Systematic studies of anticancer therapeutic combinations

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Anticancer drug combinations: the problem

• Achieving long-term control of advanced cancers will likely require effective combinations of drugs

• Knowledge of the spectrum of therapeutic combinations that might prove efficacious in particular genetic or molecular tumor contexts has been limited by issues of throughput and multiplicity
Anticancer drug combinations: possible solution

- Launch a large-scale cell line based effort to conduct in vitro combination screens
- Analogous to NCI60 pharmacologic screening effort carried out by DTP over many years
- Would leverage several advances in cell line characterization, screening throughput, and tool compound availability over the past decade
Preclinical cell line combinatorial screening project: Scenario 1A

• FNLCR-centered effort:
  – Augment available cancer cell line collection to enhance representation of particular lineages and genetic contexts (e.g., go beyond ATCC resource)
    • Add to this collection with a call to the community to contribute output of new cancer cell line generation
  – Purchase or synthesize a robust collection of chemical probes that interrogate known mechanisms of action relevant to tumor genetic or signaling pathways
    • Add to this collection with a call to the community each year
  – Create the capability to perform synergy screens of at least 5000 combinations per year (e.g., ~50 combinations across ~100 individual cell lines per year)
Example of scalable synergy screening format

Chelsea Place, unpublished
Preclinical cell line combinatorial screening project: Scenario 1B

- Combined FNLCR and distributed effort
  - Issue RFA or initiate partnerships with extramural efforts to perform combinatorial screening efforts
  - At the start, convene workshop to establish streamlined approaches, protocols, standards, etc.
  - Generate a network of connected investigators focused on combinatorial screens on particular cell line or compound collections
  - Include efforts that systematically address alternative dosing combinations
PRISM: A method for multiplexed cell line sensitivity studies

Molecular barcodes integrated into cell line genomes
Pools of 25-100 lines per well of 384-well plate
Sensitivity of 10’s of cells in background of 10,000

with permission from Todd Golub
PRISM recovers genotype-phenotype relationships

25 NSCLC cell lines grown together

viability

0 50 100%

Untreated PCR no DNA

EGFR inhibitor

ALK inhibitor

Puromycin

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Koivunen et al., Clin. Cancer Res. 2008
PRISM in vivo

24 NSCLC lines:
20 EGFR wt
4 EGFR mutant

Subcutaneous injection

immunodeficient (NSG) mice

palpable tumor

erlotinib

vehicle

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Andrew Kung
Preclinical cell line combinatorial screening project: Scenario 2

- “Anchored” combinatorial screening approach
  - Here, one member of a combination is fixed and the others are varied
  - For example, use fixed dose range of class I-selective PI3 kinase inhibitor to enable combinatorial screens in large collections of PTEN-null or PIK3CA-mutant cancer cell lines
  - This strategy may conceivably allow higher-order “compound synergy screens” that involve a fixed dose of one compound and dose ranges of two additional compounds
Preclinical cell line combinatorial screening project: Scenario 3

- Combined pharmacological and genetic perturbation approach
  - This is essentially a synthetic lethal screening approach applied to large cell line collections with key genetic or molecular commonalities
  - In these cell line contexts, “lesion A” is the drug, whereas “lesion B” is a shRNA or CRISPR library
  - The goal would be to conduct genome-scale synthetic lethal screens across large numbers (e.g., dozens) of cell lines that share a common genetic/molecular feature, whereas most prior screens have been limited to very small numbers of cell line contexts
  - (A related approach has been proposed to support the RAS project)
Examples of cell line genetic/molecular contexts and “anchor” compounds

<table>
<thead>
<tr>
<th>Genetic context</th>
<th>“Anchor” therapeutic</th>
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<tbody>
<tr>
<td>KRAS-mutant cancers</td>
<td>MEK inhibitor or class 1 PI3K inhibitor</td>
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<tr>
<td>BRAF-mutant cancers</td>
<td>RAF/MEK inhibitors</td>
</tr>
<tr>
<td>PIK3CA-mutant cancers, PTEN-null cancers</td>
<td>Alpha- plus beta-selective PI3K inhibitors</td>
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<tr>
<td>ERBB2-amplified breast cancer</td>
<td>HER-2 inhibitor</td>
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<tr>
<td>p16 deleted or cyclin D amplified cancers</td>
<td>CDK inhibitor</td>
</tr>
<tr>
<td>Myc-amplified cancers</td>
<td>Bromodomain inhibitor?</td>
</tr>
<tr>
<td>NRAS-mutant cancers</td>
<td>MEK or ERK inhibitor</td>
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Advantages of a FNLCR-sponsored combinatorial cell line screening effort

- Clearly on the critical path to durable control of cancer
- Represents a natural extension/upgrade of a longstanding strength of FNLCR (NCI-60 screening)
- Ability to blend FNLCR-centered efforts with coordinated extramural projects
- Opportunity to bring new technologies (e.g., PRISM?) into the FNLCR envelope
- Areas of synergy with the RAS project