CELL-BASED SCREENS OF DRUG COMBINATIONS AT NCI

SUSAN HOLBECK

DEVELOPMENTAL THERAPEUTICS PROGRAM

DIVISION OF CANCER TREATMENT AND DIAGNOSIS

NATIONAL CANCER INSTITUTE

Division of Cancer Treatment and Diagnostics

NATIONAL CANCER INSTITUTE

NATIONAL INSTITUTES OF HEALTH

NEED FOR DRUG COMBINATIONS

Single agents are rarely curative

Even responding patients will relapse

Strategies

"Rational" combinations hit multiple nodes in a pathway, or hit parallel pathways

Comprehensive approaches to combination discovery

- siRNA
- empiric screens

TWO PARALLEL COMBINATION DRUG SCREENS AT NCI

- **Comprehensive screen of approved cancer drugs**

- **Combination screening of investigational agents**

THE NCI ALMANAC

TESTING ~ ALL PAIRWISE COMBINATIONS OF APPROVED CANCER DRUGS

The NCI ALMANAC (A Large Matrix of AntiNeoplastic Agent Combinations)

Currently just over 100 small molecule oncology drugs are FDA-approved.

Test all possible pairwise combinations of these

- ~5000 drug pairs

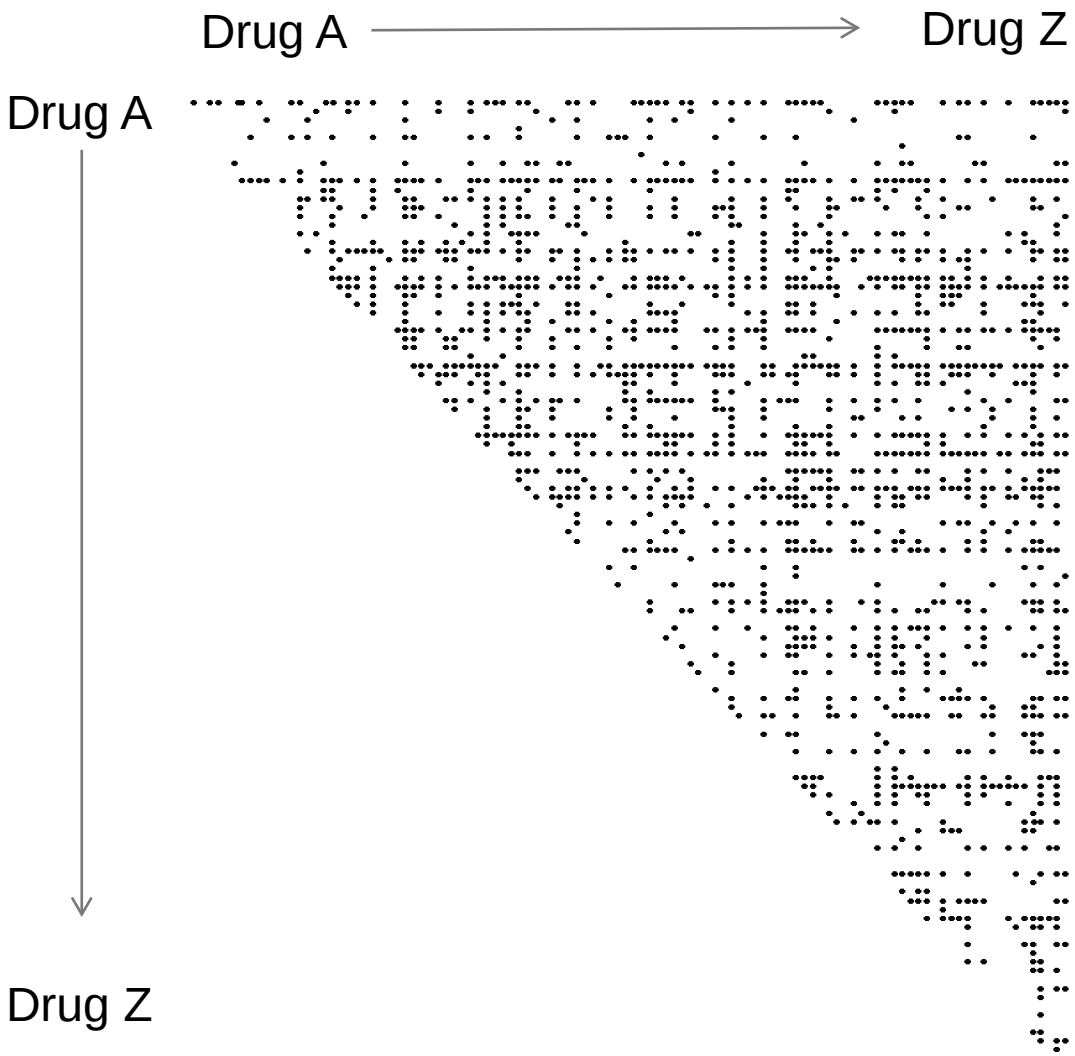
Test each drug pair in each of the cell lines in the NCI-60 panel.

- ~300,000 experiments
- ~4.3 million wells

Screen run at 2 contract locations

- ~$4 million over 2 years

Approved drug pairs in clinicaltrials.gov



Search for “cancer”
Parse out drug names

Only about one quarter of approved drug pairs are found.

Approx. 3700 approved drug pairs have no clinical trials.

Can we discover beneficial pairs that can be put into clinical trials?

WHY THE NCI-60?

Large database of drug action

Large catalog of molecular characterization

Most of the cell lines will grow as xenografts

Molecular characterization of the xenografts derived from the NCI-60, at passages 1, 4 and 10

Possibility for predictive biomarker discovery

MOLECULAR CHARACTERIZATION OF THE NCI-60

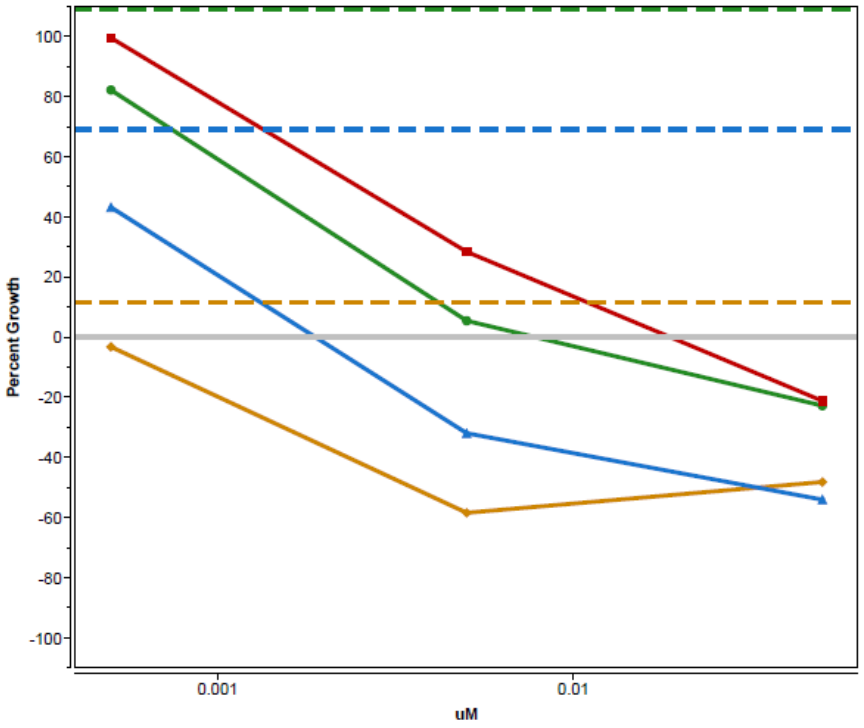
Larger scale projects

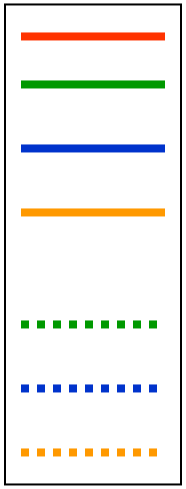
- Exome sequencing
- mRNA microarrays
  - multiple platforms
- SNP arrays
- CNV
- Proteins by MS
- Proteins by RPPA
- miRNA
- CpG methylation
- Metabolomics

Smaller focused projects

- SNPs in cancer relevant genes
- Protein and phospho-proteins
- Activity measurements
- Karyotype

