Preclinical combination studies using cancer cell lines

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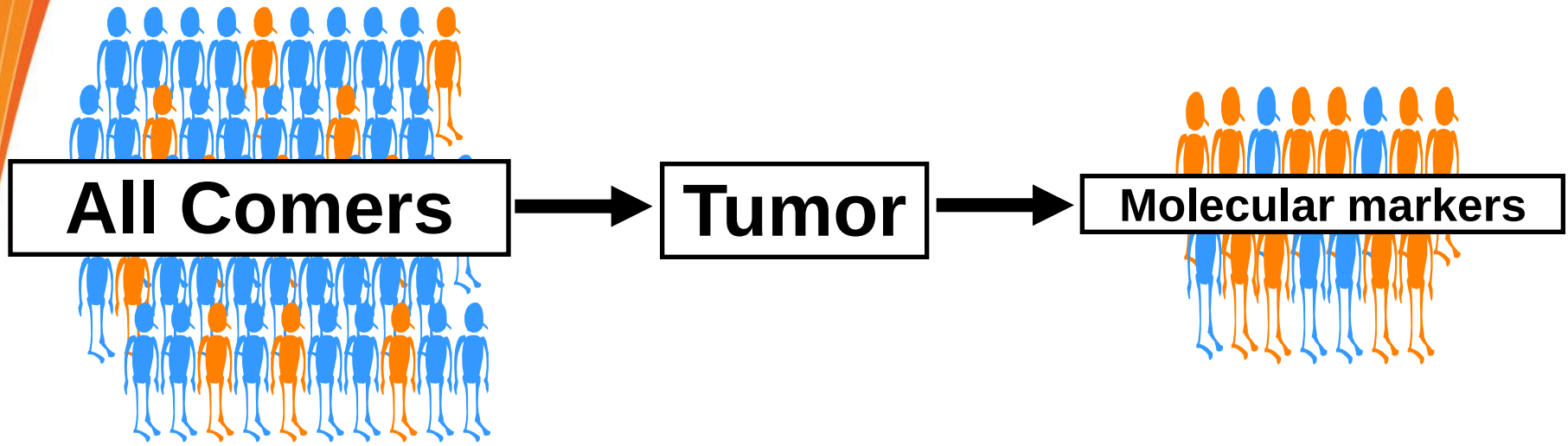
A population-based analysis of cancer cell lines: *Can we model clinical trials?*

"300 Cell Line Project"



The challenge:

- To identify tumor types more likely to respond
- To identify biomarkers that predict response
- To define the relationship of the predictors to the biology of the inhibitor

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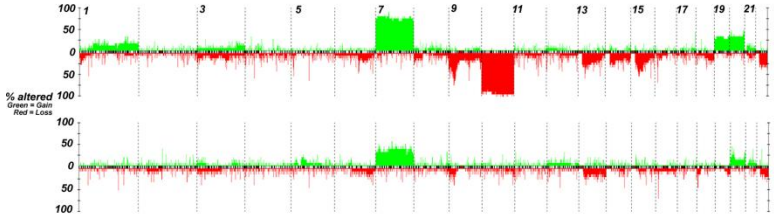
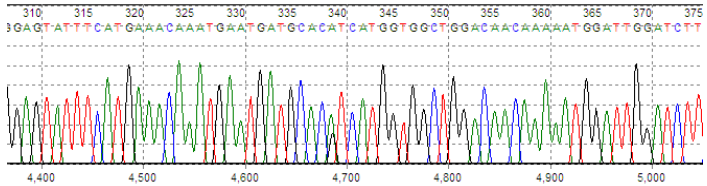
Cancer Cell Line Analysis

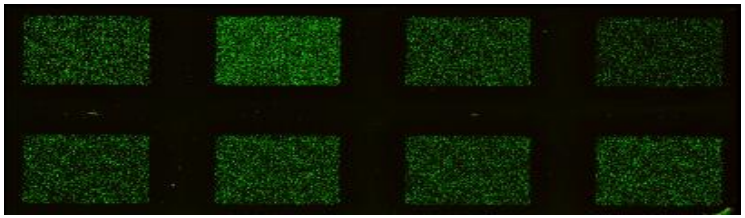
High density genome-wide DNA copy number analysis



Selected sequence analysis of cancer and target genes

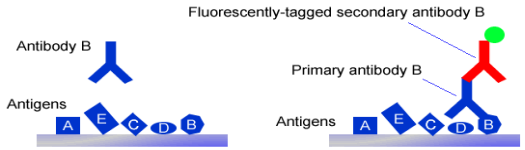


mRNA profiling (Affymetrix)
miRNA profiling (Agilent)



Reverse Phase Protein Microarray

Phosphoprotein analysis
(pre and post treatment)



Metabolomic analysis
(cancer cell lines; isogenic cell lines)

