HMS LINCS Center: Pharmaco Response Signatures and Disease Mechanism

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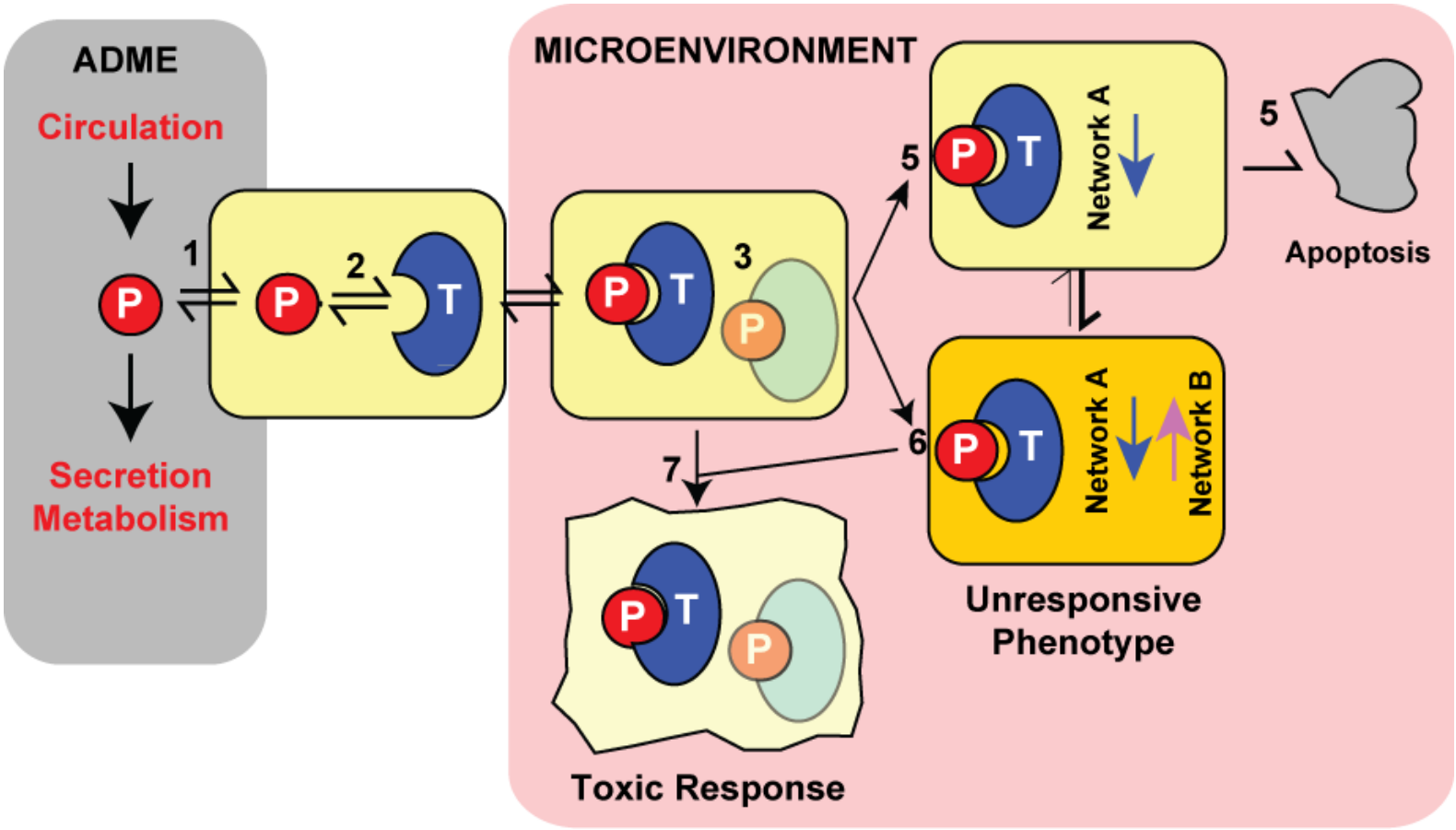
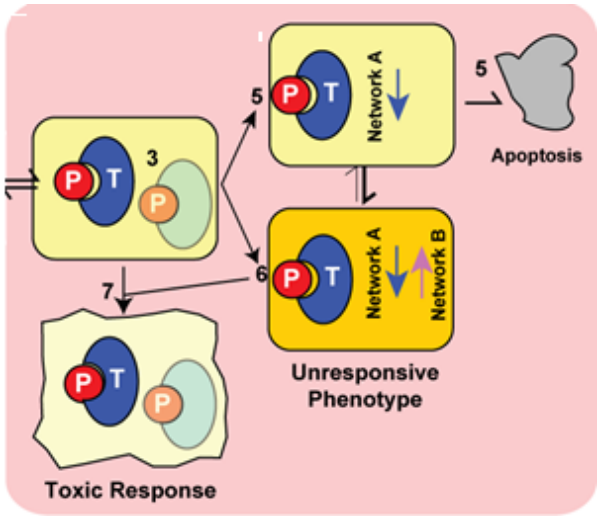
Presentation Outline

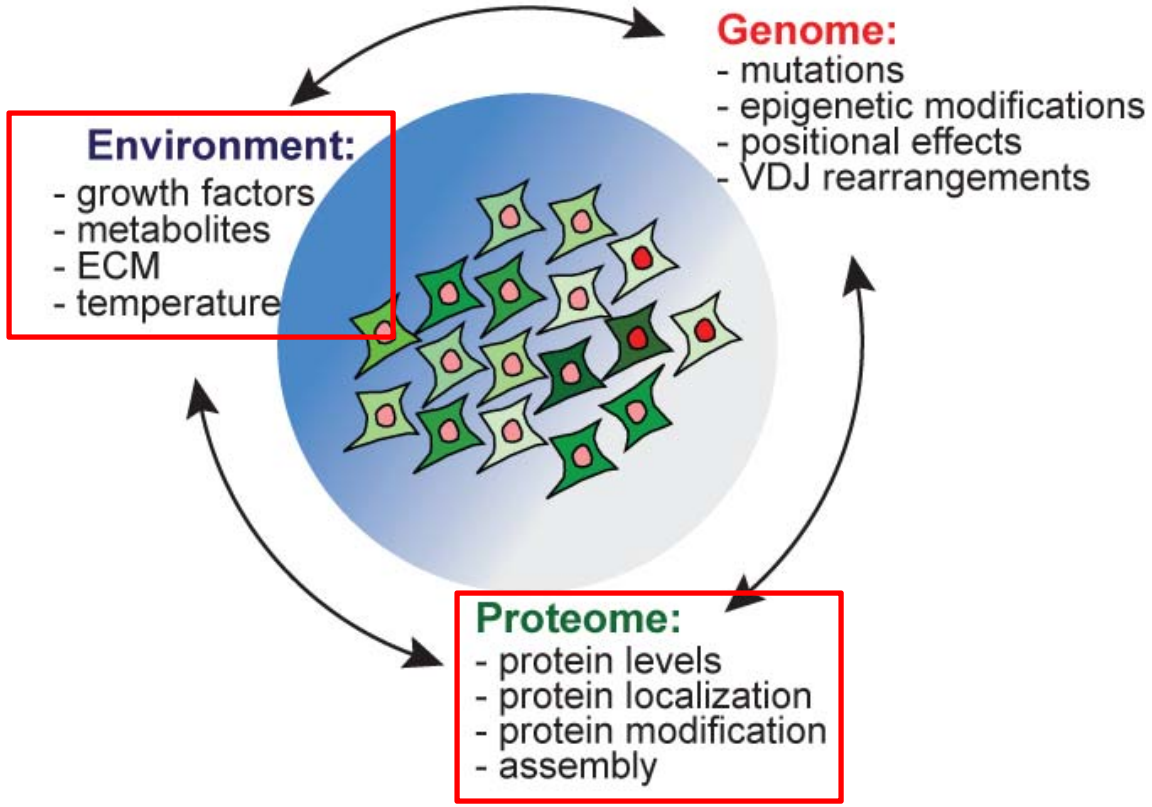
- *Goals*
- *Approach*
- *Research Vignette I:*
  - *Perturbagen dose-response*
- *Research Vignette II:*
  - *Perturbagen Predictors*
- *Summary*

Cellular Response To Perturbation
Simple view of drug response determinants

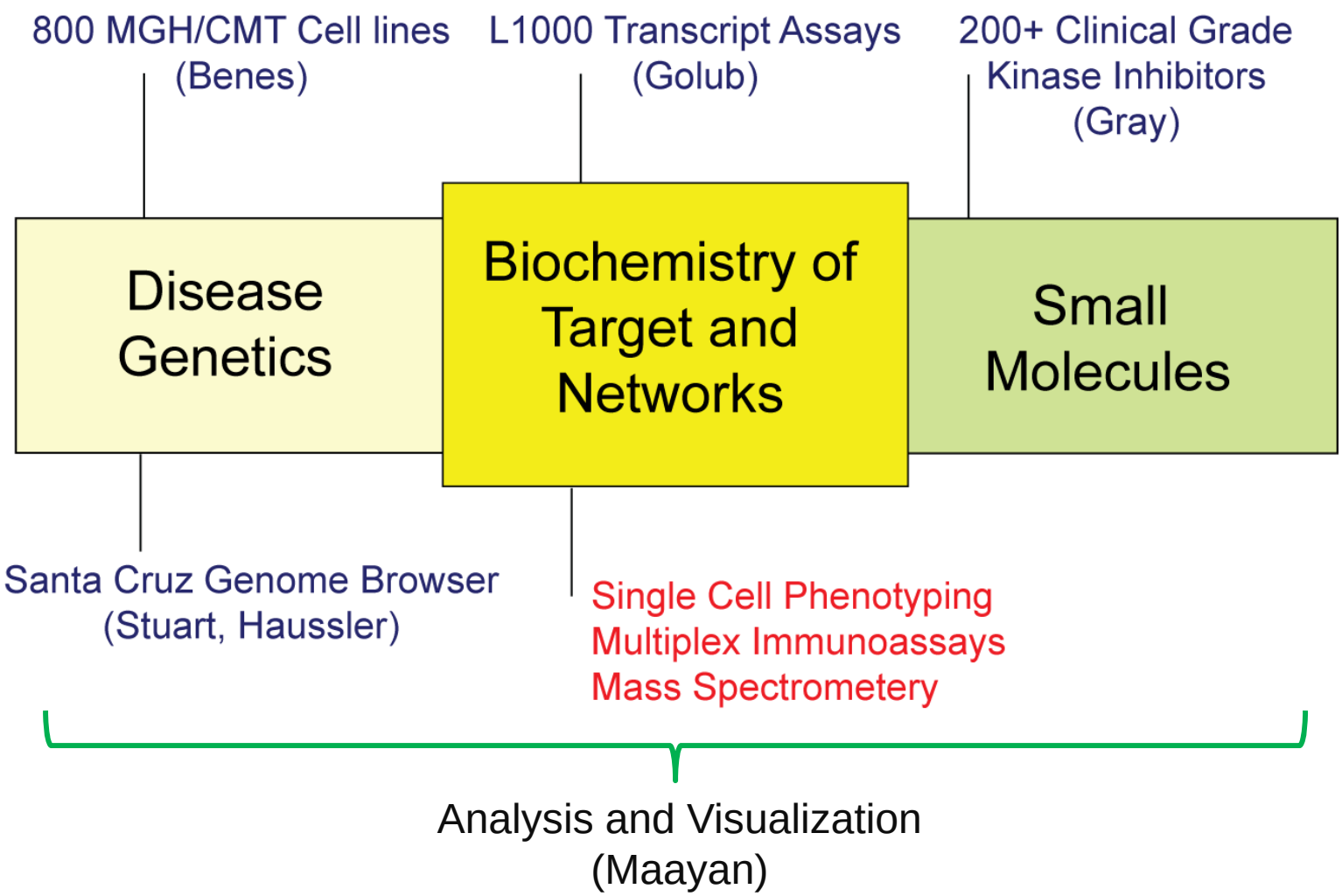


Factors that contribute to heterogeneity in response to perturbation





HMS LINCS Assays and Approaches

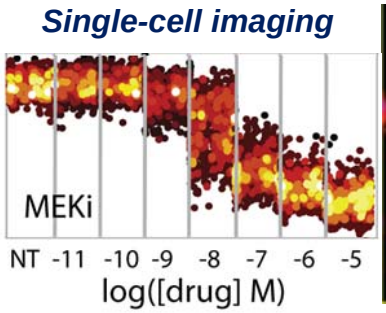


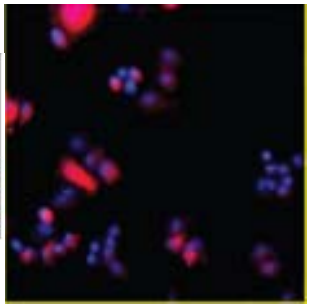
LINCS@HMS

Data Types

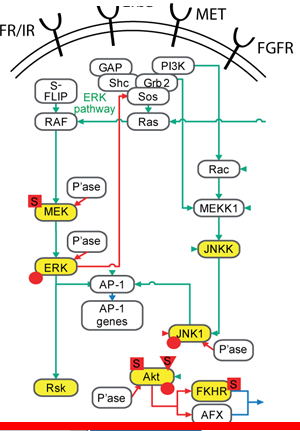
UCSC Genome browser

Single-cell imaging





Pathway biochemistry



HMS LINCS Database

Guest
HMS LINCS Login

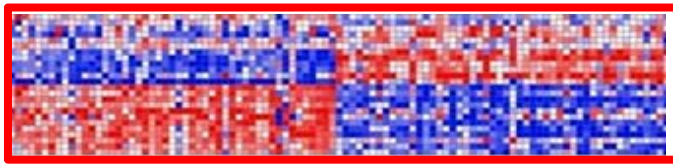
Browse...
Reagents
Reagent Wells
Libraries