COMBO DATA: EXAMPLE
3X3 CONCENTRATION MATRIX
COMBO SCORE



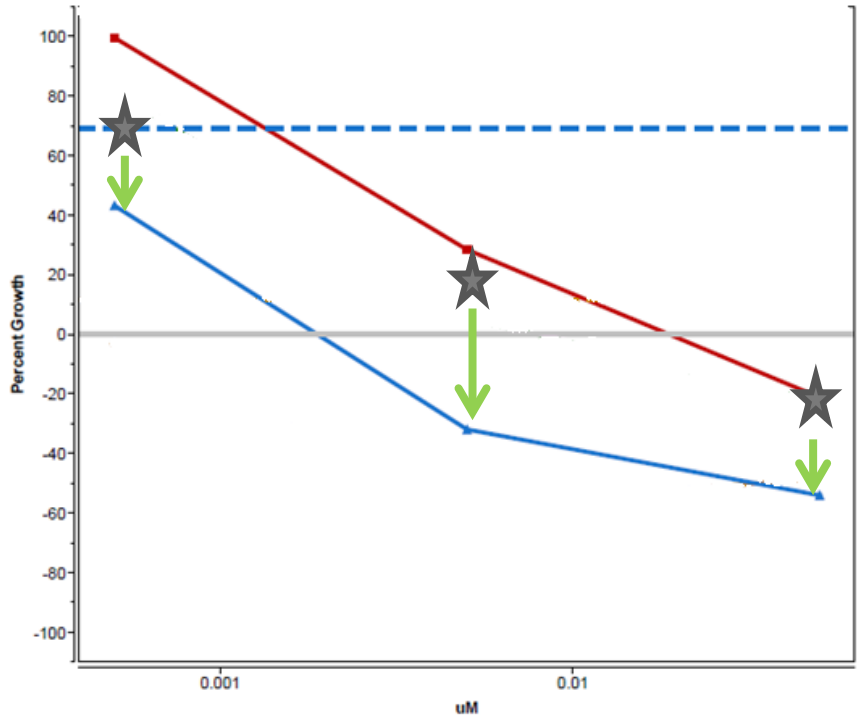


Agent 1 alone
Agent 1 + low dose Agent 2
Agent 1 + med dose Agent 2
Agent 1 + high dose Agent 2

low dose Agent 2 alone
med dose Agent 2 alone
high dose Agent 2 alone

microM agent 1

COMBO DATA: EXAMPLE
3X3 CONCENTRATION MATRIX
COMBO SCORE

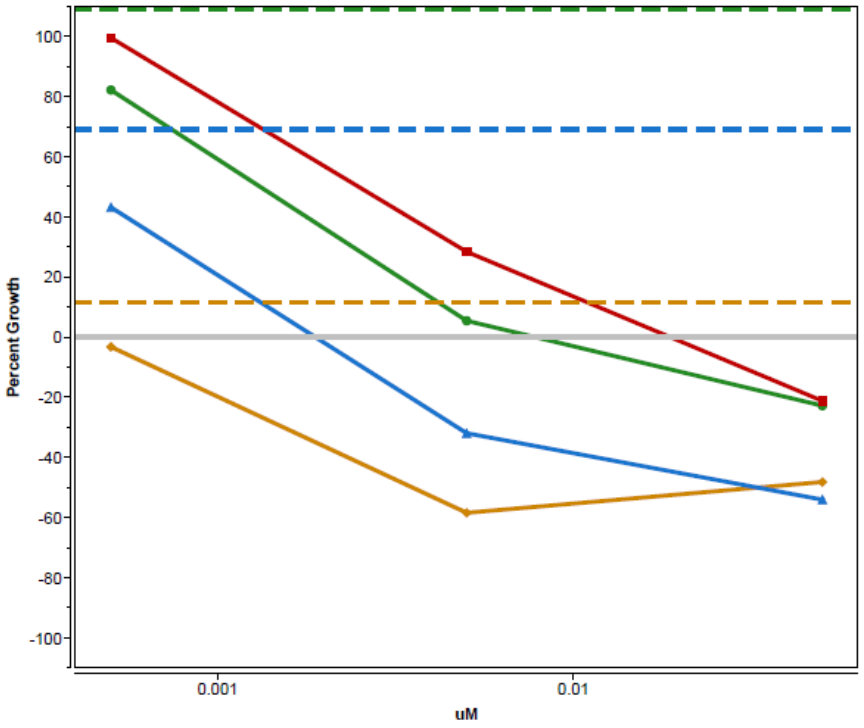


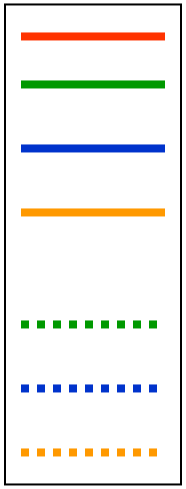
microM agent 1

Agent 1 alone
Agent 1 + med dose Agent 2
med dose Agent 2 alone

Expected if additive
Increased over additive

COMBO DATA: EXAMPLE
3X3 CONCENTRATION MATRIX
COMBO SCORE



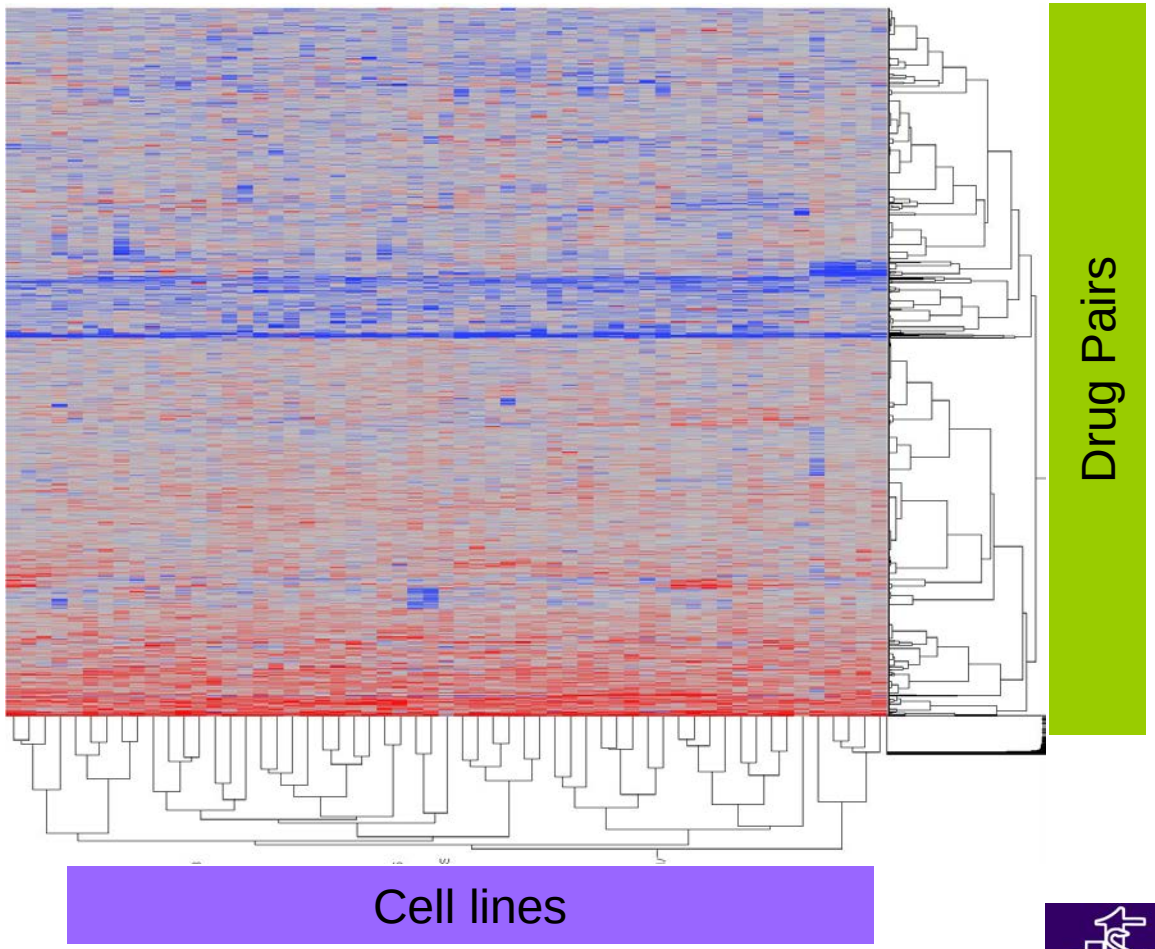


Agent 1 alone
Agent 1 + low dose Agent 2
Agent 1 + med dose Agent 2
Agent 1 + high dose Agent 2

