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

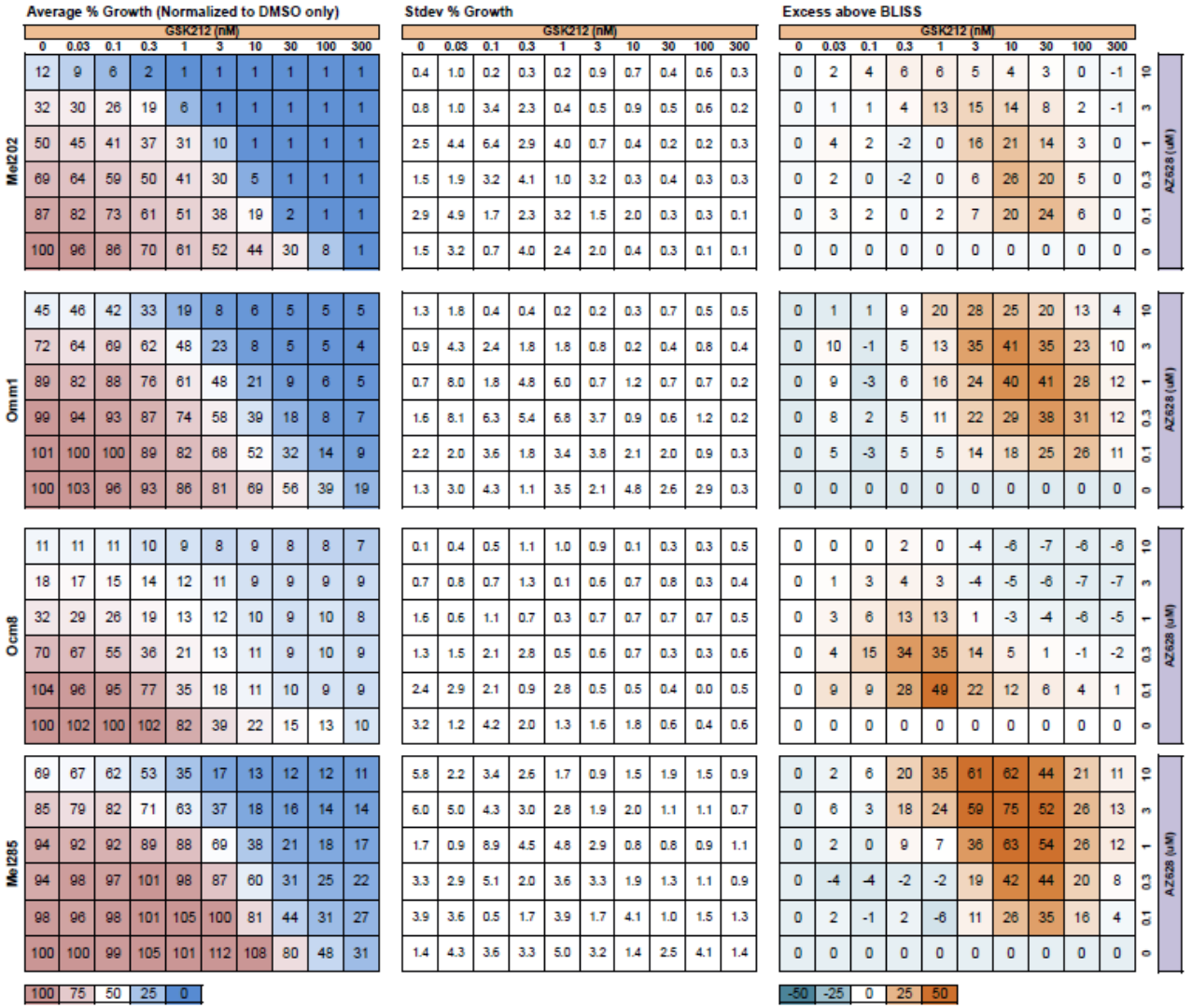
Anticancer drug combinations: possible solution