Studies

Search >>
Columns (add/remove) >>

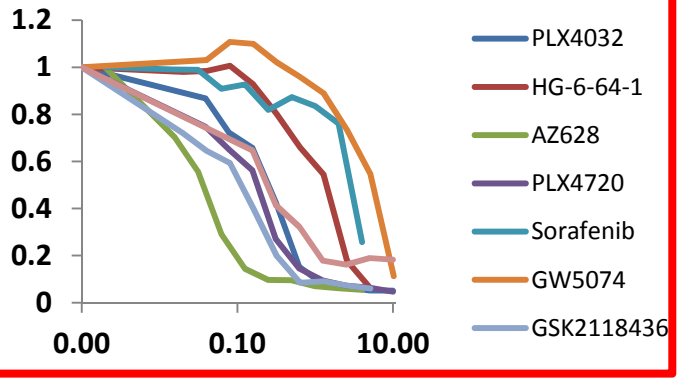
Page 3 of 5 (93 rows) Rows 20 Sort by Study ID Ascending Export CSV

Study ID	Title	Lab Head	Study Head	Library Screen Type	Date Data Received	Date Loaded	Date Publicly Available
300041	GNF2: MGH/Sanger Institute growth inhibition data (3 dose)	Benes, Cyril	Benes, Cyril	Small Molecule	06/30/2011	07/15/2011	07/15/2011
300042	Imatinib: MGH/Sanger Institute growth inhibition data (3 dose)	Benes, Cyril	Benes, Cyril	Small Molecule	06/30/2011	07/15/2011	07/15/2011
300043	NVP-TAE684: MGH/Sanger Institute growth inhibition data (3 dose)	Benes, Cyril	Benes, Cyril	Small Molecule	06/30/2011	07/15/2011	07/15/2011

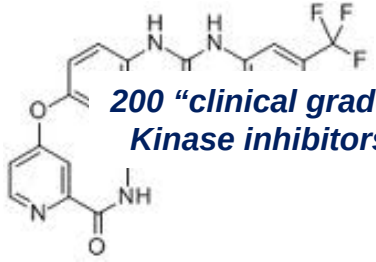


Transcription L1000 Assays

Multi-drug, multi-cell line dose response

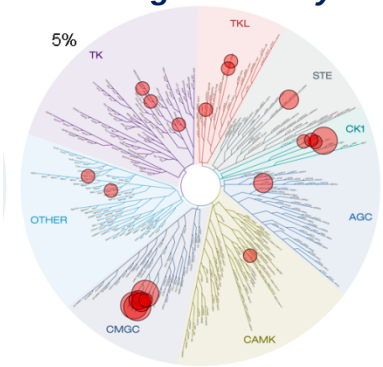


Drug Properties



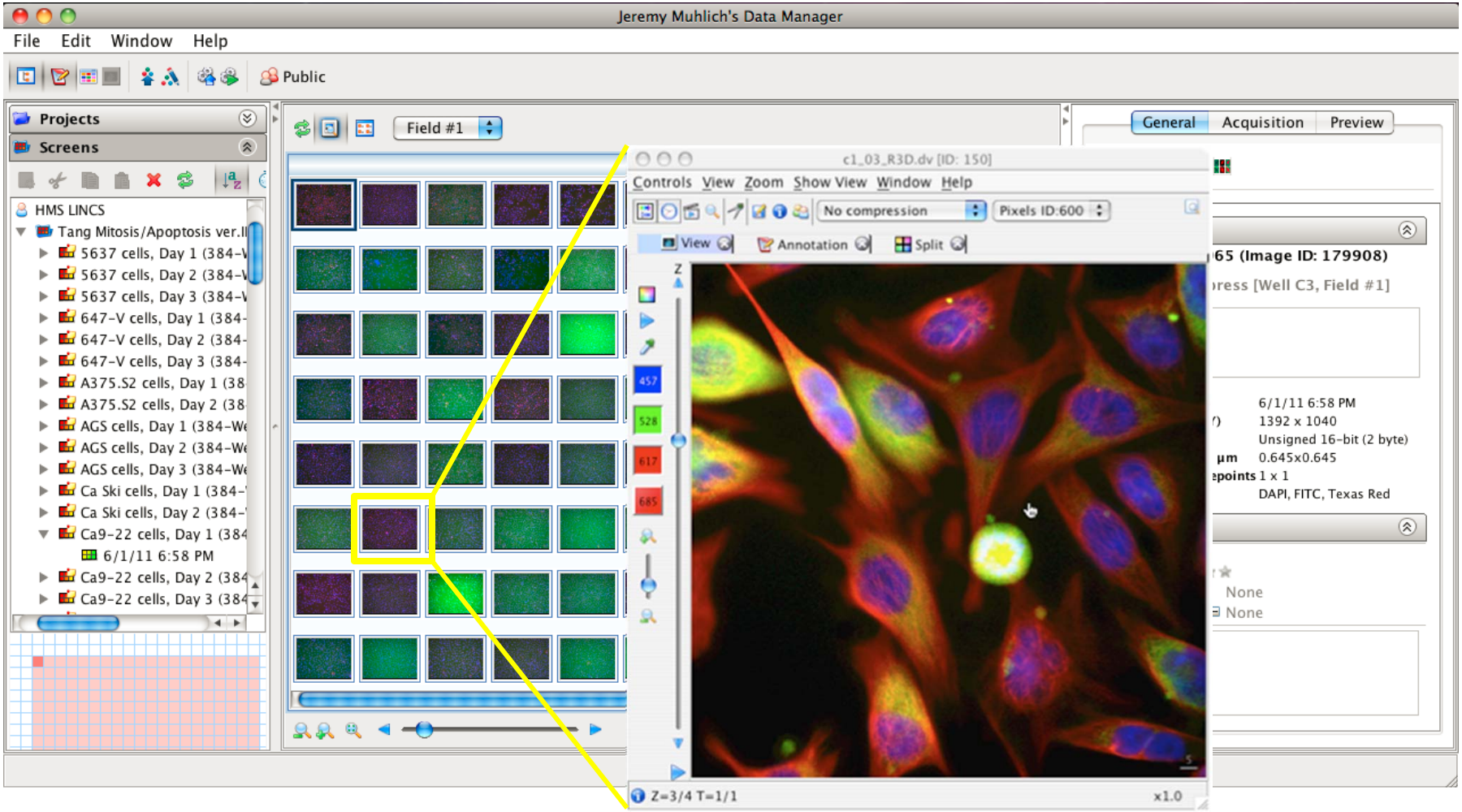
200 "clinical grade" Kinase inhibitors

Drug selectivity



The KINOMEscan and mass spec with Steve Gygi

Extensive single-cell and time resolved data - *Demo 4*



Goals

1. DATA

Multiplex biochemical, phenotypic and transcriptional data on cellular response to perturbation:

Focus on clinical grade kinase inhibitors

Across banks of genomically characterized cancer lines

Apply to diseases other than cancer and normal cells:

Stem cells, hepatocytes, cardiomyocytes

Rheumatoid arthritis, mitochondrial disease,

2. TOOLS

To compute perturbagen-response signatures:

Model complexity of response with dose, time and space

Develop network-level mathematical models:

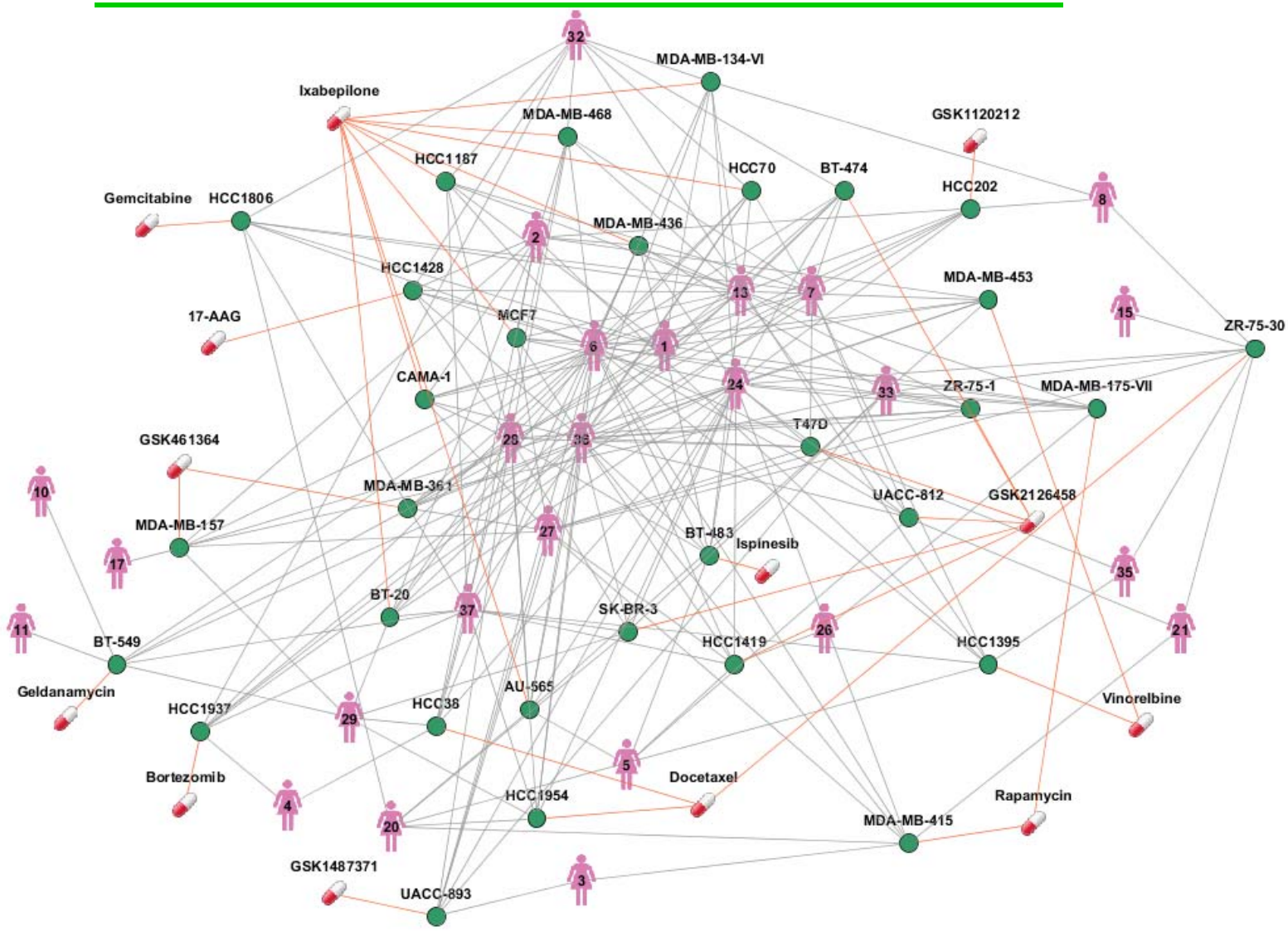
3. ACCESS

***Disseminate diverse data and models*:**

Date and metadata standards – publication process

Papers on use cases and applications

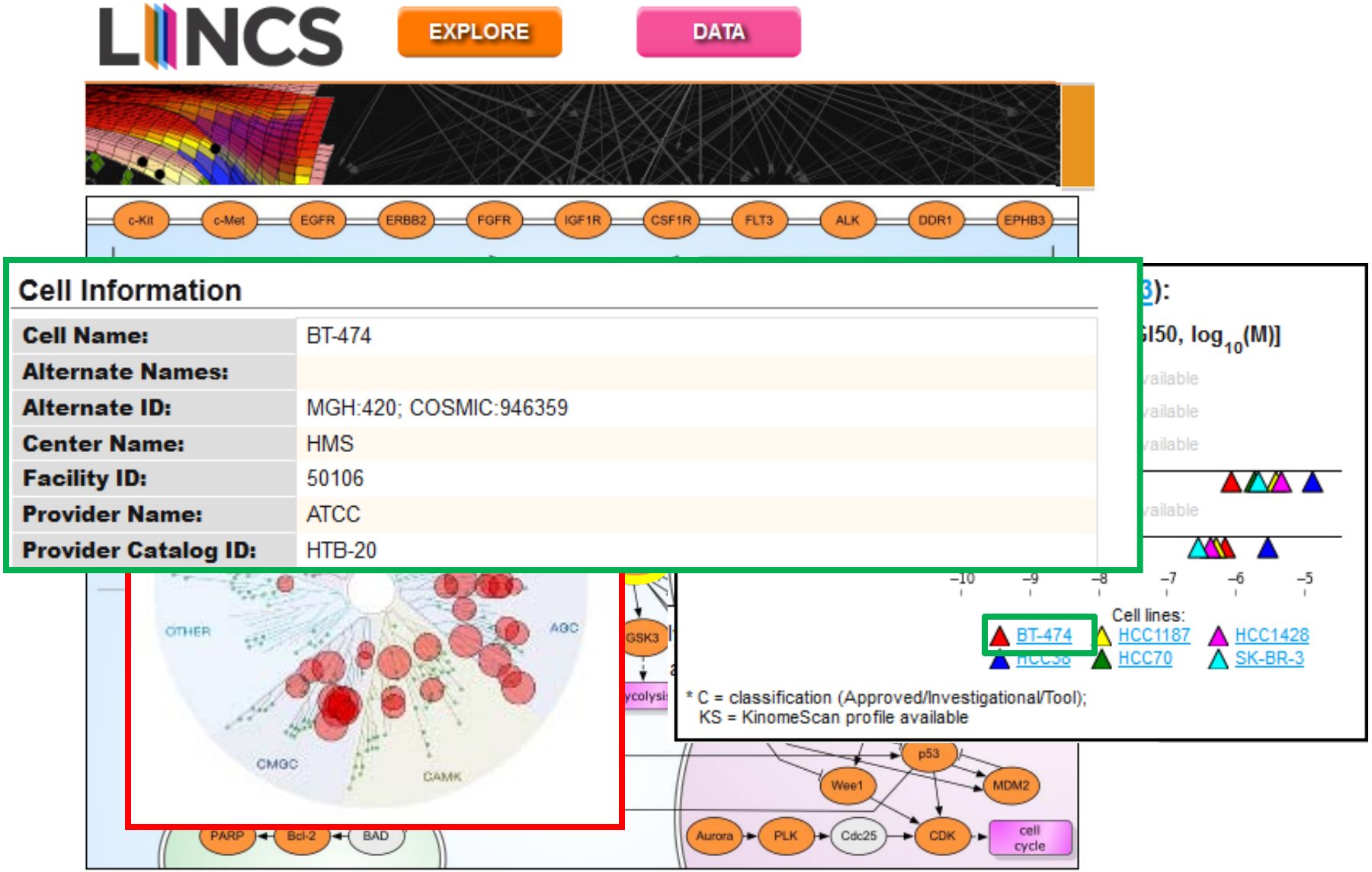
Predicting perturbagen response in cell lines: no cell line like a patient but panel covers the landscape



Cells Currently Under Analysis

1. 70 Breast Cancer cell lines (NCI-ICBP45 set)
2. 30 Melanoma lines and other BRaf-V600E tumors
3. 10 Liver Cancer (HCC) Cell lines
4. 8 Lines with mitochondrial disease alleles (V. Mootha)
5. 8 Normal and rheumatoid arthritis synovial fibroblasts (BI)
6. Stem-cell derived cardiomyocytes (GE)
7. Differentiated and undifferentiated stem cells (HSCI)

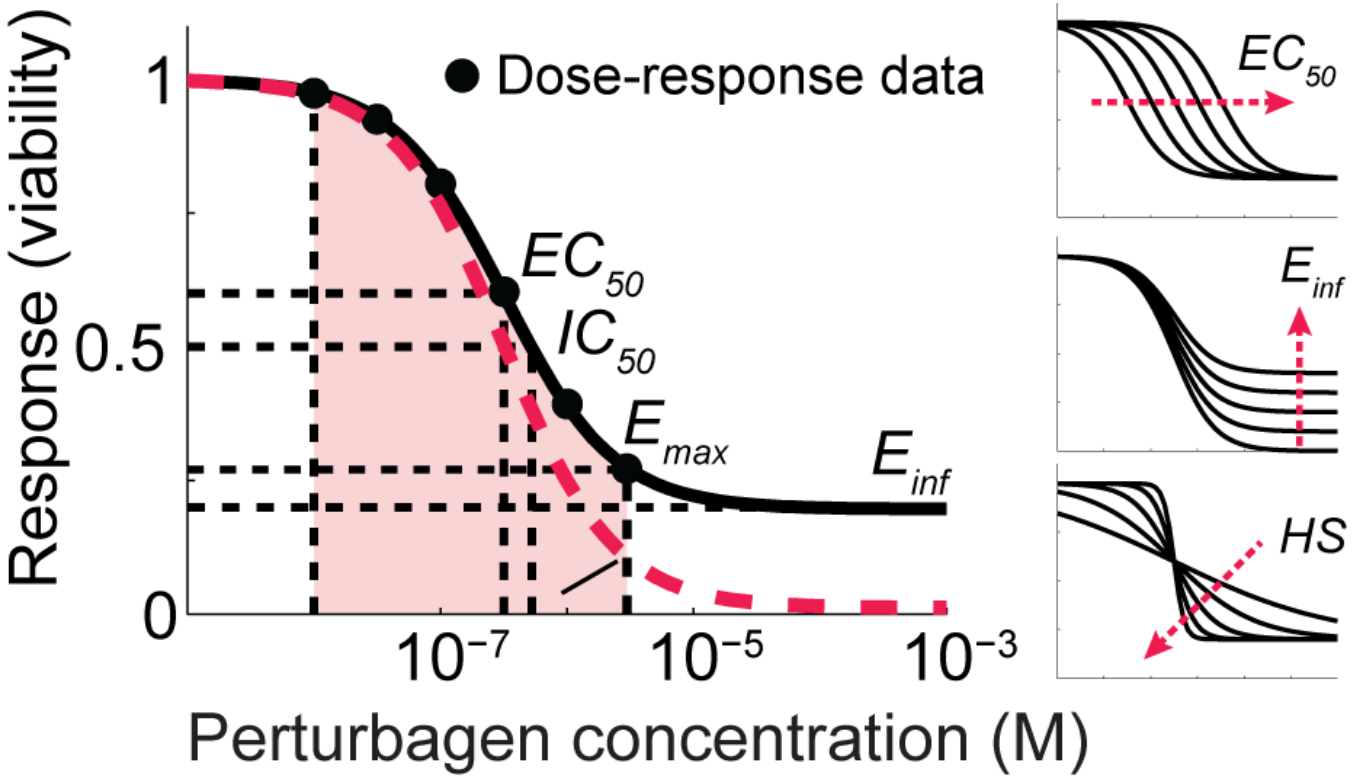
Diverse user interfaces emphasizing pathways- *Demo 7*



Research Vignette I:

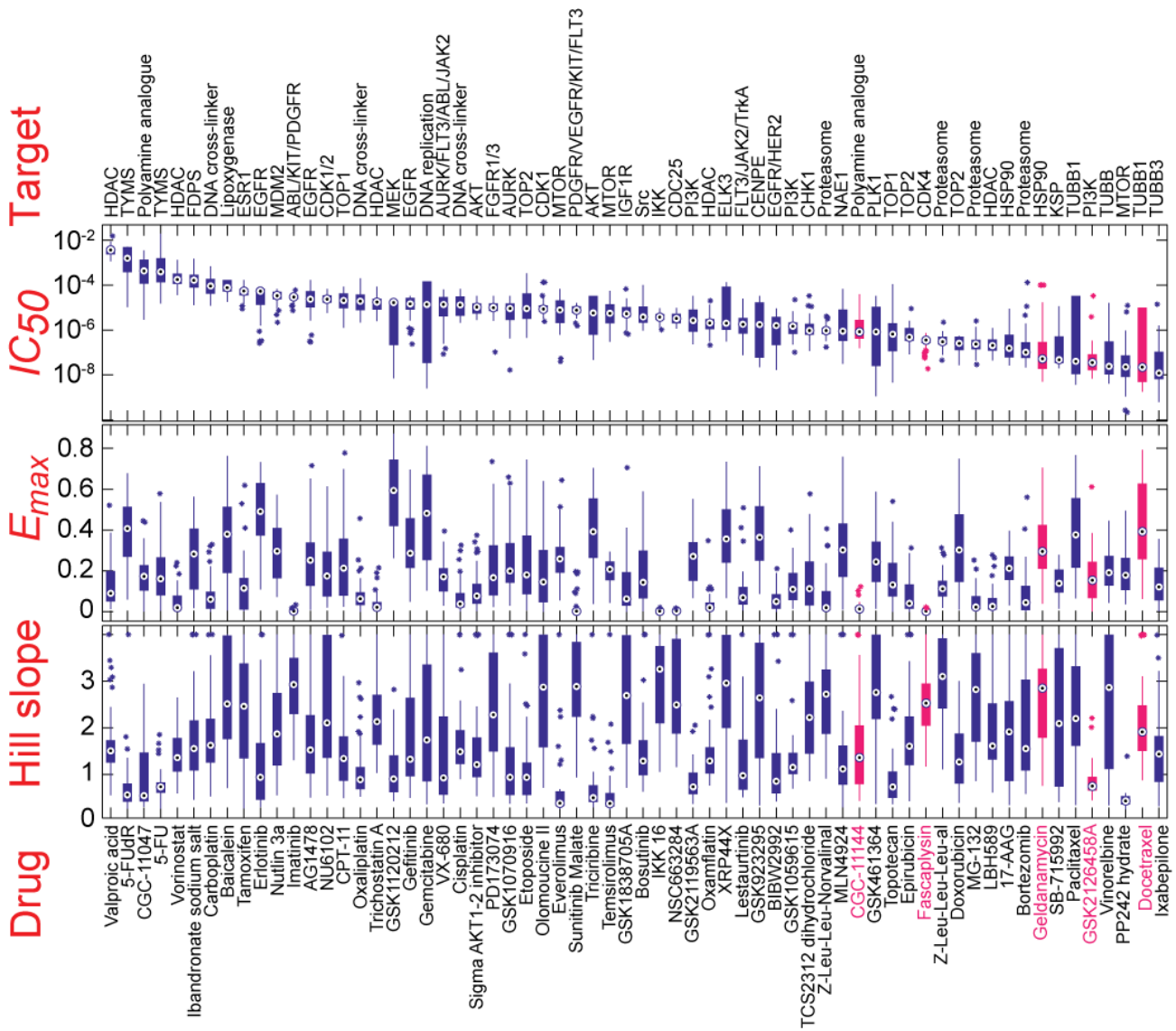
Perturbagen dose-response

Parameterizing a canonical dose-response curve

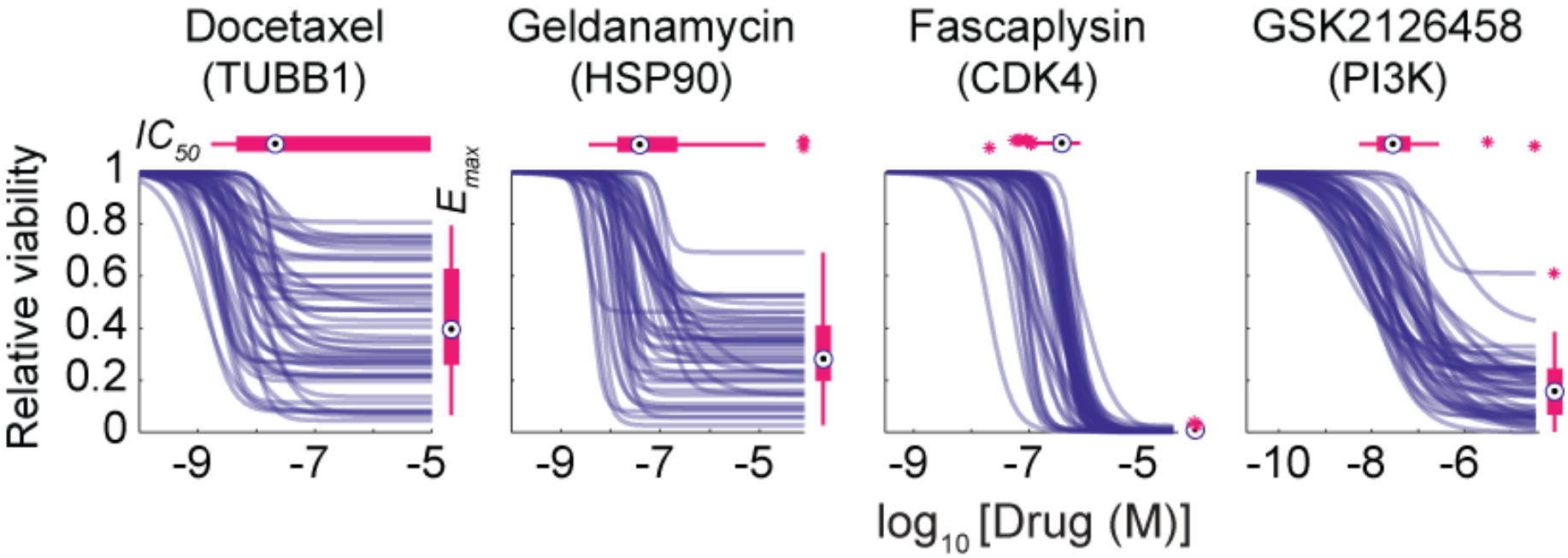


$$y = E_{\infty} + \left(\frac{E_0 - E_{\infty}}{1 + \left(\frac{D}{EC_{50}}\right)^{HS}} \right)$$