low dose Agent 2 alone
med dose Agent 2 alone
high dose Agent 2 alone

microM agent 1

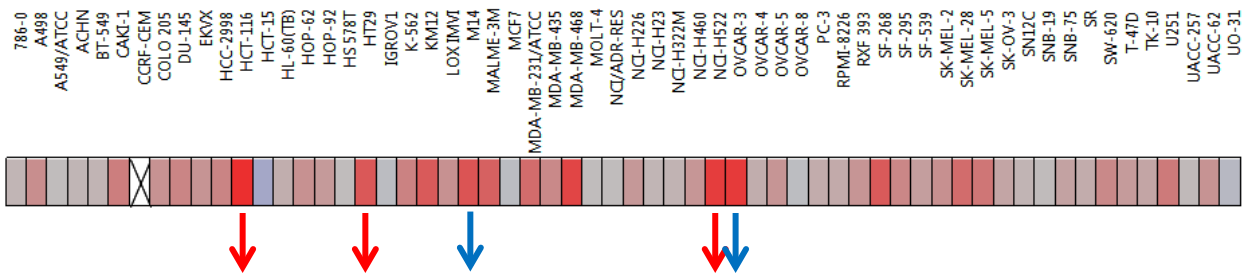
COMBO SCREEN RESULTS COMBOSCORE BASED ON BLISS INDEPENDENCE



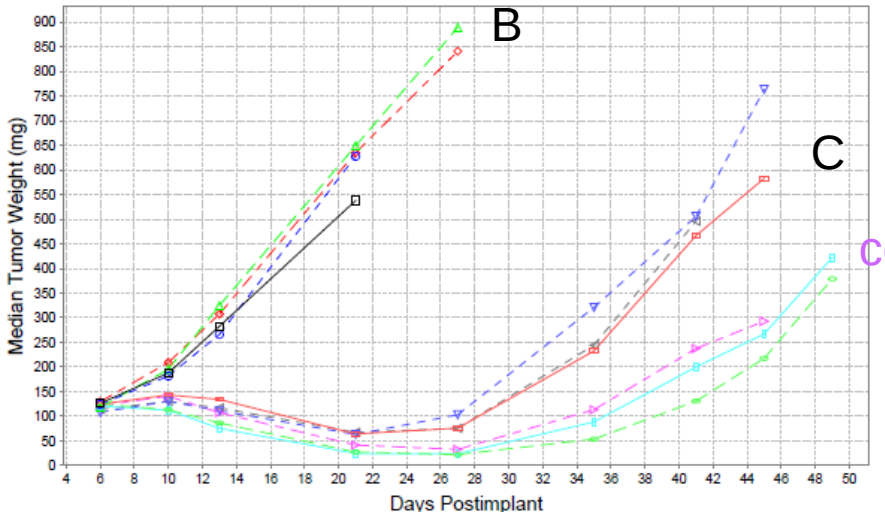
Red =
Better than additive

Blue =
Worse than additive

EXAMPLE 1: BORTEZOMIB + CLOFARABINE



Red arrows: Combo active in xenografts
Blue arrows: no xenograft benefit over single agents



Trial of the Combination of Bortezomib and Clofarabine in Adults With Relapsed Solid Tumors

This study is currently recruiting participants. (see Contacts and Locations)

Verified July 2014 by National Institutes of Health Clinical Center (CC)

Sponsor:
National Cancer Institute (NCI)

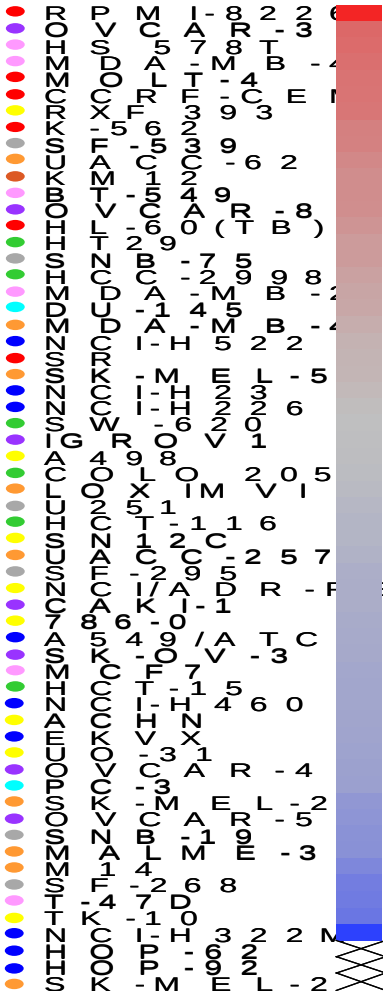
Information provided by (Responsible Party):
National Institutes of Health Clinical Center (CC) (National Cancer Institute (NCI))

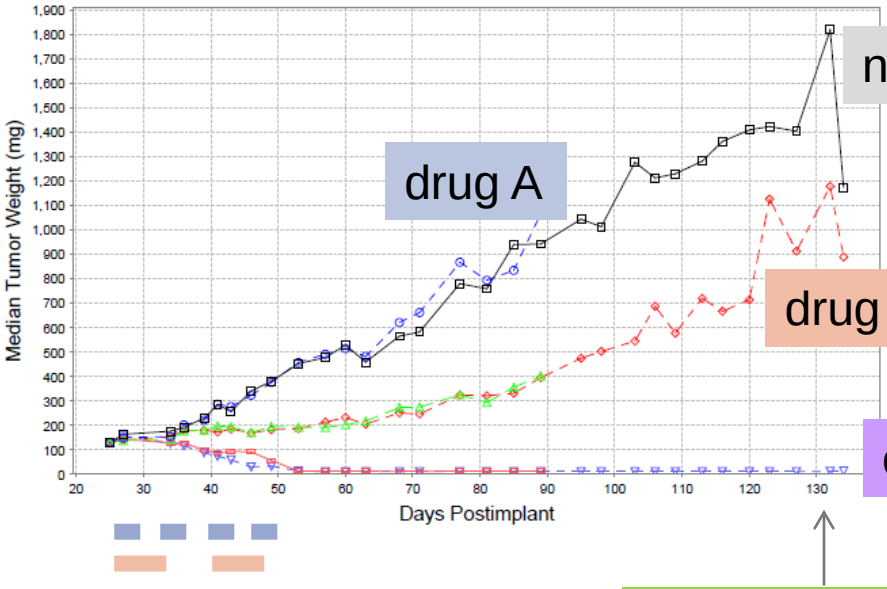
ClinicalTrials.gov Identifier:
NCT02211755

First received: August 6, 2014
Last updated: September 23, 2014
Last verified: July 2014
History of Changes

EXAMPLE 2:
A DRUG PAIR THAT IS BENEFICIAL IN TRIPLE-NEGATIVE BREAST CANCER MODELS

TNBC





Period of drug treatment

Tumor-free animals months after treatment completed

NCI ALMANAC DATA TO BE PUBLIC

Manuscript in final stages

Web site developed to

- **Browse the data**
- **Display the data**
- **Download the data**

NCI ALMANAC Study Results

The NCI ALMANAC study results may be navigated using four different methods. You may choose to view the data from a heat map containing the relative results from all drug pairs tested. You may also select a specific drug pair from drop-down lists. Alternatively, you may view the data from a heat map containing all results from a particular drug and optionally a modifier mechanism. Finally, you may generate a heat map showing how well each mechanism tested for a particular drug.

Navigate NCI ALMANAC results by:

- **Analyzing a heat map with results from all drug pairs**
- **Selecting both drugs in the combination from lists**
- **Selecting a test drug and optionally a modifier mechanism**
- **Finding an effective modifier mechanism from a heat map**

