergistic pairs

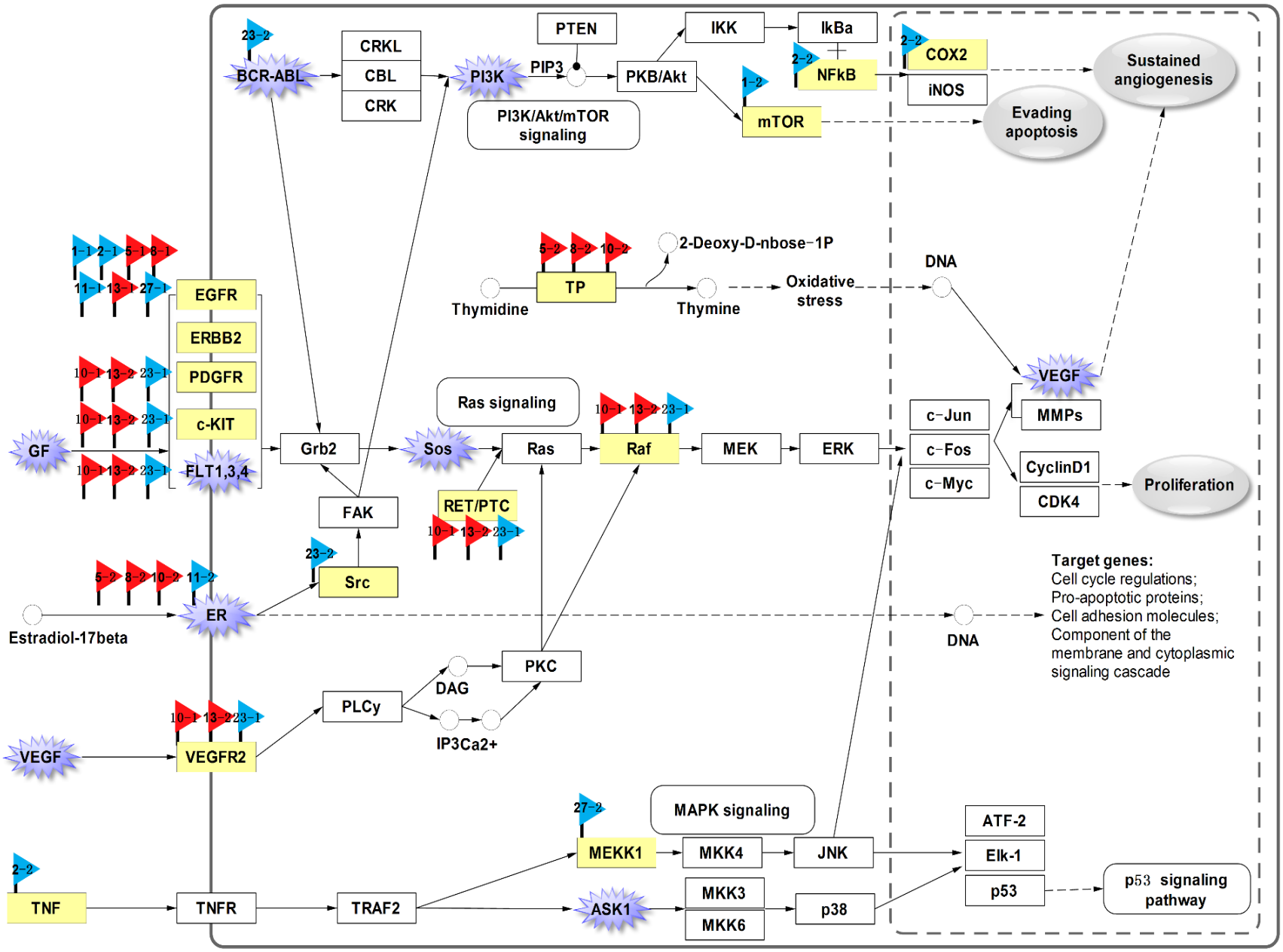
Rank	Drug1#	Drug2#	Cancer type	Result
4	Gefitinib	Everolimus	Breast cancer	
11	Gefitinib	Thalidomide	Breast cancer	
9	Gefitinib	Tamoxifen	Colorectal cancer	
15[a]	Gefitinib	Erlotinib	Small cell lung cancer	
17[a]	Erlotinib	Sunitinib	Endometrial cancer	

Co-administrations of Erlotinib and Sorafenib inhibited tumor growth and dissemination *in vivo*.