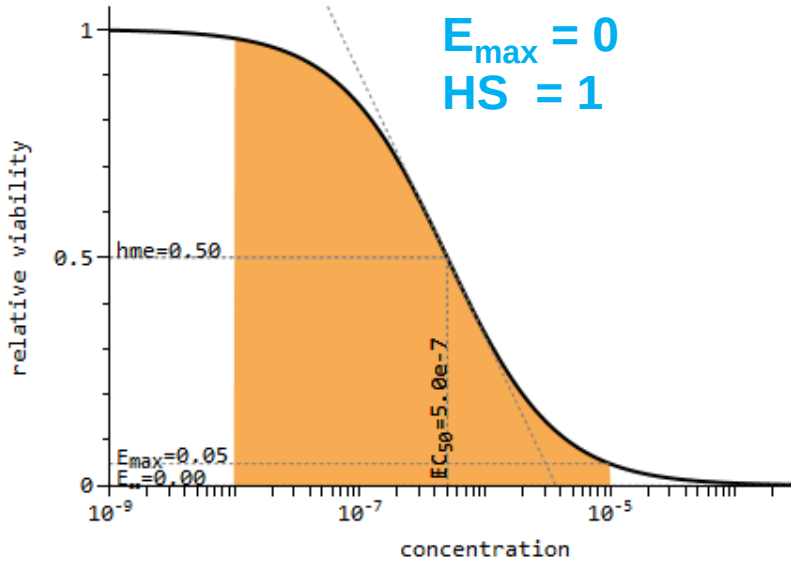
Extensive variation for parameters other than IC_{50}

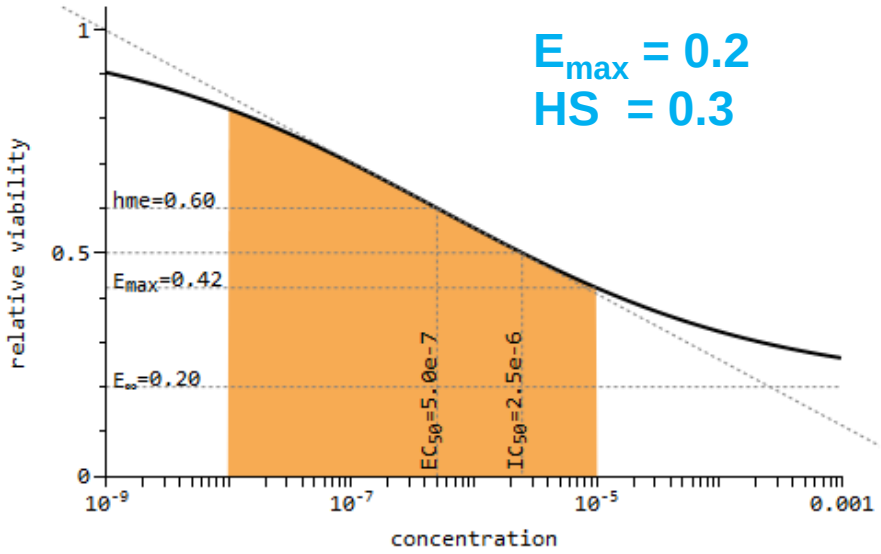


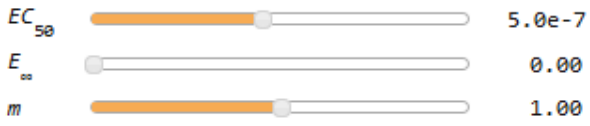
Examples of different types variation

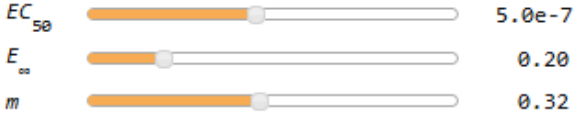


On-line exploration of dose-response curves - Demo 7

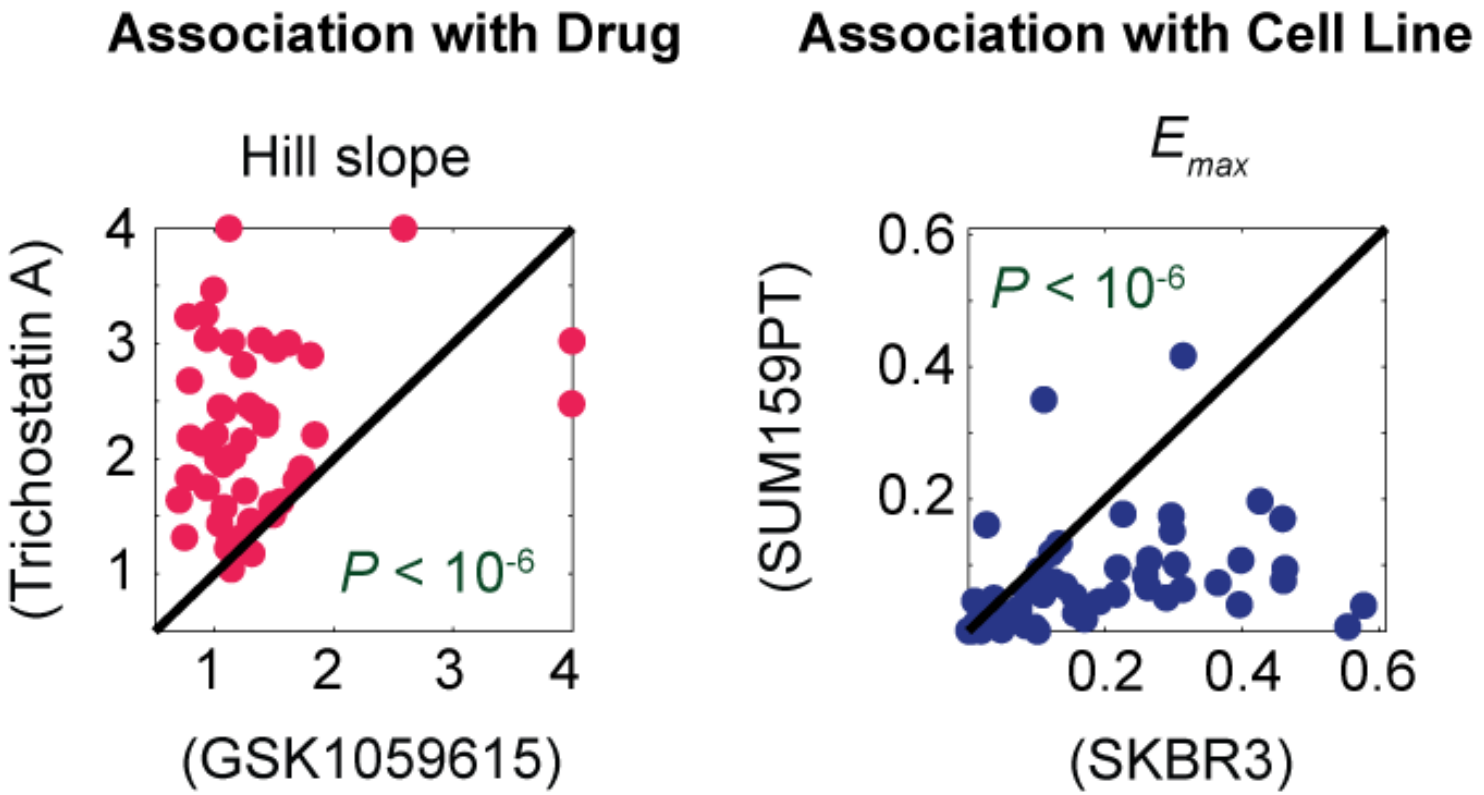




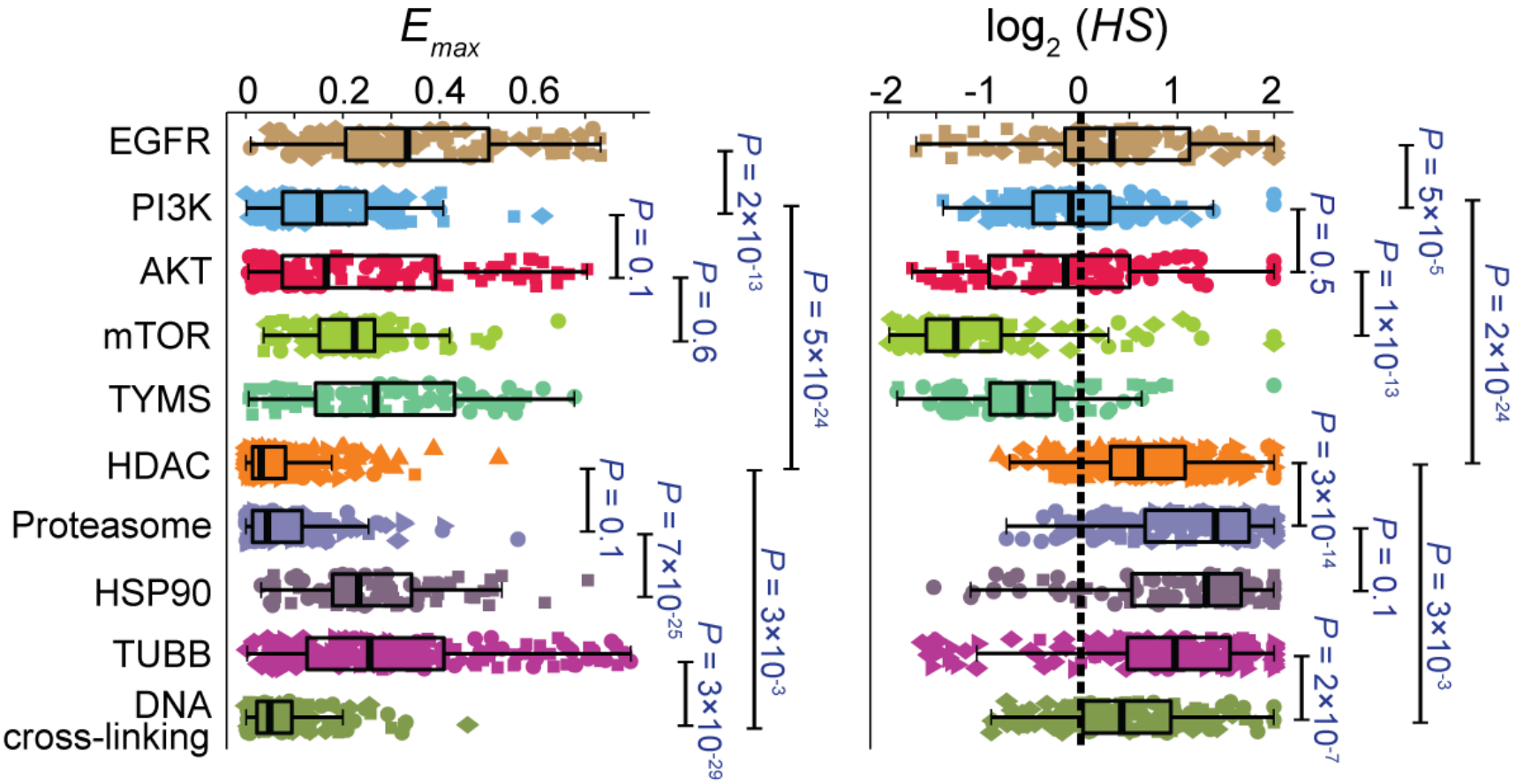




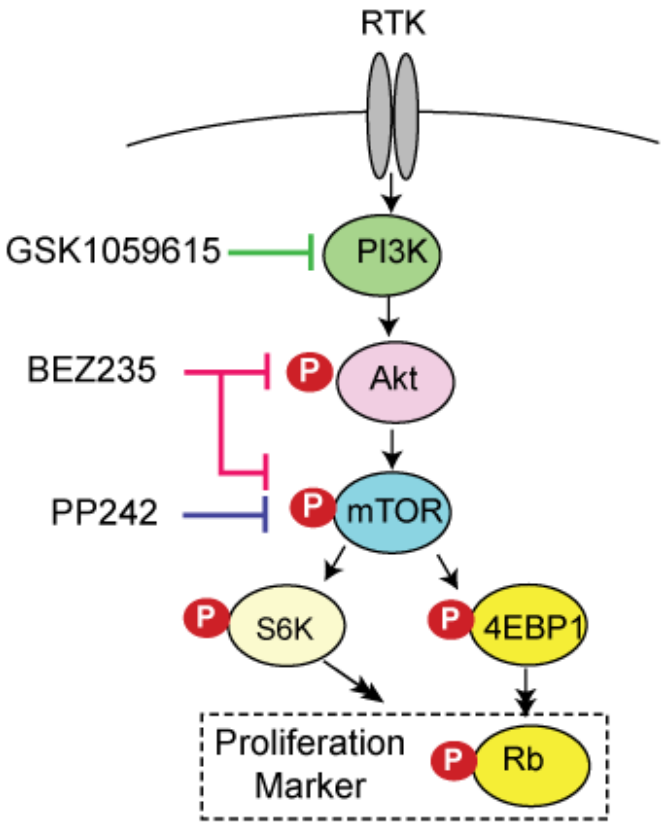
Variation can be associate either with perturbagen or cell line (by mutual information)