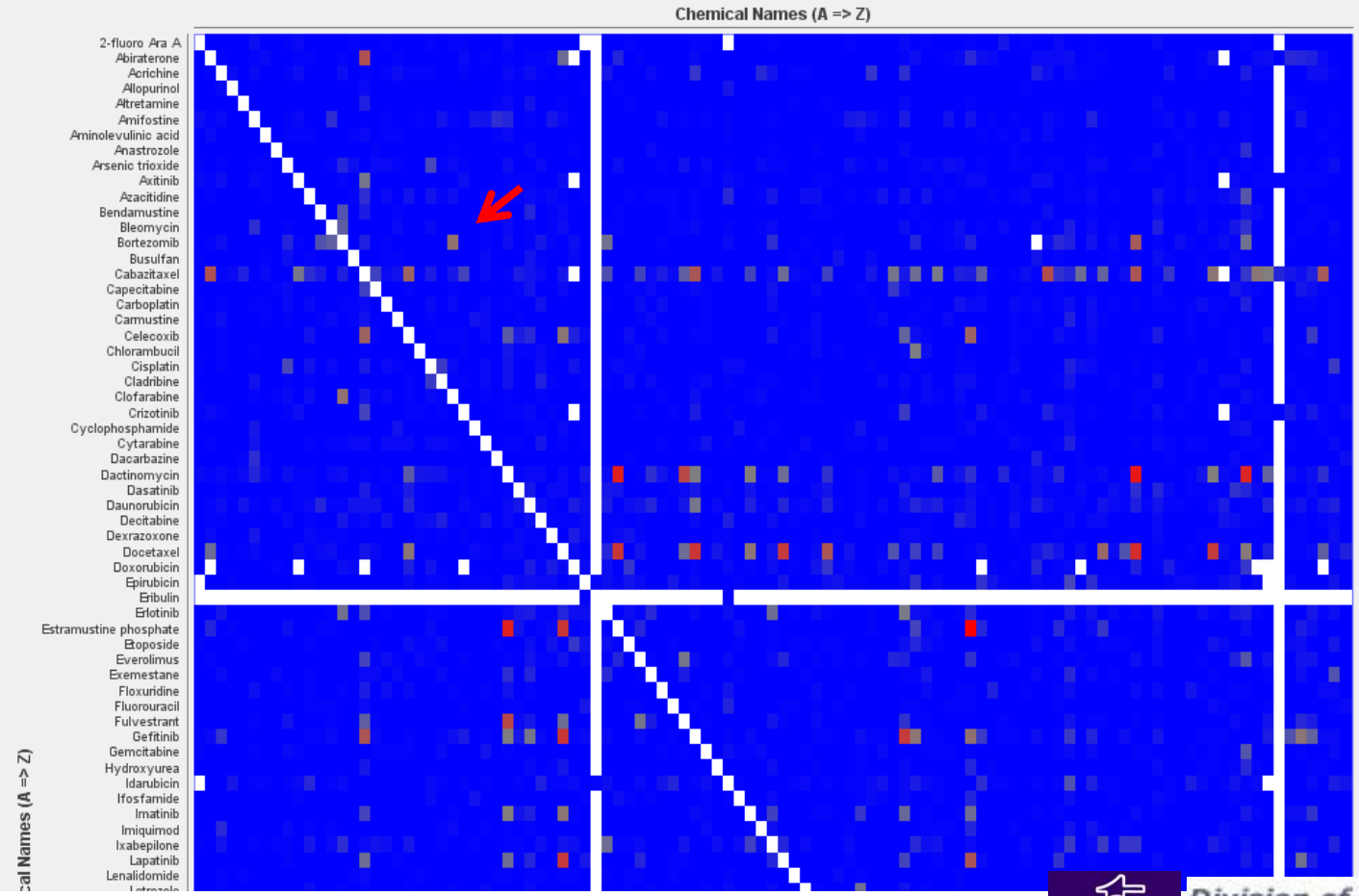
NCI ALMANAC Study Results

The heat map below represents a set of drugs tested in pairs in order to evaluate their collective efficacy against various types of cancer. As shown in the scale, the drug pairs with the higher score values in the heat map are represented by the color red, and generally indicate an effective result against the 60 cancer cell lines that were tested in these studies. Drugs in the heat map are alphabetized. Scroll over a cell to see its drug pair and calculated score value.

Click a cell in the heat map below to view results by cell line for a particular drug combination.

Calculation Type:

- (•) Number of Cell Lines Meeting Goal Efficacy
- ( ) Mean Score From All Cell Lines Tested
- ( ) Maximum Score From All Cell Lines Tested



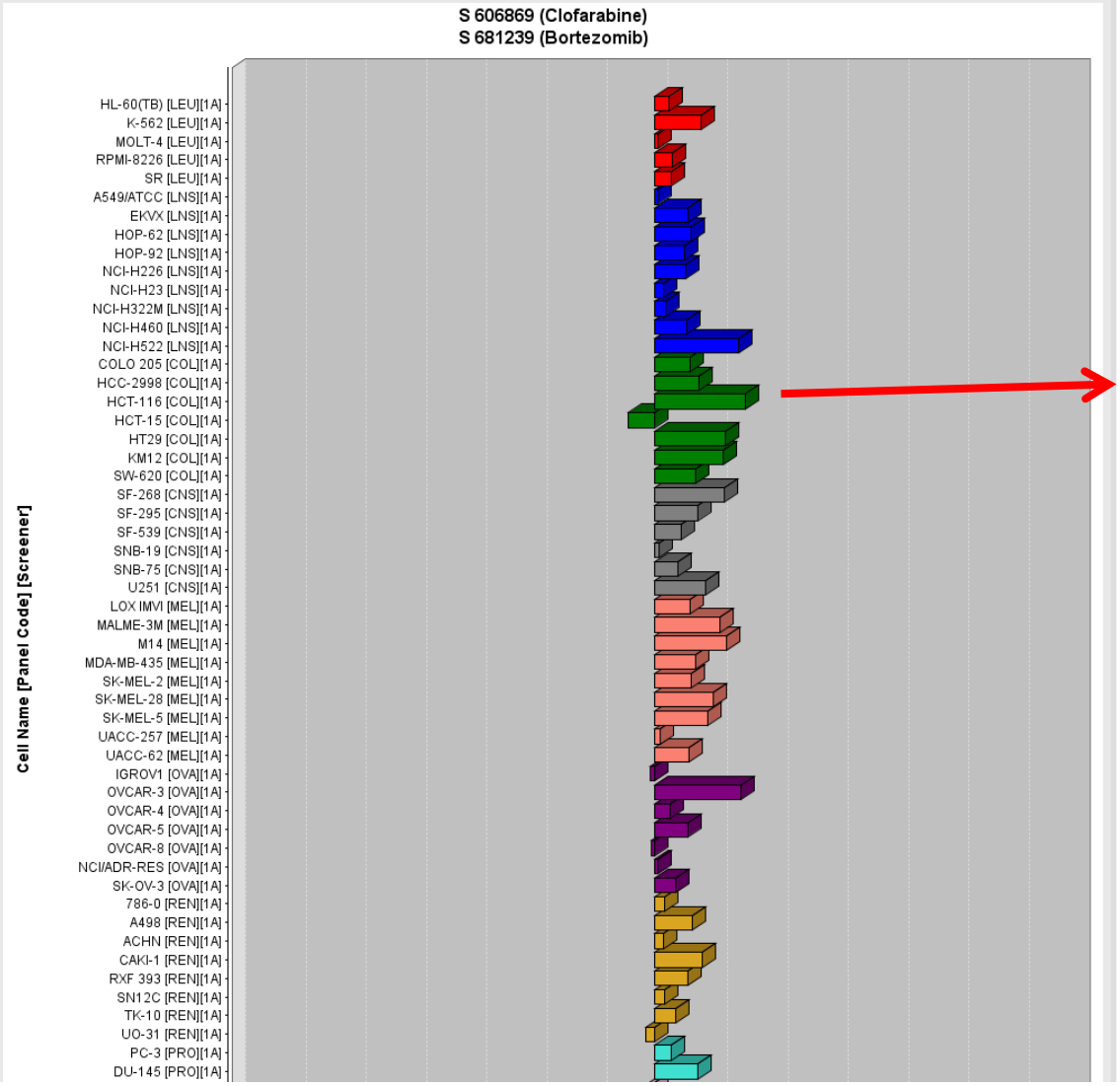
Division of Cancer Treatment and Diagnostics

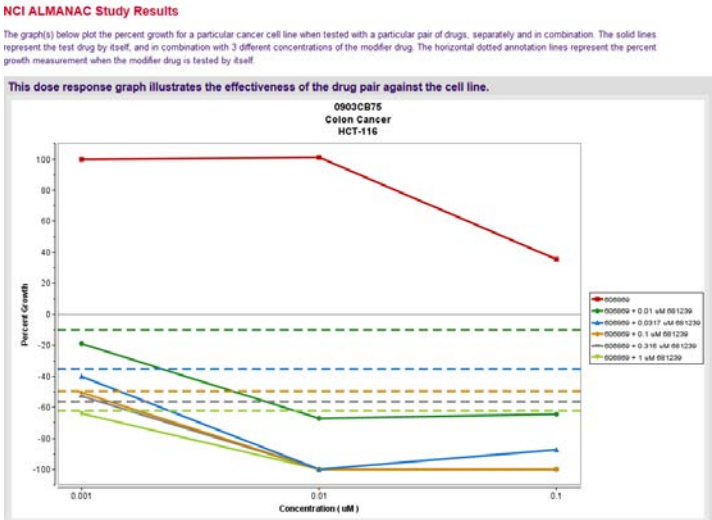
National Cancer Institute

National Institutes of Health

NCI ALMANAC Study Results

Click a bar in the chart below to view the detailed results for a particular cancer cell line.