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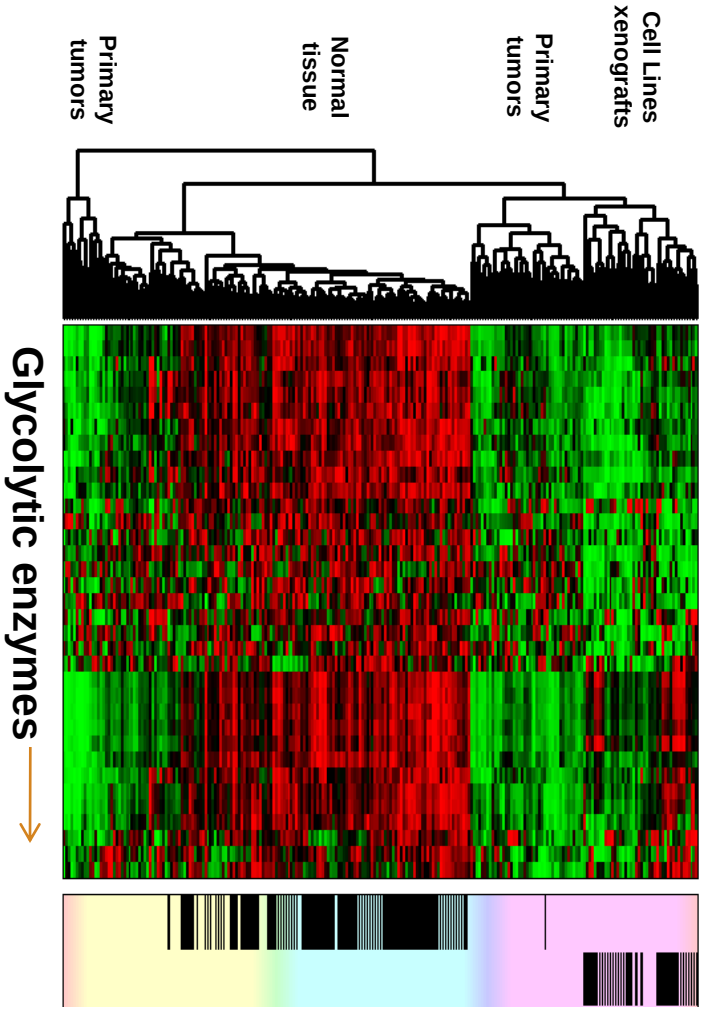
Tumor cell lines vs. Primary tumors: *e.g. metabolic differences*

- In many ways, cell lines are faithful models of tumors.
  - Signal transduction pathways at transcript level (Cancer Cell 10(6): 515-27)
  - DNA copy number alterations (Cancer Res 67(8): 3594-600)

- Metabolic pathways of tumors are not accurately modeled in cell lines:
  1. Enzymes in metabolic pathways identified.
  2. Transcript ‘signature’ compared between tumors, cell lines and cell line xenografts.
  3. Clustering analysis shows that cell lines and xenografts cluster together, separate from tumors (e.g. glycolysis in lung cancers).



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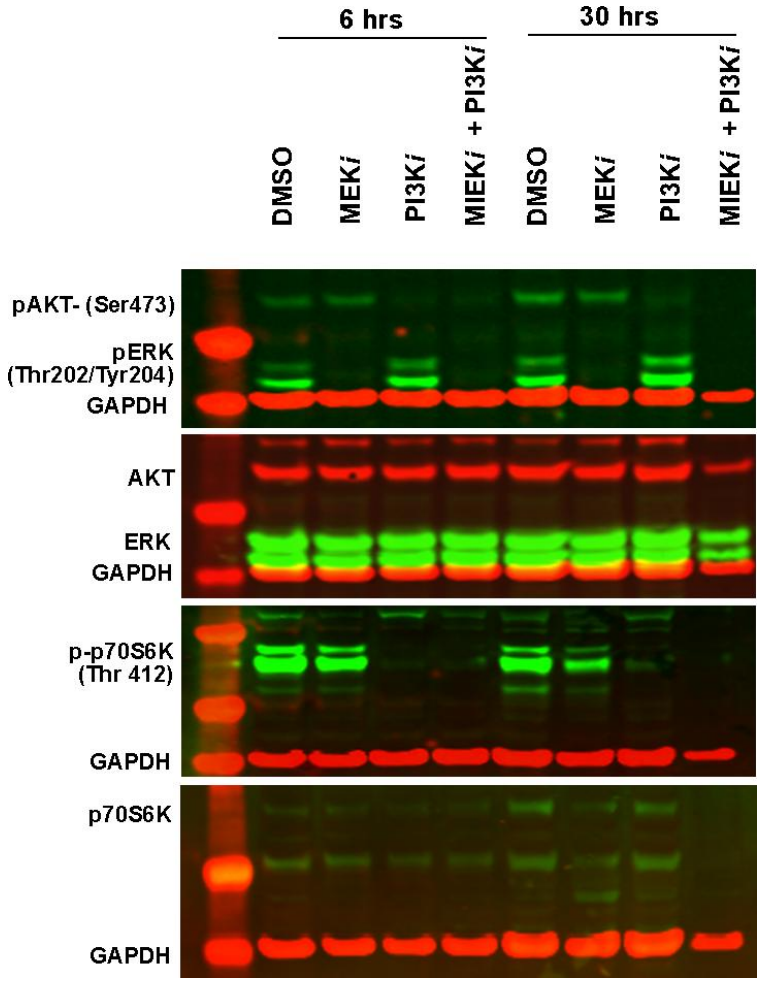
Combination Studies: PI3K inhibitor + MEK inhibitor