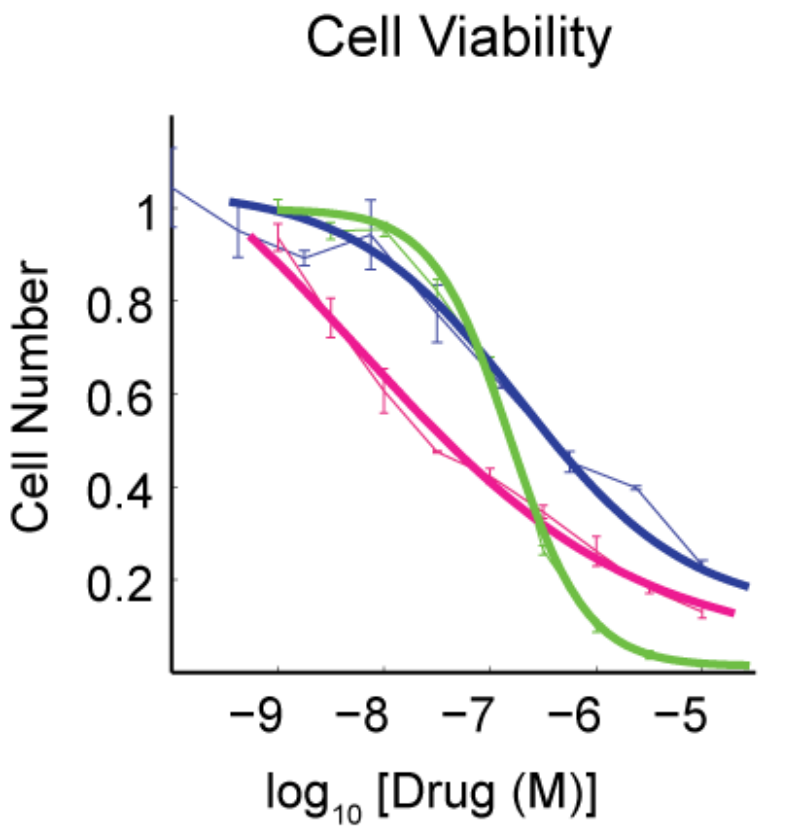


Type of variation is common across a perturbagen class



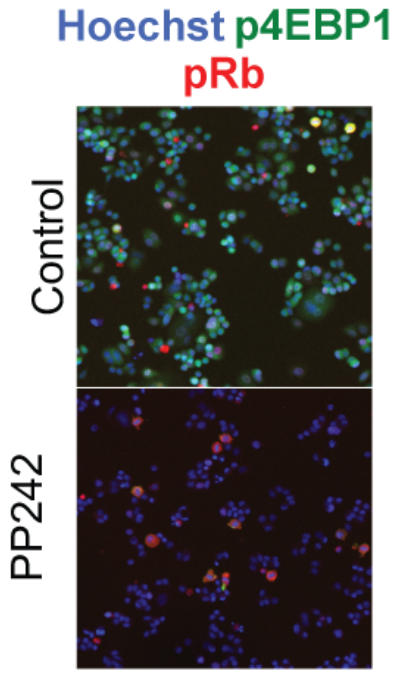
Probing origins of variation in E_{max} and Hill Slope

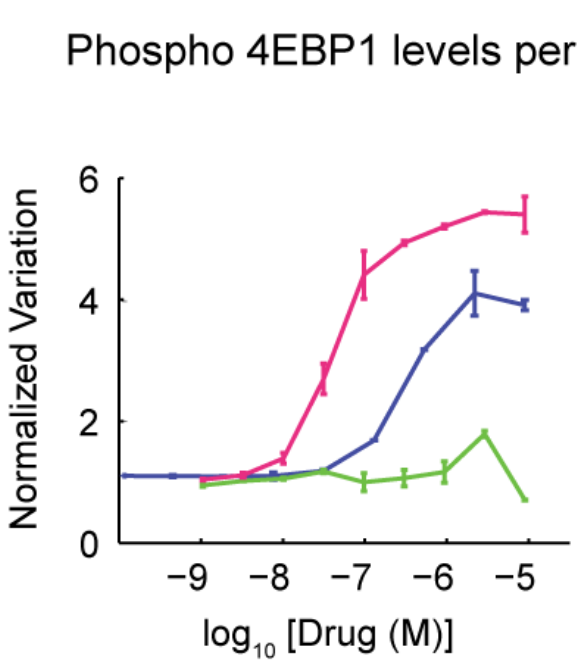


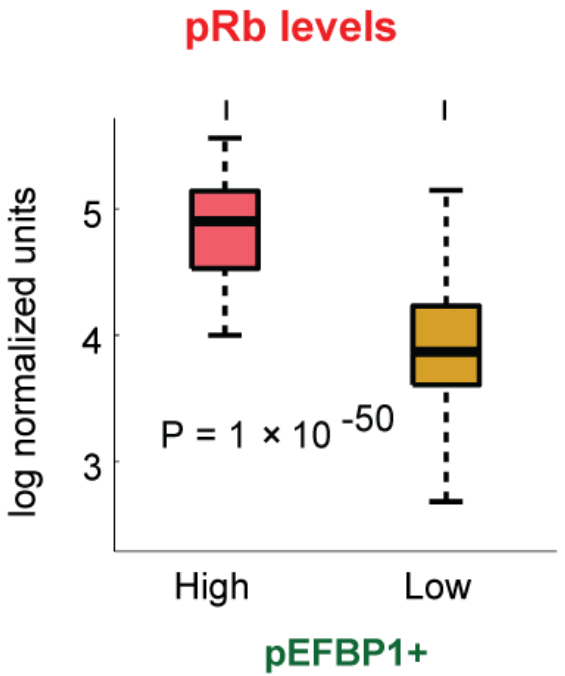


HCC1954 Her2+ Breast Cancer Cells

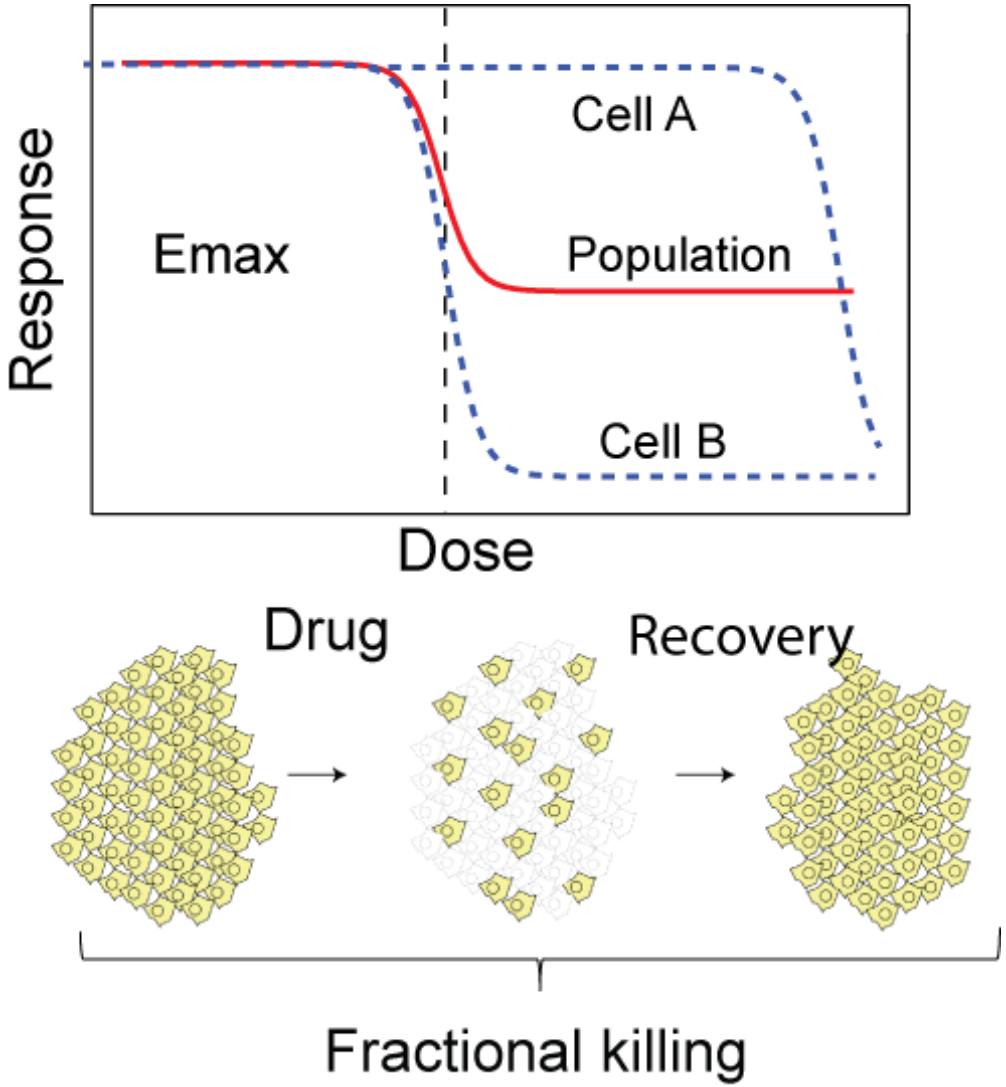
Hill slope is lowest when cell-to-cell variation is highest (poster 15)



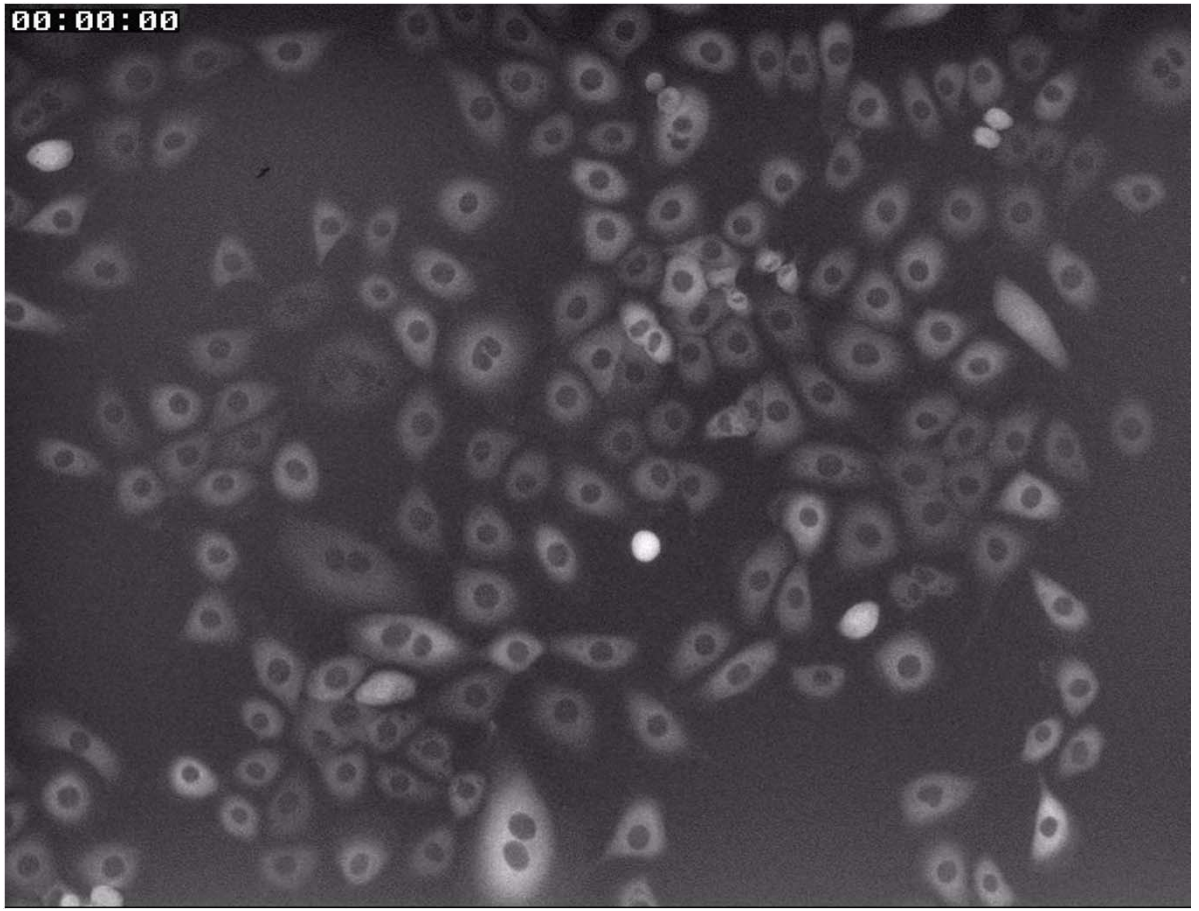




Cell-to-cell variability: origin of fractional response?