Division of Cancer Treatment and Diagnostics

NATIONAL CANCER INSTITUTE

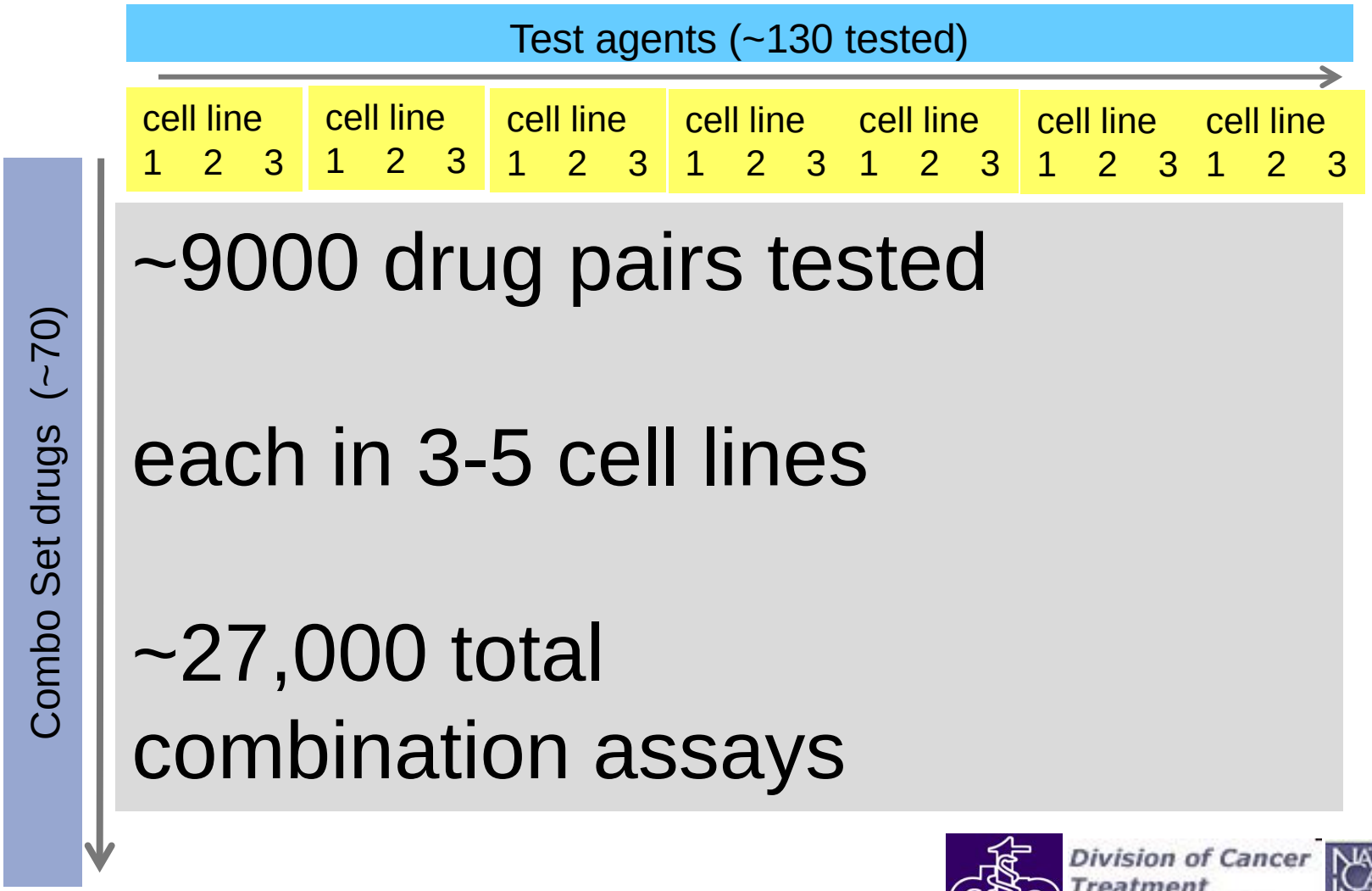
NATIONAL INSTITUTES OF HEALTH

TWO PARALLEL COMBINATION DRUG SCREENS AT NCI

- Comprehensive screen of approved cancer drugs

- **Combination screening of investigational agents**

COMBO TESTING OF INVESTIGATIONAL AGENTS



~9000 drug pairs tested

each in 3-5 cell lines

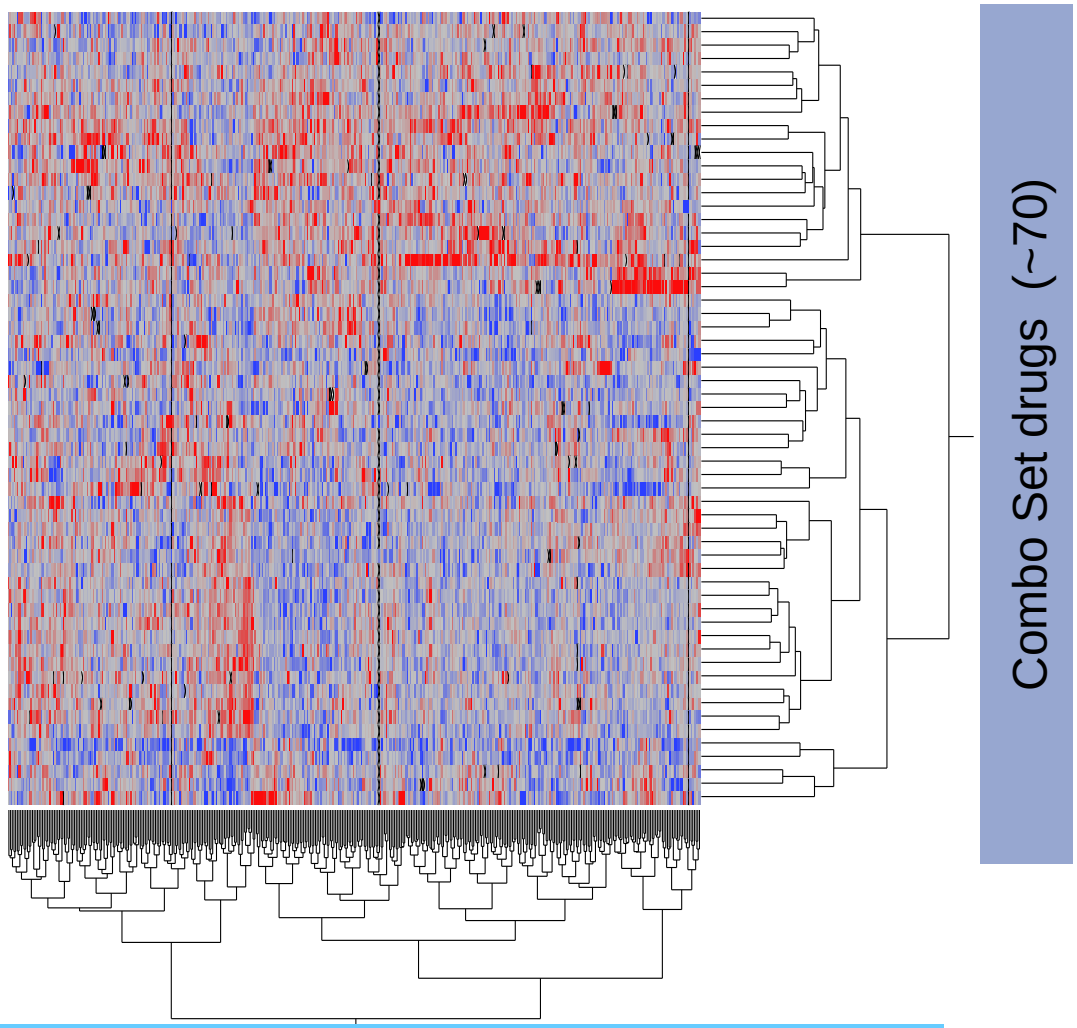
~27,000 total combination assays

Division of Cancer Treatment and Diagnostics

NATIONAL CANCER INSTITUTE

NATIONAL INSTITUTES OF HEALTH

INVESTIGATIONAL COMBO DATA

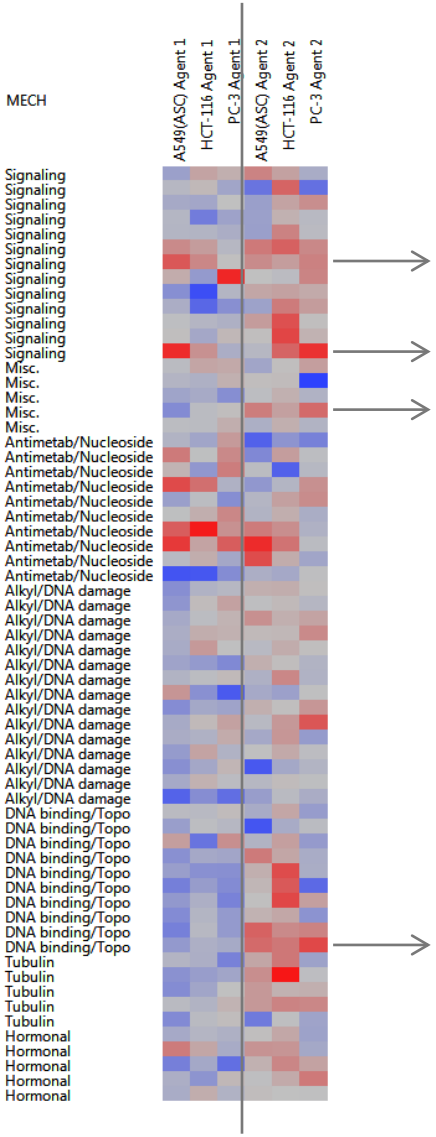


Test agents (~130 tested) and cell lines (3-5)