Strategic co-inhibition of 'semi-parallel' pathways activated in tumors

- Strong evidence of cross-talk between RAF-MEK-ERK and PI3K-AKT signaling via MEK-EGFR-PI3K feedback loop.
- Induction of PI3K Pathway activation associates with resistance to MEK inhibition.

- Dosing KRAS+ colon cancer cells
  - PI3K*i* @ 100 nM
  - MEK*i* @ 200 nM
  - x 2 time points
- p-p70S6K reduced with PI3K*i,* less so with MEK*i.*
- Co-administration of PI3K*i* and MEK*i* more completely ablates both pAKT, pERK, p-p70S6K.



HCT-116 colon cancer cells

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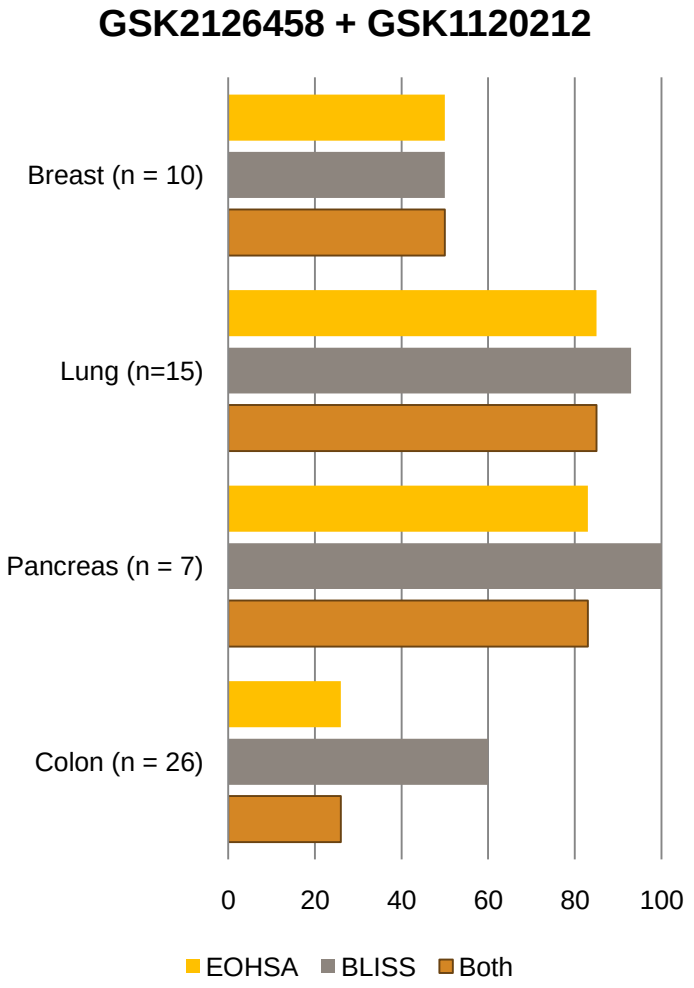
PI3K ‘458 + MEK’212 combination shows high rates of synergy in cell line proliferation assays

Analyzing two metrics of combination efficiency:

1. Pancreatic tumors have high rates of synergy, regardless of how this is measured.
2. Colon cancer cells harboring strong oncogenic mutations of KRAS demonstrate greater percent improvement over best single agent (compared to wild-type cells).
3. ER-/PR- breast cell lines show more synergy (80%) vs. ER+/PR+ tumors (20%).
4. In lung cancer cells STK11/RAS co-occuring mutations do not have increased rates of synergy despite increased efficacy of MEK inhibition in this genotype *(Br J Cancer. 100:370-5).*