Cell-to-cell variability likely to have significant dynamic component (Gefitinib at ~0.2 Cmax)



Research Vignette II:

Perturbagen Predictors

Determining the information content of perturbation profiles

Measure

***Biochemical profile*:**
Basal Cell State
Ligand Perturbed State

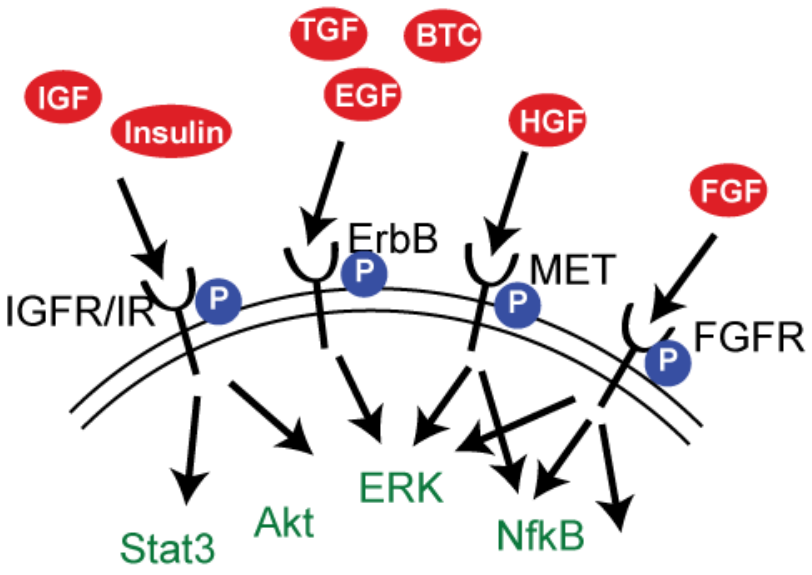
Predict

Phenotype (viability):
Drug Perturbed State

Measurement on ~40 breast cancer lines
Prediction for 40 drugs

Measure

Biochemical assays – 0 – 90 min



24 Growth factors and Cytokines X 2 concentrations

20 receptor Tyrosine Kinases phosho and total

4 immediate-early signaling kinases X 4 time-points

Pending:

Additional signaling kinases
Transcriptional responses
Additional cell lines
Additional drugs

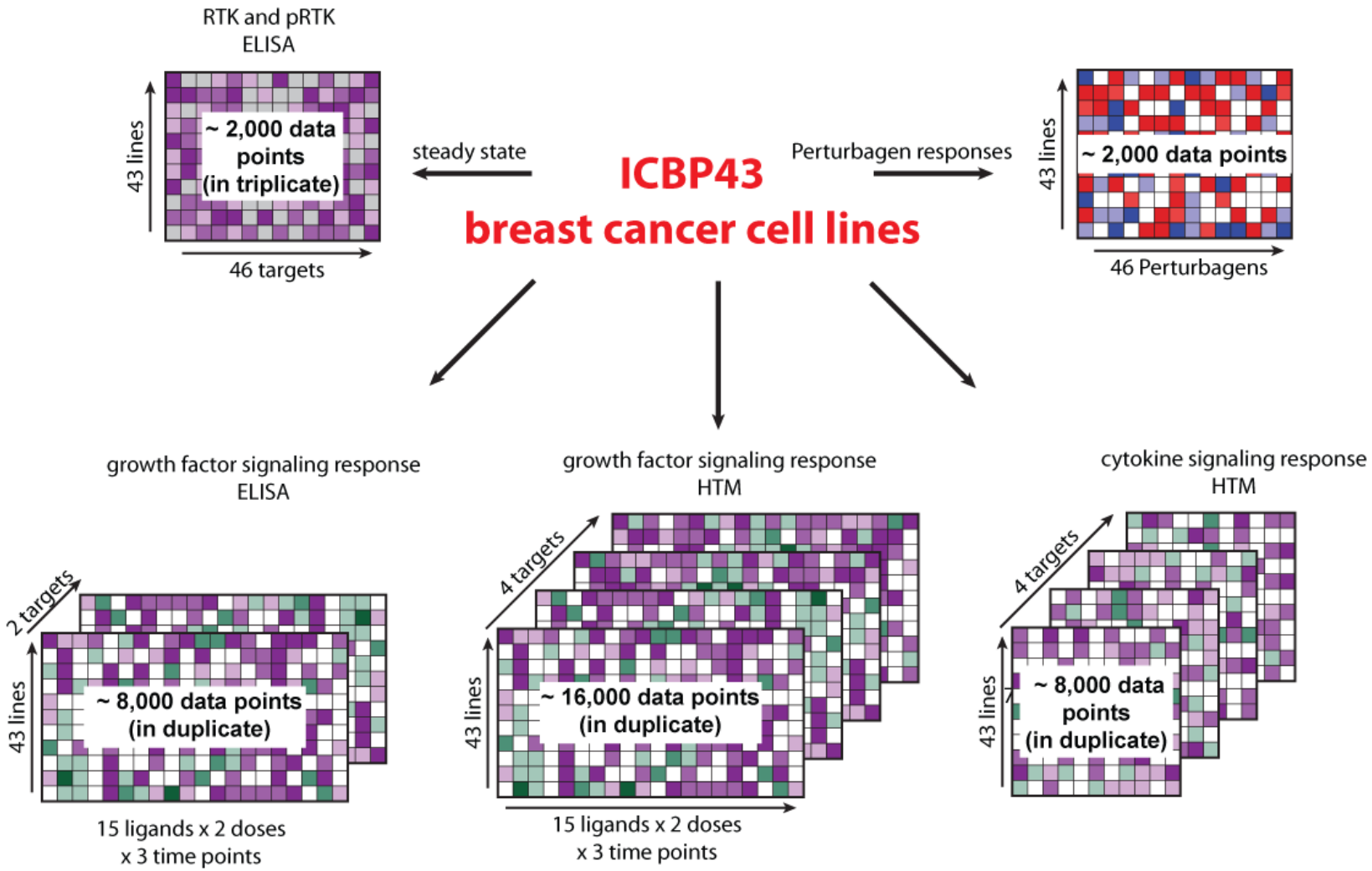
Predict

Viability (day 3)

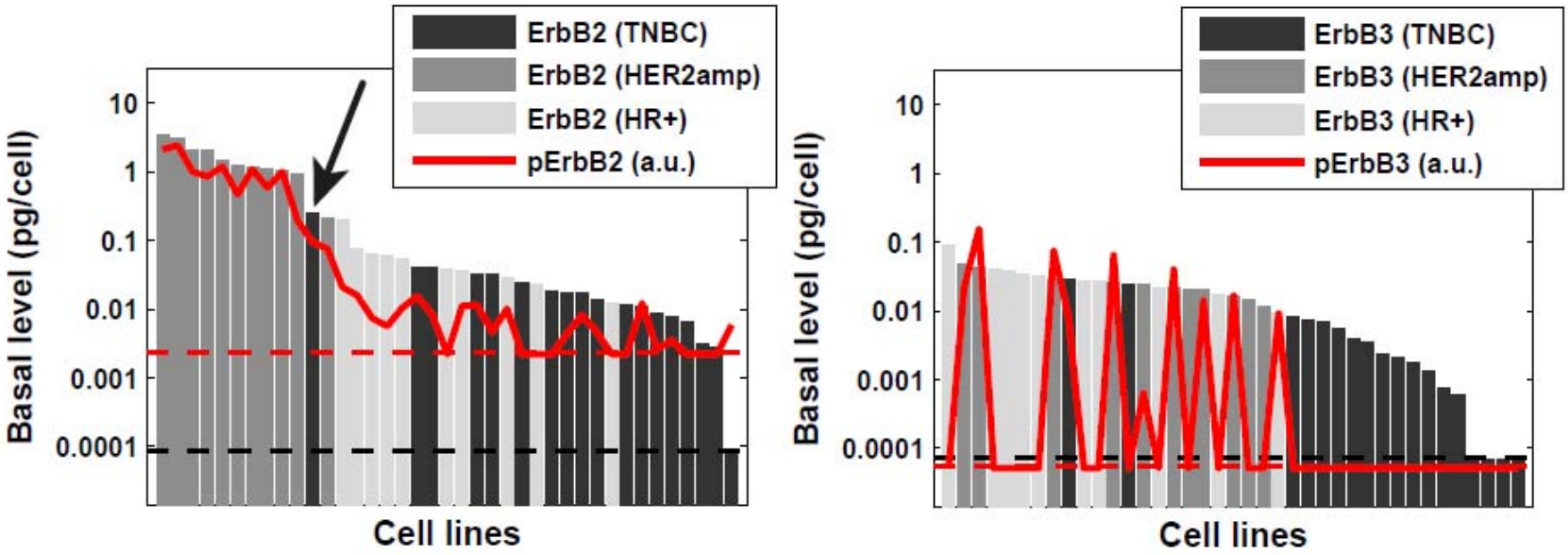
40 targeted anti-cancer drugs

Heiser et al., 2012
PNAS, 109(8):2724

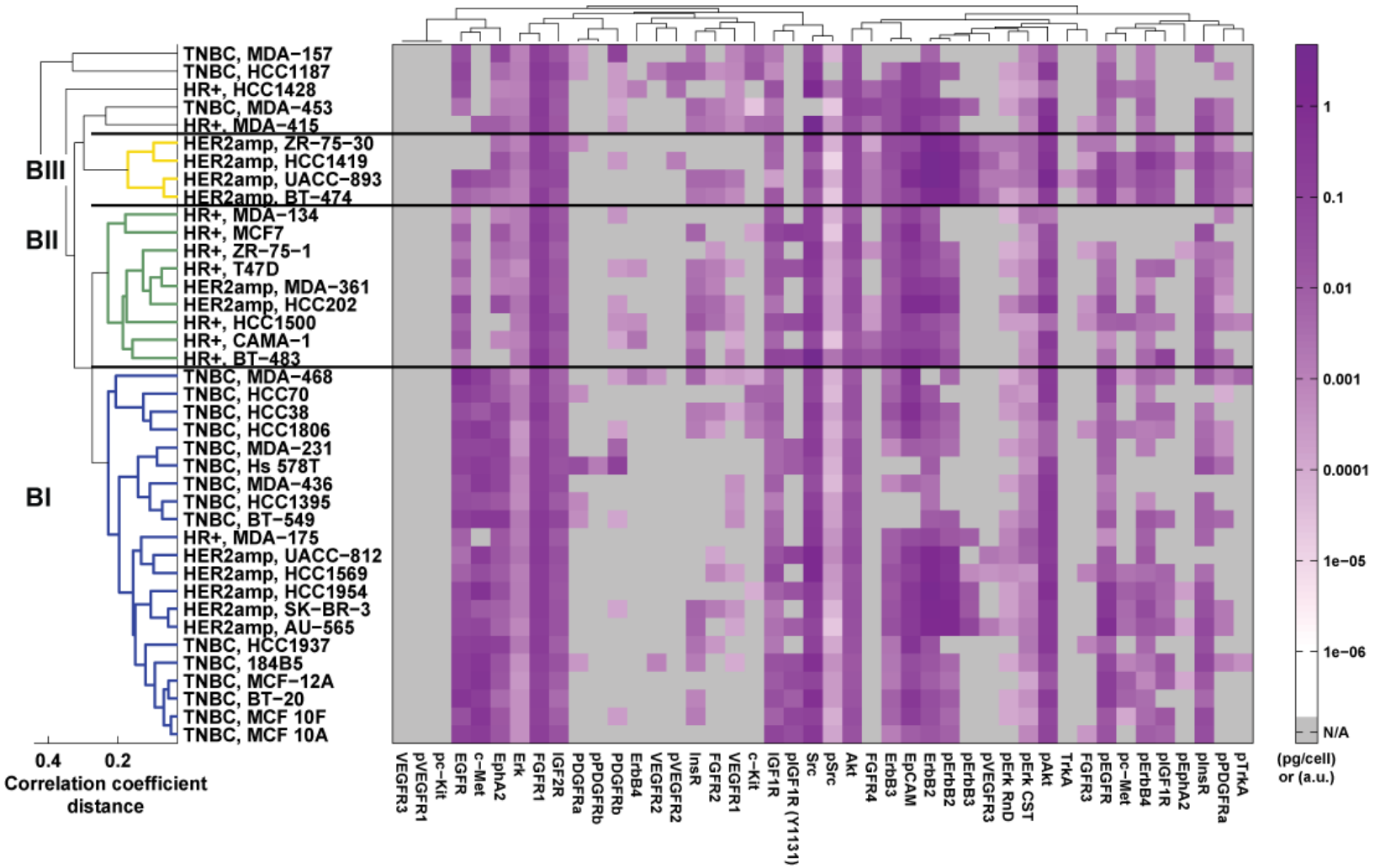
Overall data set ~ $3x10^5$ unique biochemical measurements