EXAMPLES FROM THE INVESTIGATIONAL COMBO SCREEN

- **Test agents with the same molecular target have similar activity patterns**
- **Patterns of combination benefit reveal a potential new mechanism for an investigational agent**

AGENTS WITH SAME TARGET
SIMILARITIES AND DIFFERENCES



Drug 1

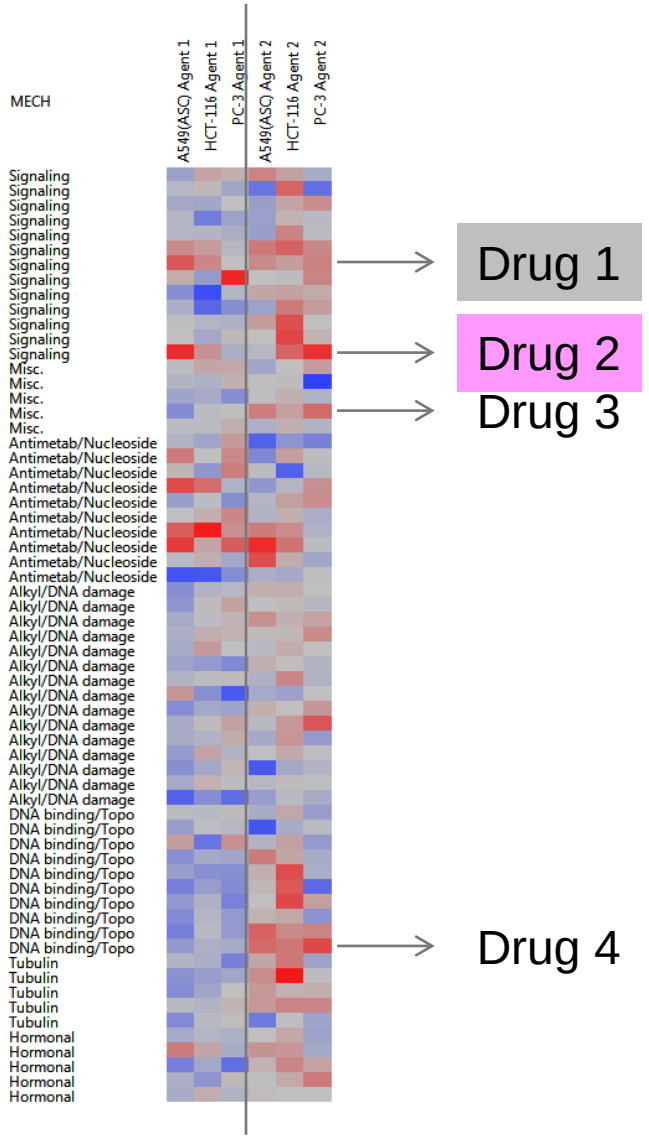
Drug 2

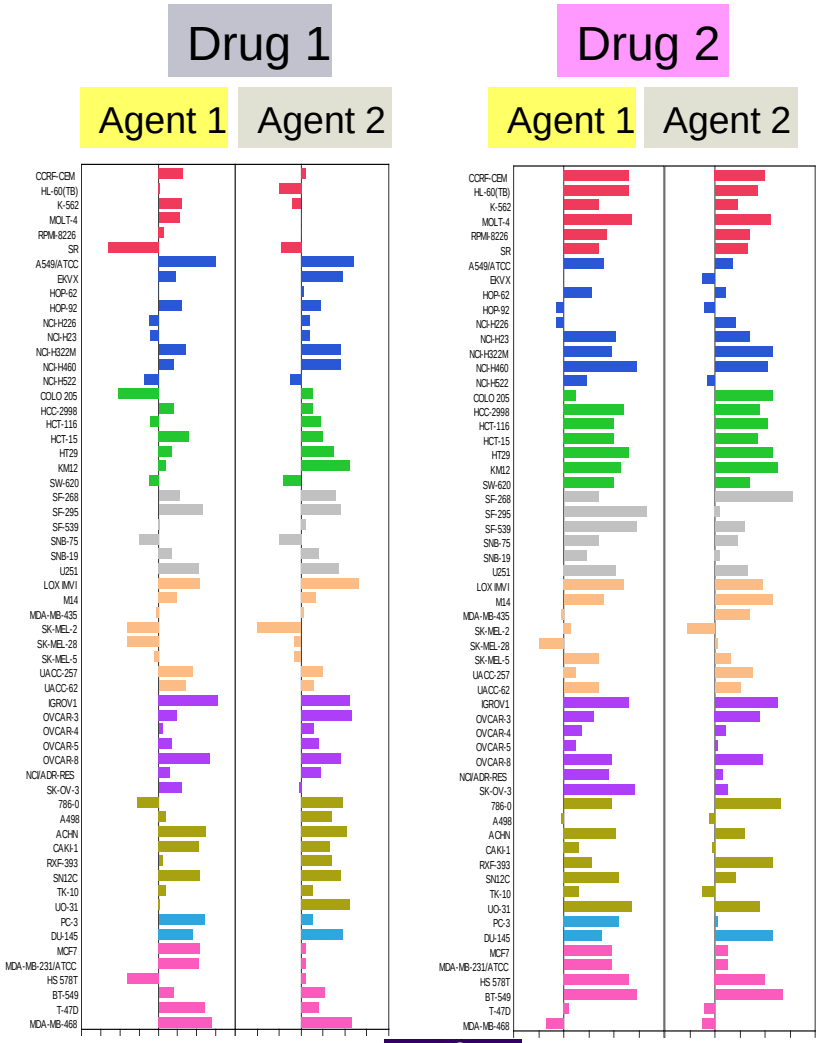
Drug 3

Drug 4

Select 4 "hits"
Test each of these drugs in the NCI-60
- with Agent 1
- with Agent 2

