Searching Synergistic Drug Combinations to Treat Cancer

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Overview

• MOA of drug synergy

• Model of anti-cancer synergistic drugs: RACS

• Validation

• Clinical cases
Background

• Single drug therapies:
  – Limited effects
  – Side effects

• Drug combinations:
  – Synergy
  – Low toxicity
  – Challenge: huge amounts of possible combinations

<table>
<thead>
<tr>
<th>Number of Single drugs</th>
<th>Number of all 2-drug combinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>45</td>
</tr>
<tr>
<td>100</td>
<td>4,950</td>
</tr>
<tr>
<td>1000</td>
<td>499,500</td>
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No. of FDA-Approved Drugs

The number of total drugs

The number of drug combinations


total combination
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.

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

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

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

**Drug target-based features**

- Positive samples (labeled samples)
- Background samples (unlabeled samples)
- Reshuffling
- Statistical test
- Discriminating features derived from targeting networks:
  - MI, Dis, DCI, EffD, EffB, EffE, MP,U

**Genomics-based parameters**

- Single drug-treated microarrays
- Reshuffling
- Parameters derived from drug-treated gene expression profile
- Statistical test
- Filtering parameters:
  - DEG_Overlap, Pathway_Coverage

**Manifold ranking**

- Preliminary ranking
  - Rank | Drug pair | Synergy possibility
  - 1    | stars    | 0.61
  - 2    | stars    | 0.58
  - 3    | dots     | 0.58

**Final ranking**

- Rank | Drug pair | Synergy possibility
- 1    | dots     | 0.53
- 2    | dots     | 0.50
- 3    | dots     | 0.49
- 4    | dots     | 0.47
- 5    | dots     | 0.46
- 6    | dots     | 0.43
NCI-DREAM challenge: Best 0.61

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

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

0.61: Merely better than random guess

Detailed Ranking of DIGRE

![Graph showing predicted ranking versus DREAM ranking with a PC-index of 0.61]
Significant improvement on DREAM data of DLBCL cells
Significant improvement on DREAM data of DLBCL cells
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

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

- **DEG**
  - Patient tumor tissue Vs. adjacent normal

- **RACS**
  - Matching to cell line

- **Side-effects**
  - Tested on PDX
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

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