Correlations between protein levels and activity are rare

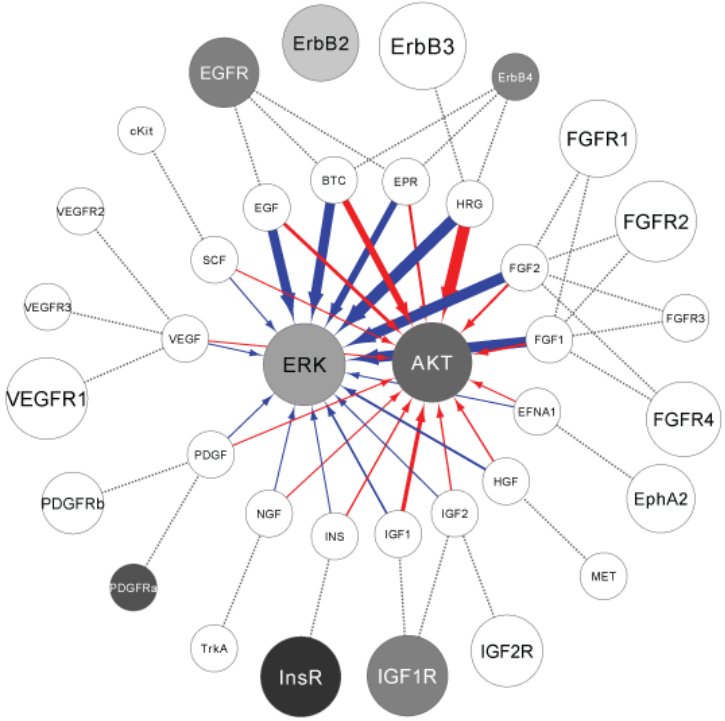


Receptor profiles cluster by clinical subtype - with further subdivision (of Her2^{amp} lines)

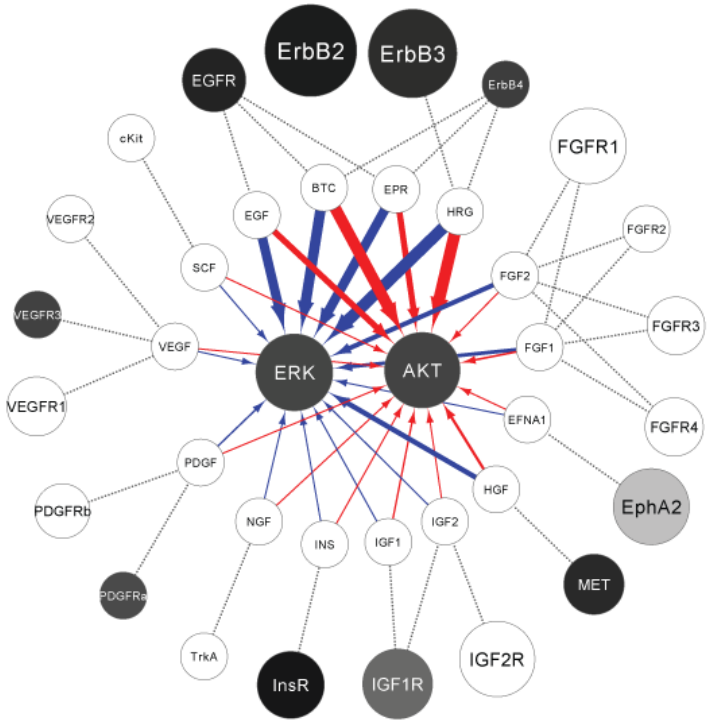


Clustering generates prototypical cell classes

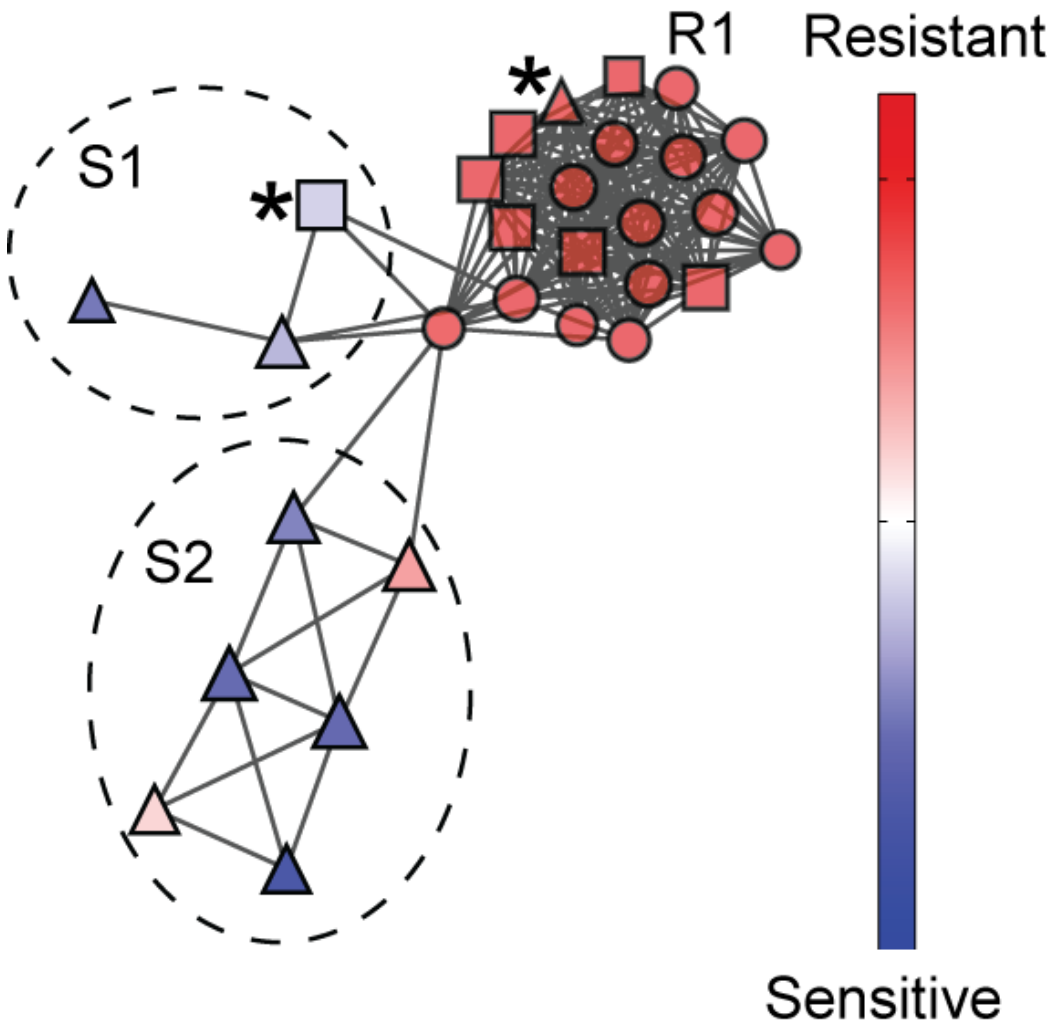
Cluster SCII



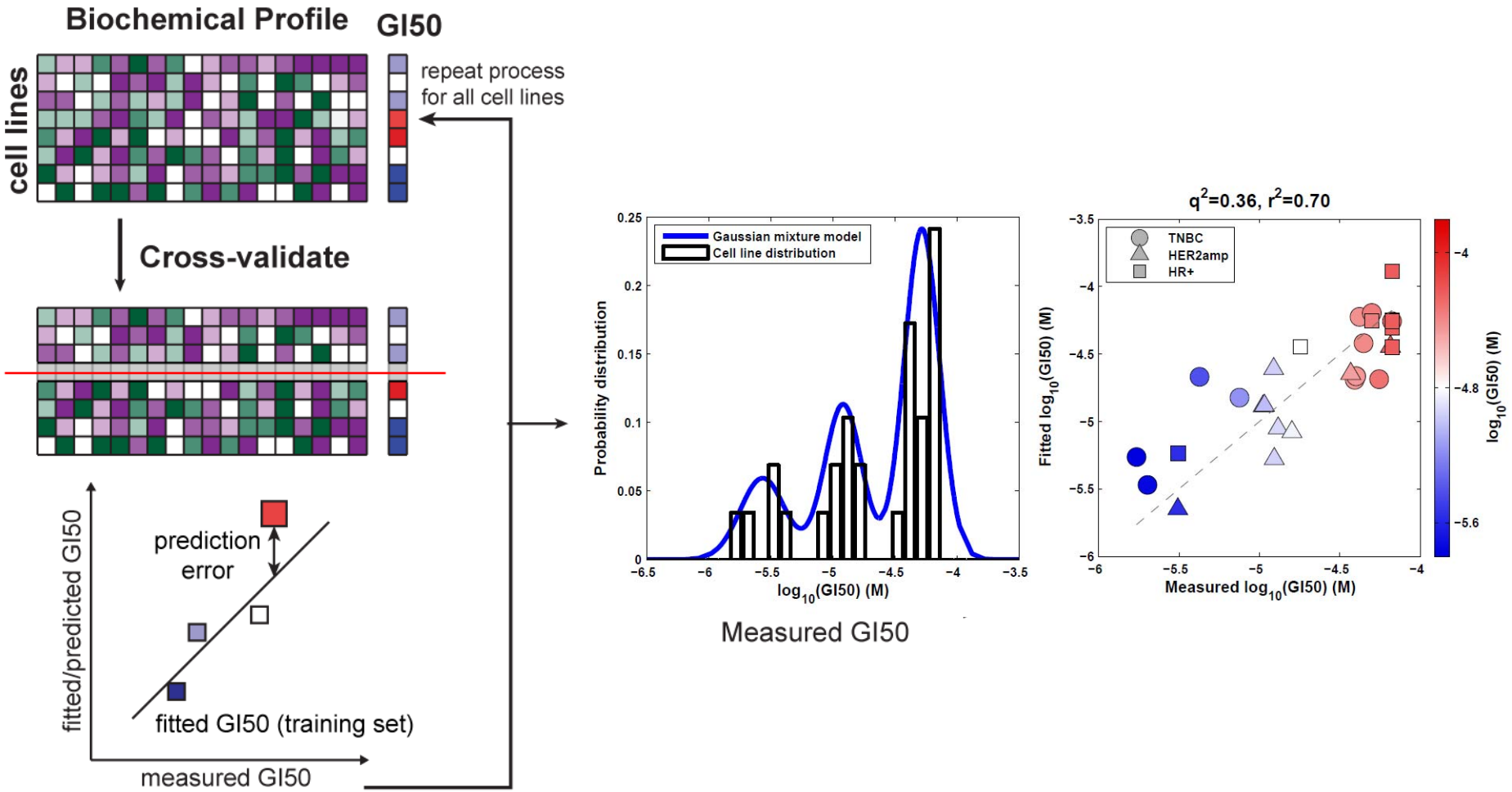
Cluster SCIII



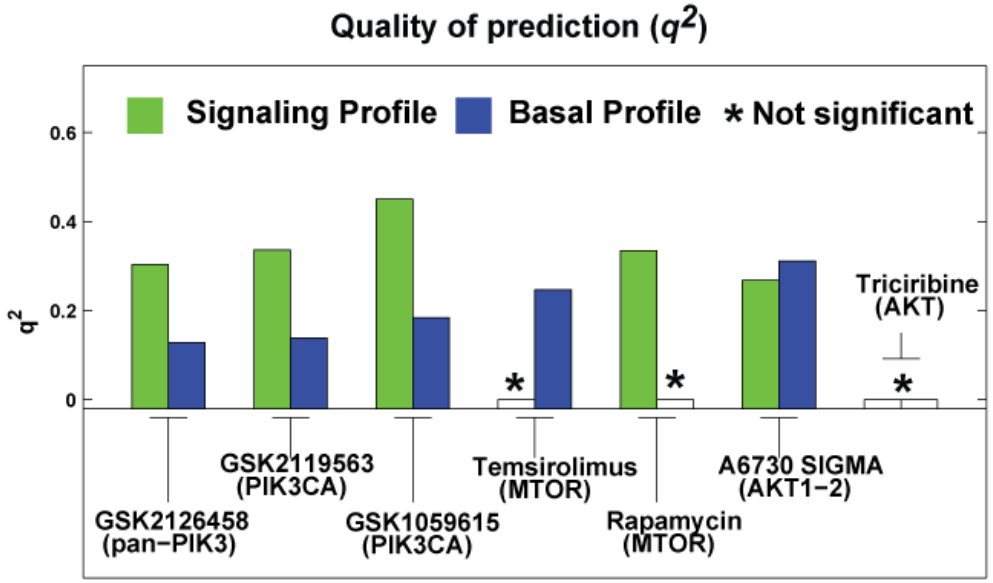
Profile data contains information on drug sensitivity