DRUGS 1 & 2 COMBINED WELL WITH BOTH AGENTS



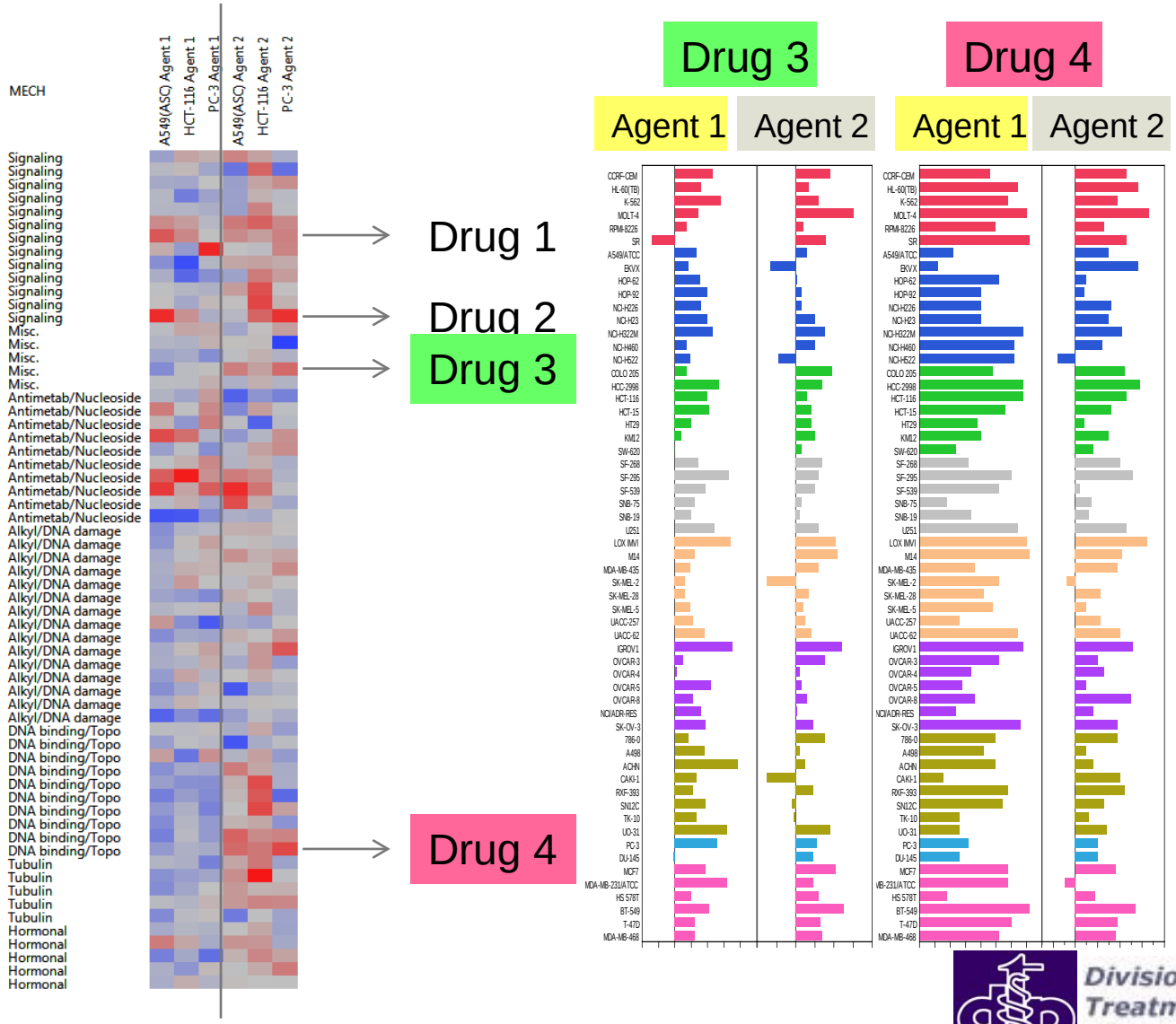


Division of Cancer Treatment and Diagnostics

NATIONAL CANCER INSTITUTE

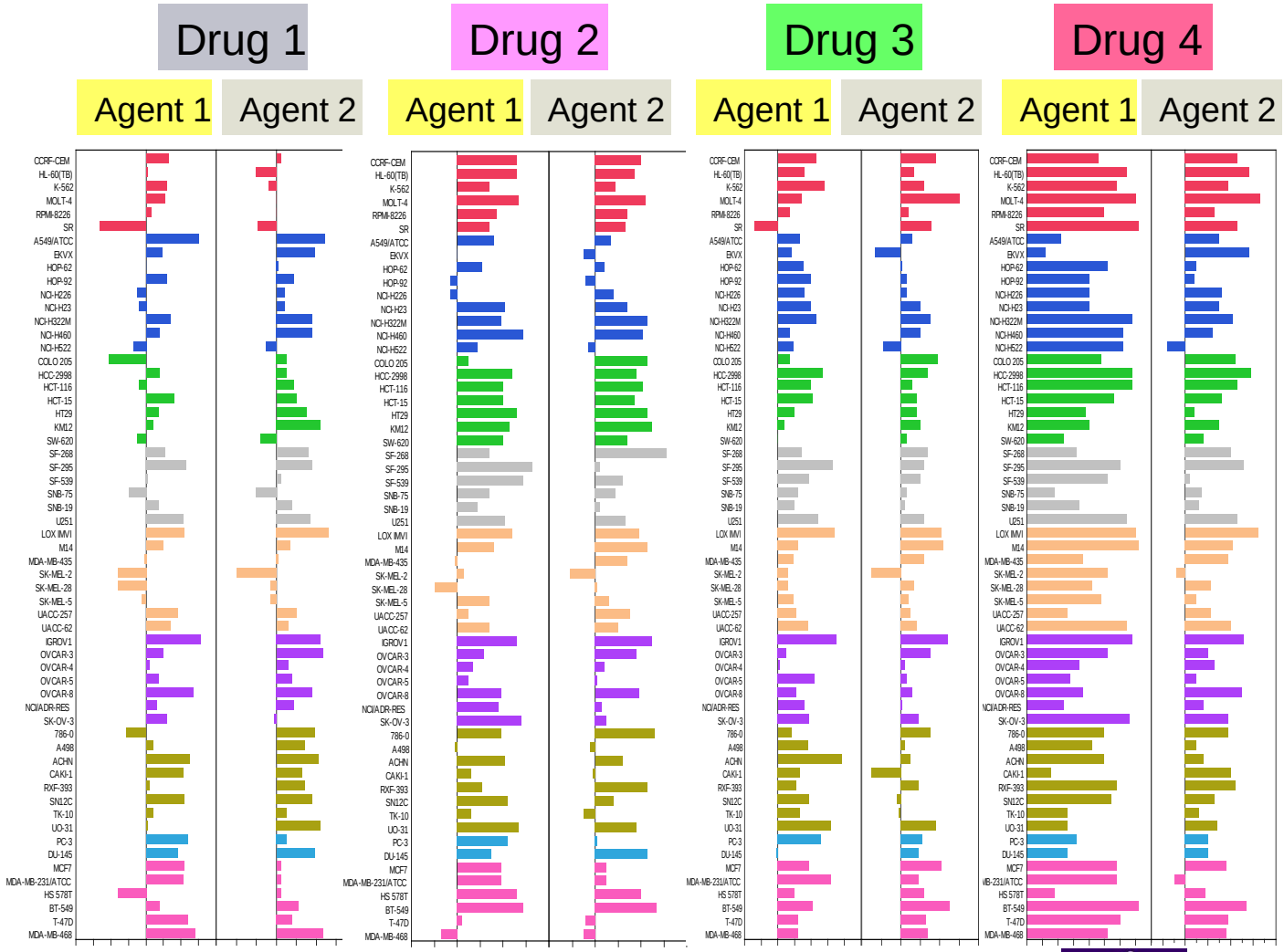
NATIONAL INSTITUTES OF HEALTH

DRUGS 3 & 4 COMBINED WELL WITH ONLY AGENT 2



2 AGENTS WITH SAME TARGET

ADDITIONAL TESTING WITH 4 HITS FROM THE SCREEN

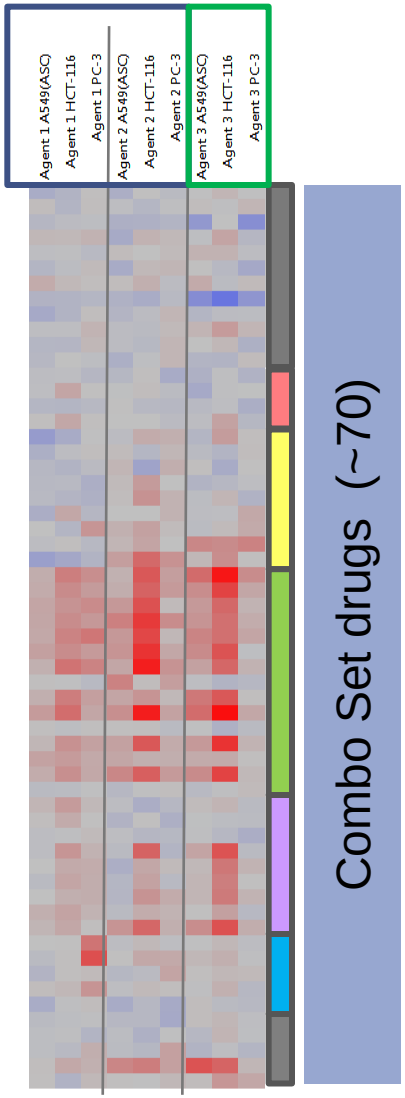


Cell line profiles are similar between Agent 1 & Agent 2

Patterns of cell lines benefiting differ between the 4 drugs

Possibility to think about "MATCH" style combo trials

COMBO SCREEN: CLUES AS TO MECHANISM

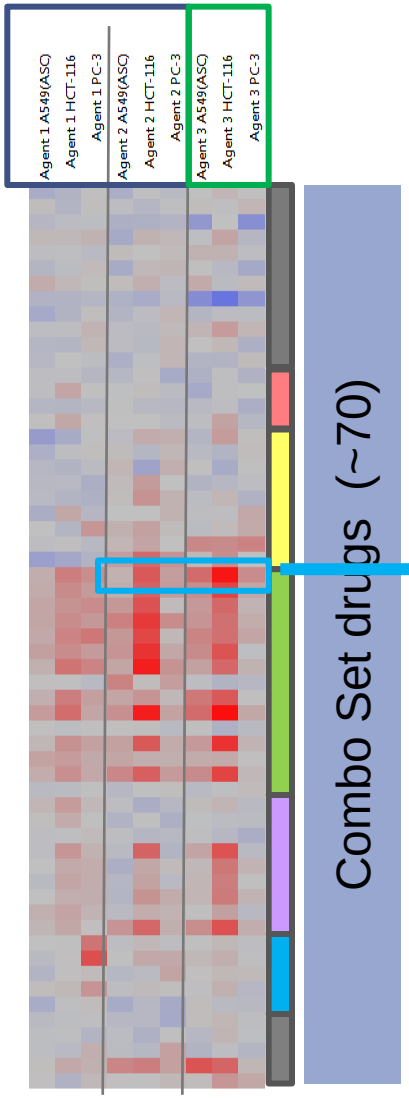


2 agents expected to sensitize cells to DNA damage

1 agent with completely different target -- or maybe not

Similar patterns of Combo Set drugs that give greater than additive activity with these 3 Test Agents