***EOHSA** – Percentage improvement over best single agent

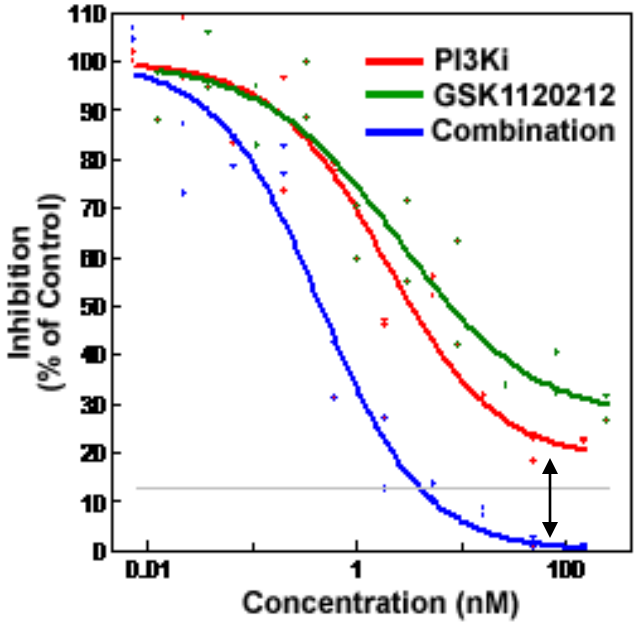
****BLISS** – Percentage improvement over predicted additivity

predicted Additivity = $E_a + E_b - (E_a * E_b)$

PI3K'458 + MEK'212 combination shows high rates of synergy for inducing cell death

- A substantial increase in ***cell death**** is seen in a large proportion of cell lines tested.
  1. *Colon*: 30%
  2. *Pancreas*: 57%
  3. *Lung: 100%*
  4. *Breast: 60%*
- Among those with substantial increases in ***cell death***, all showed synergy by at least one measurement.

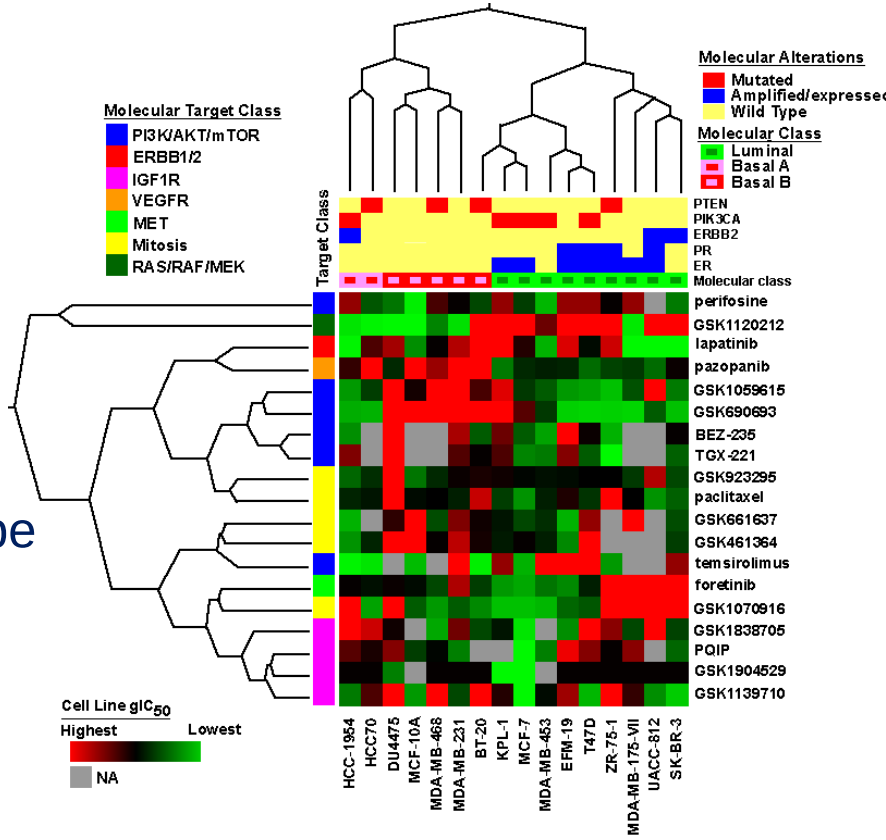
e.g. Colon cancer cell line



* measured by the percent increase in cell death compared to most efficacious single agent (> 20% increase)

Translational Medicine: *Genomics data in cancer cell lines*

- High throughput proliferation screens have been done and released publicly for 19+ compounds.
  - This includes PI3K/AKT, VEGF, mitotic and RTK inhibitors.
  - Direct comparisons of response profiles shows that similar classes have similar patterns.
- Accompanying genomic data can be used to predict cell line response profiles
  (*e.g. ER/HER2 status predicts response to PI3K/AKT inhibitors).*
- Genomics data for ~300+ cell lines released to public:
  https://cabig.nci.nih.gov/caArray_GSKdata/



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