- 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

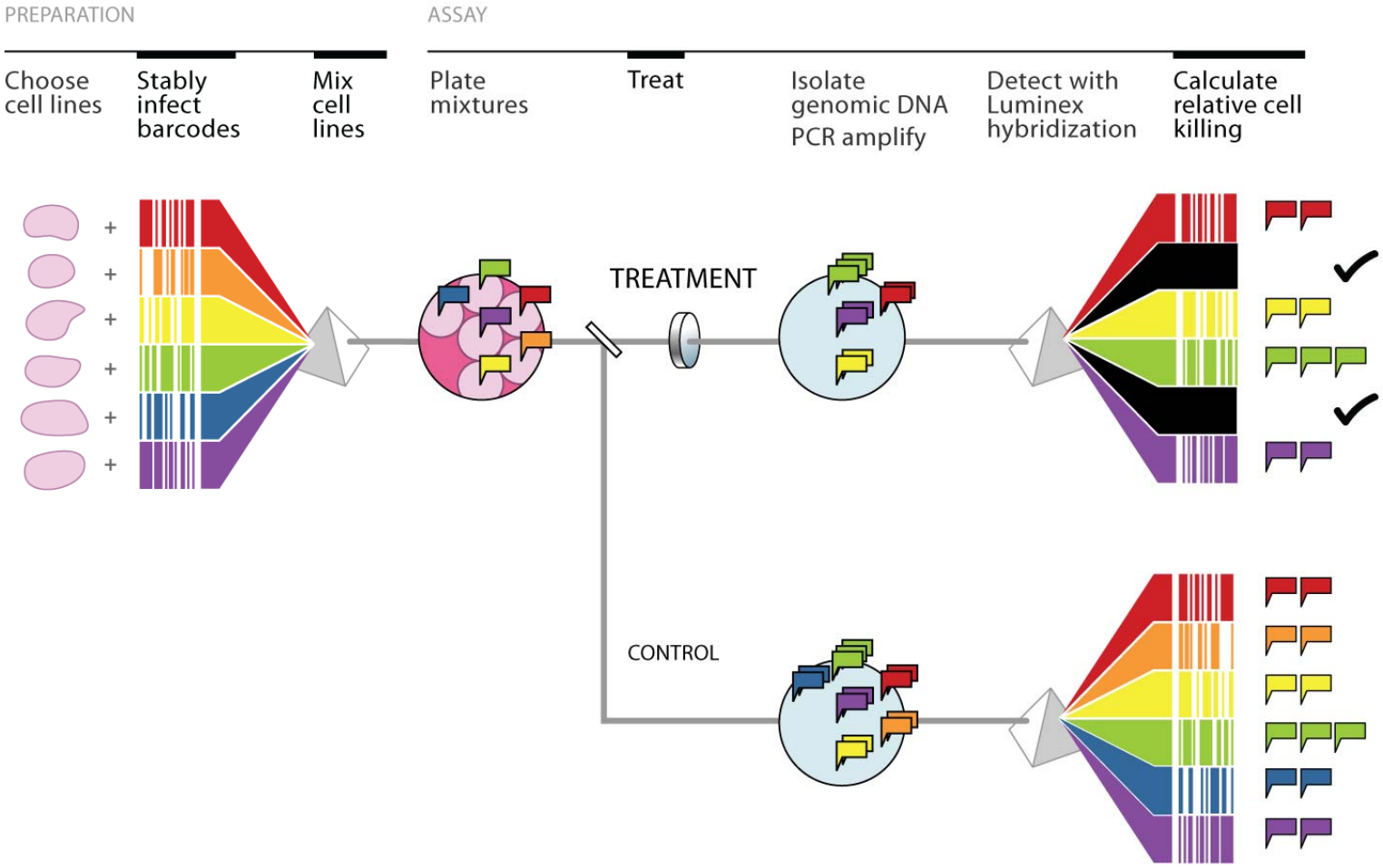


Chelsea Place, unpublished

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

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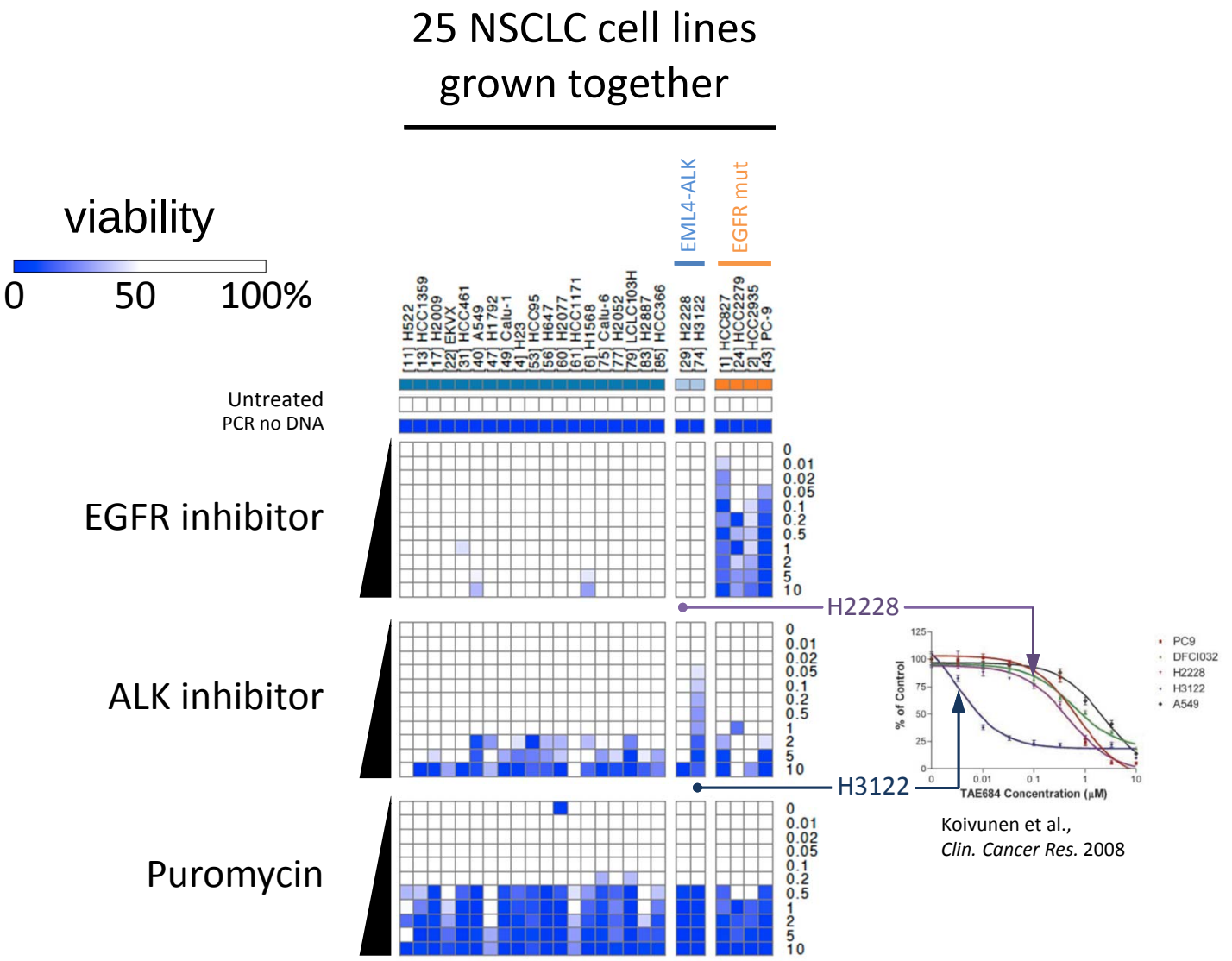
PRISM recovers genotype-phenotype relationships



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PRISM *in vivo*

24 NSCLC lines:

20 *EGFR wt*

4 *EGFR mutant*

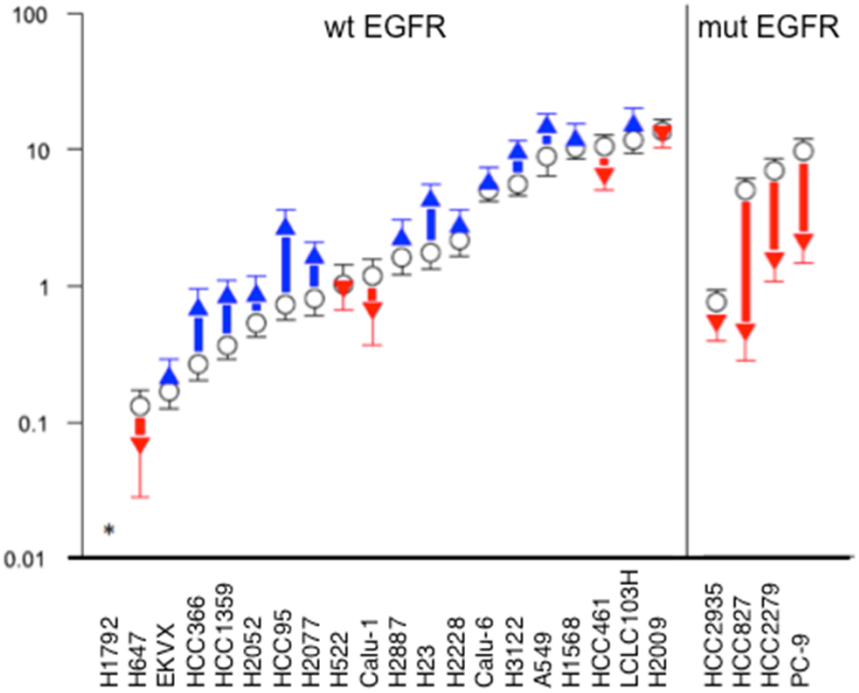
Subcutaneous injection

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

Genetic context	“Anchor” therapeutic
KRAS-mutant cancers	MEK inhibitor or class 1 PI3K inhibitor
BRAF-mutant cancers	RAF/MEK inhibitors
PIK3CA-mutant cancers, PTEN-null cancers	Alpha- plus beta-selective PI3K inhibitors
ERBB2-amplified breast cancer	HER-2 inhibitor
p16 deleted or cyclin D amplified cancers	CDK inhibitor
Myc-amplified cancers	Bromodomain inhibitor?
NRAS-mutant cancers	MEK or ERK inhibitor

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