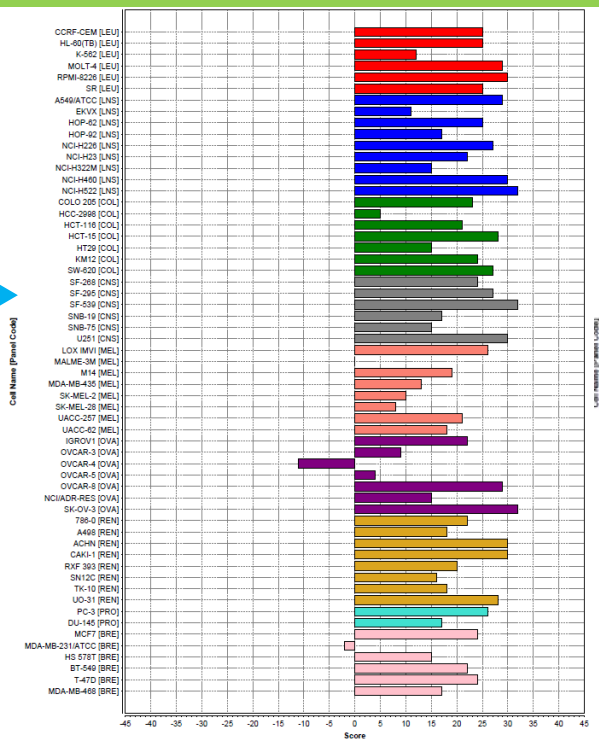
COMBO SCREEN: CLUES AS TO MECHANISM

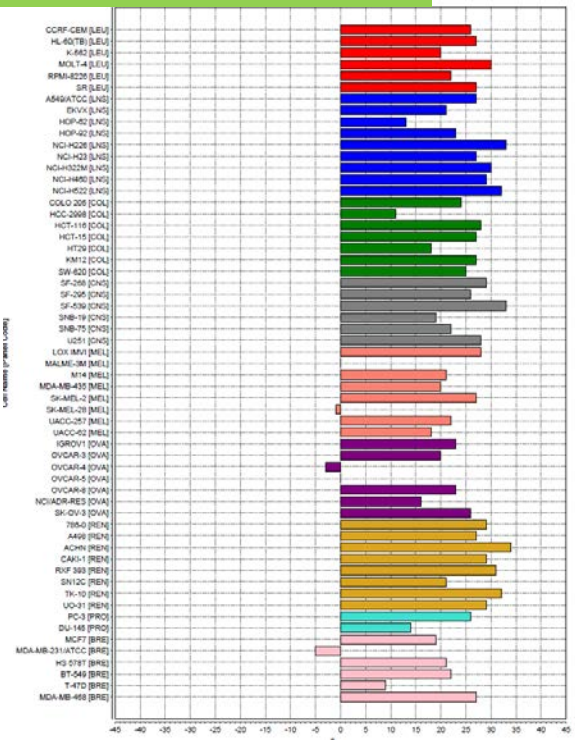


2 agents expected to sensitize cells to DNA damage

1 agent with completely different target -- or maybe not

Similar patterns of cell lines with combo benefit





Division of Cancer Treatment and Diagnostics

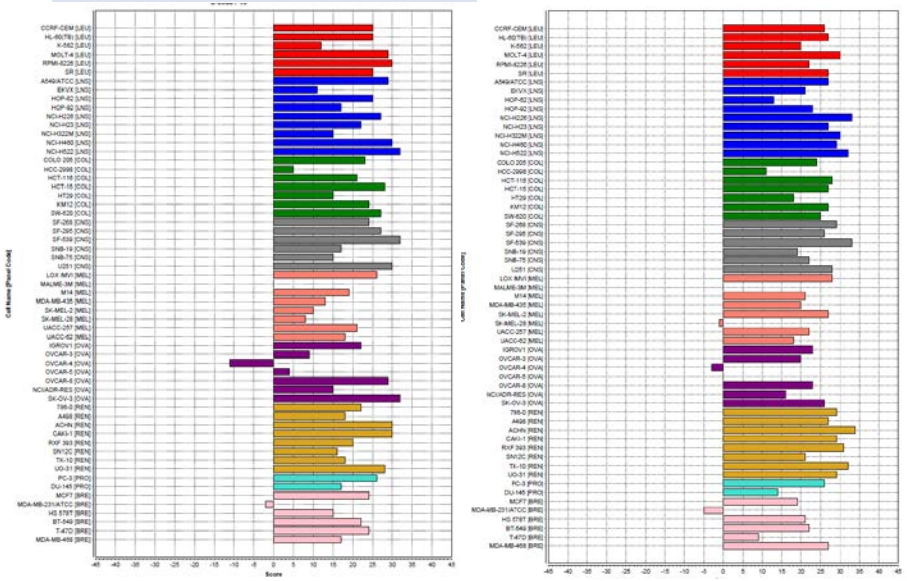
NATIONAL CANCER INSTITUTE

NATIONAL INSTITUTES OF HEALTH

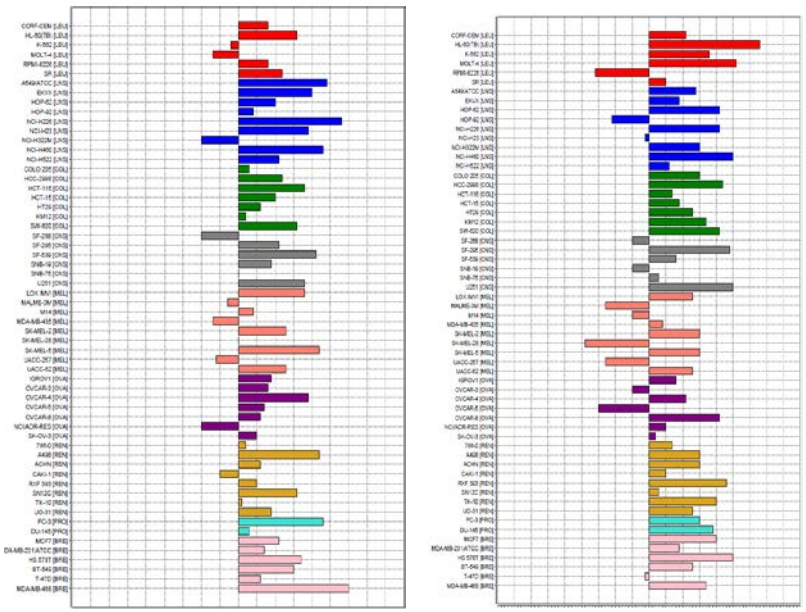
TEST COMBINATION WITH 2 ADDITIONAL AGENTS

Agent 1: expected to synergize with Alkylating agents

Agent 2: Unexpected results



2 additional agents with similar mechanism to that reported for Agent 2



SUMMARY

NCI ALMANAC - tested ~ 5000 drug pairs of FDA-approved oncology drugs in 60 cell lines

- One novel combination has entered clinical trials
- Trial design in progress for a second novel combination

NCI Investigational Combination Screen - tested ~ 9000 drug pairs in 3-5 cell lines

- Similarities and differences for agents with the same or overlapping mechanisms
- Surprising result suggests different mechanism for an investigational agent

PEOPLE

Jim Doroshow

Jerry Collins

Dick Camalier

Myrtle Davis Millin

Melinda Hollingshead

Marie Hose

Shivaani Kummar

Dianne Newton

Eric Polley

Larry Rubinstein

Karen Schweikart

Penny Svetlik

SRI International

Univ of Pittsburgh