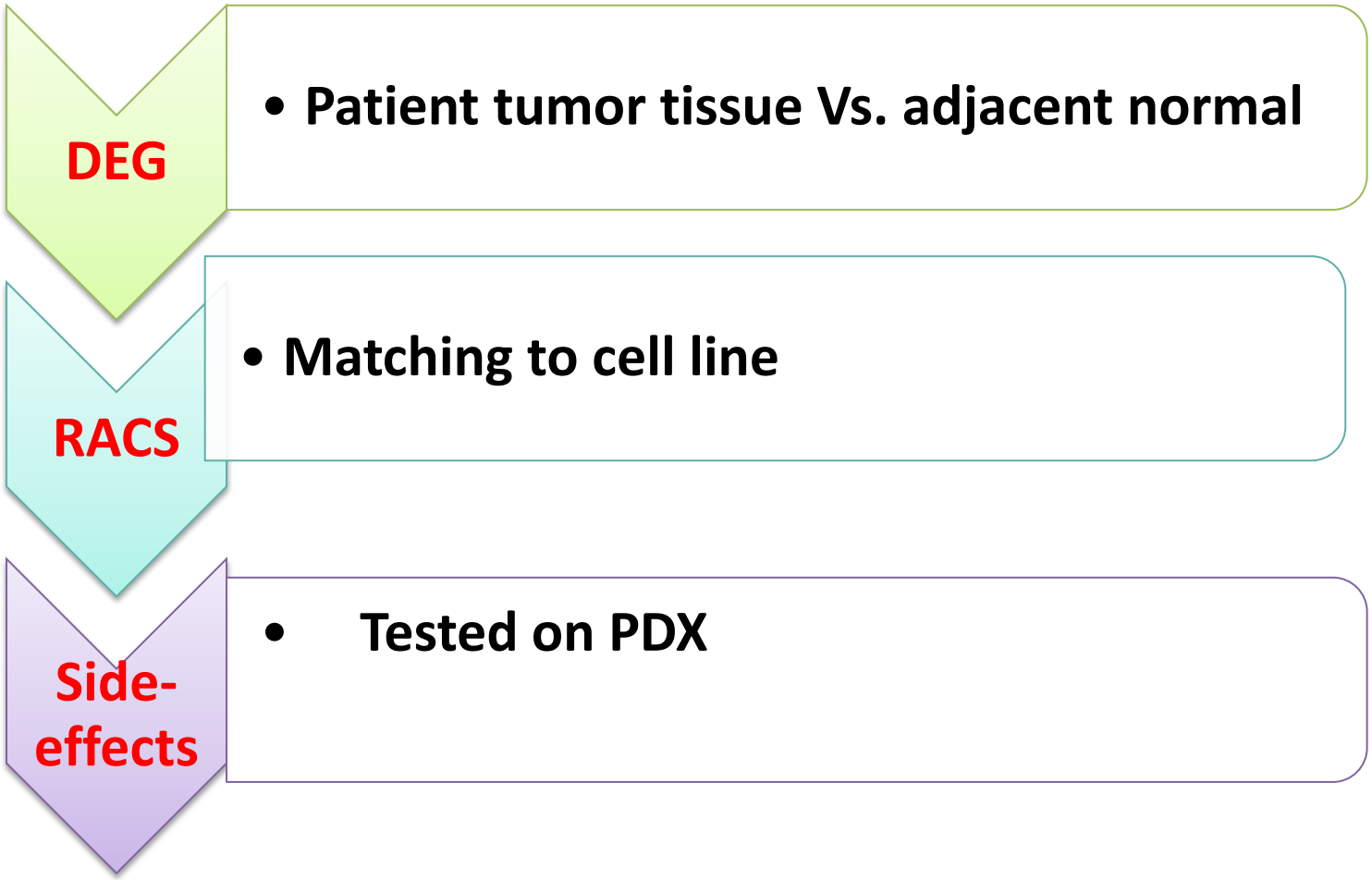






Yi Sun, et al, Nature Communications,Sep 28, 2015.

Clinical Application



Summary

RACS

1. Synergistic anti-cancer drugs based on personal genomics profile
2. Being optimized for clinical application
3. Side-effect tested on PDX before clinical use

- Natural compounds may be highly useful in designing future synergistic therapy.

Thanks!

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1. *Brief Bioinform. 2017* May
2. *Nature Communications*, 2015, Sep 28
3. *Brief Bioinform.* 2012 Aug 11.
4. *Nucleic. Acids Res.*2011 Jan;39:D1055-9.
5. *Journal of Proteome Research*, 2010 Apr 5;9(4):1648-58.
6. *Nat. Rev. Drug Discov.*, 2009 Feb;8(2):111-28.
7. *Drug Discovery Today;* 2009 14(11-12):579-588.

- 863 funding
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- Shanghai Center of Bio-information Technology