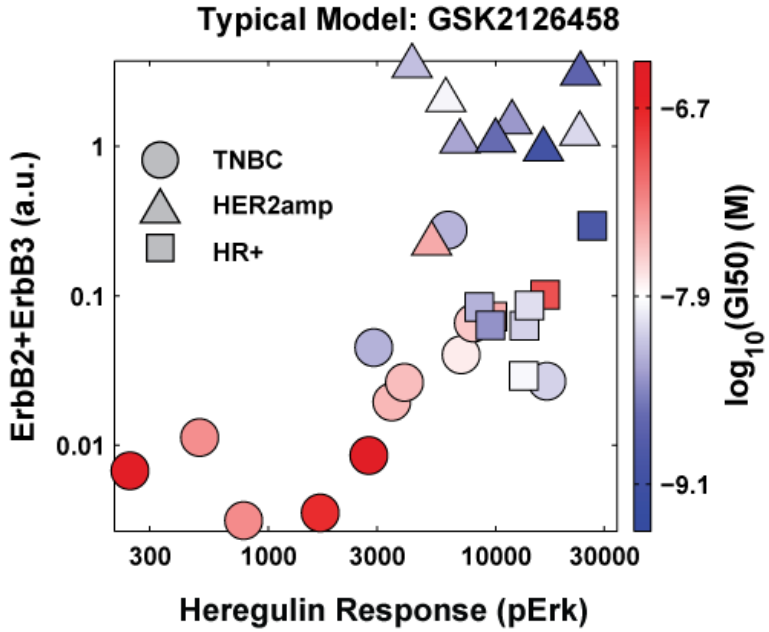


Constructing a response predictor by PLSR

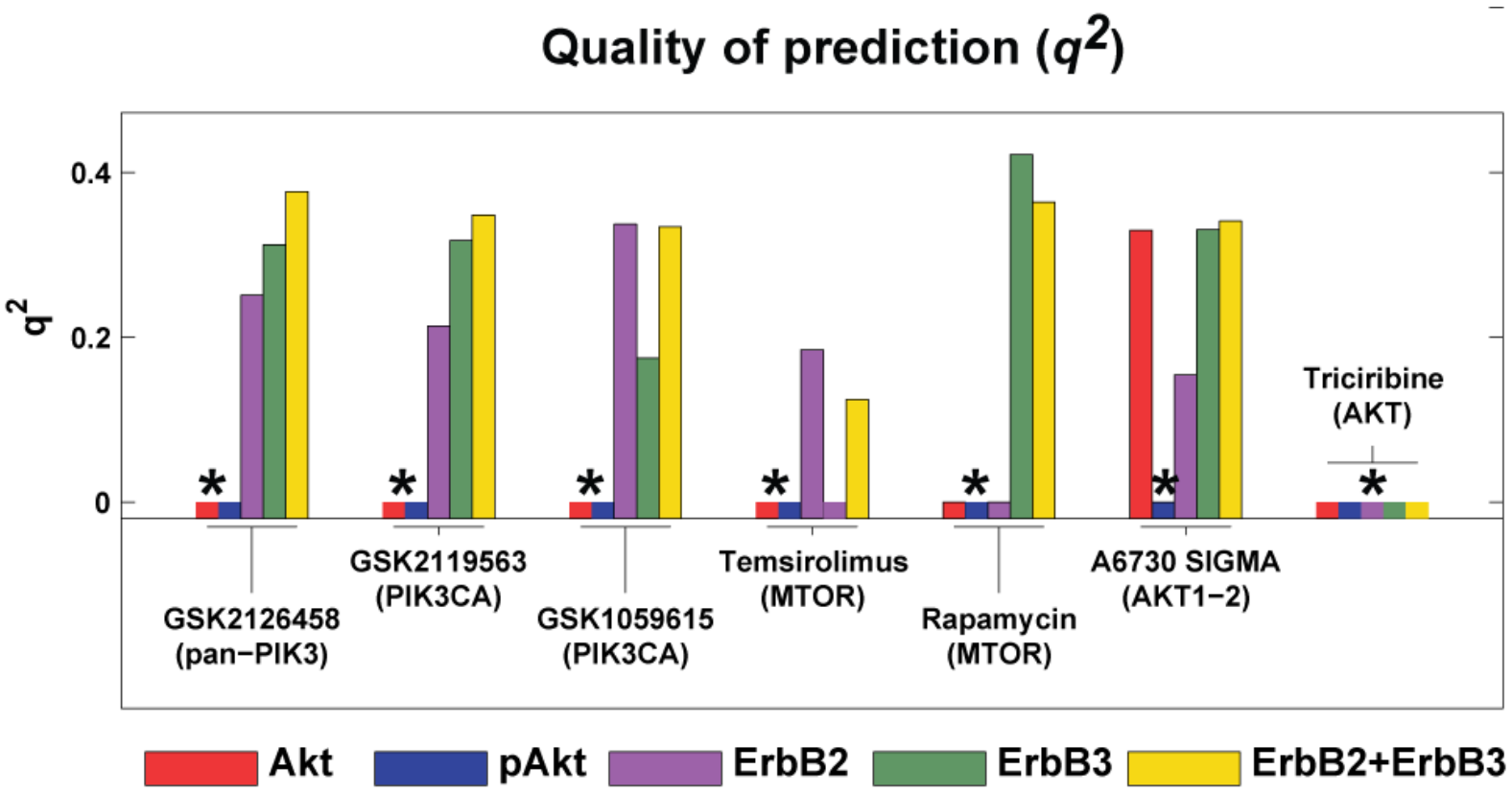


Response predictors for PI3K/Akt inhibitors

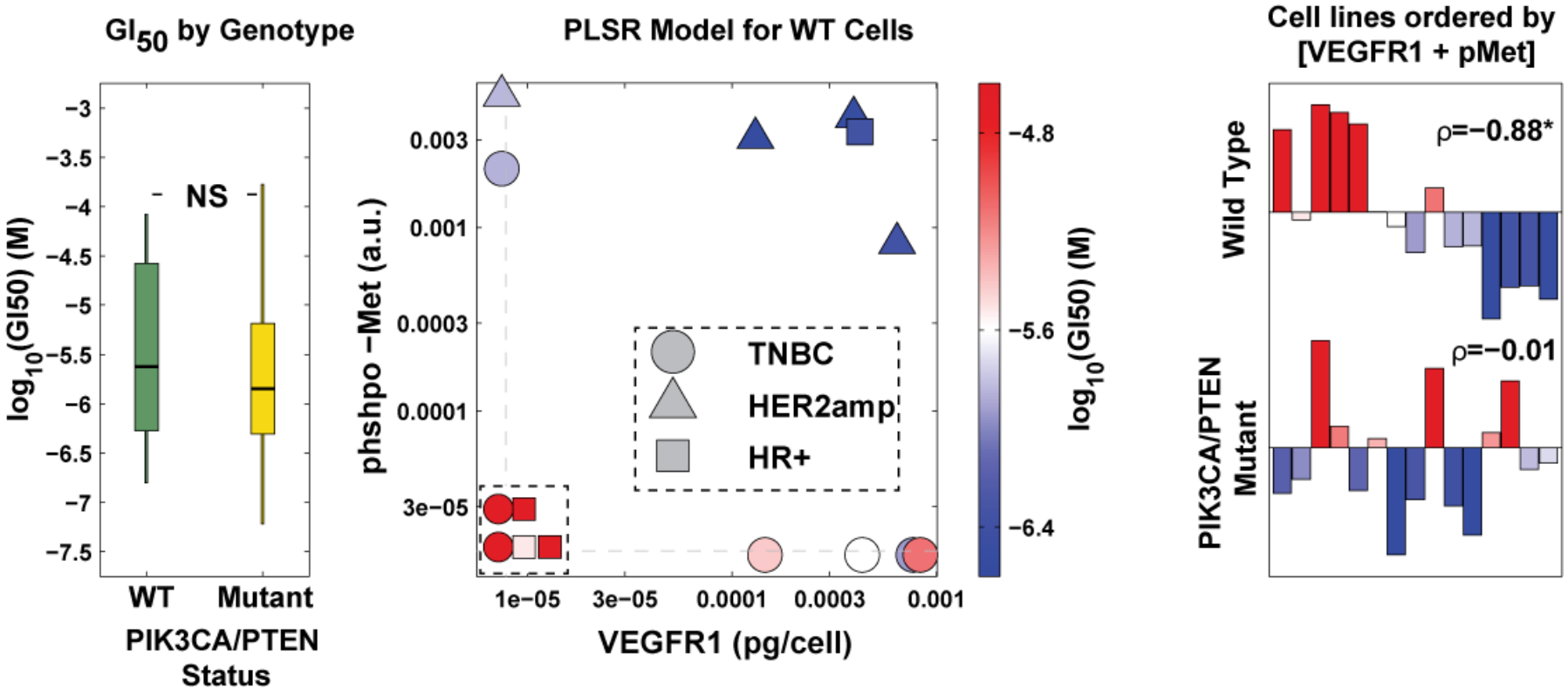




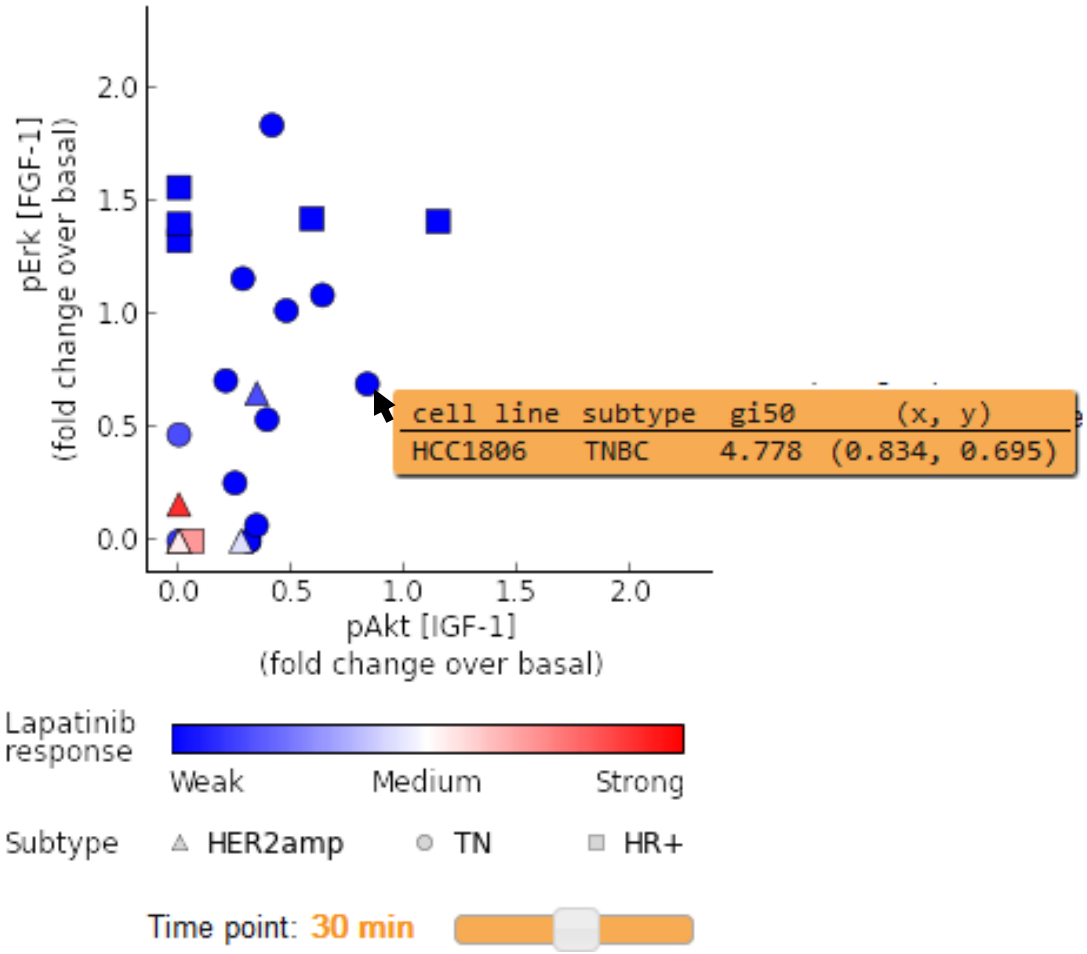
Response predictors for PI3K/Akt inhibitors: Receptors not Akt (or pAkt) are important variables



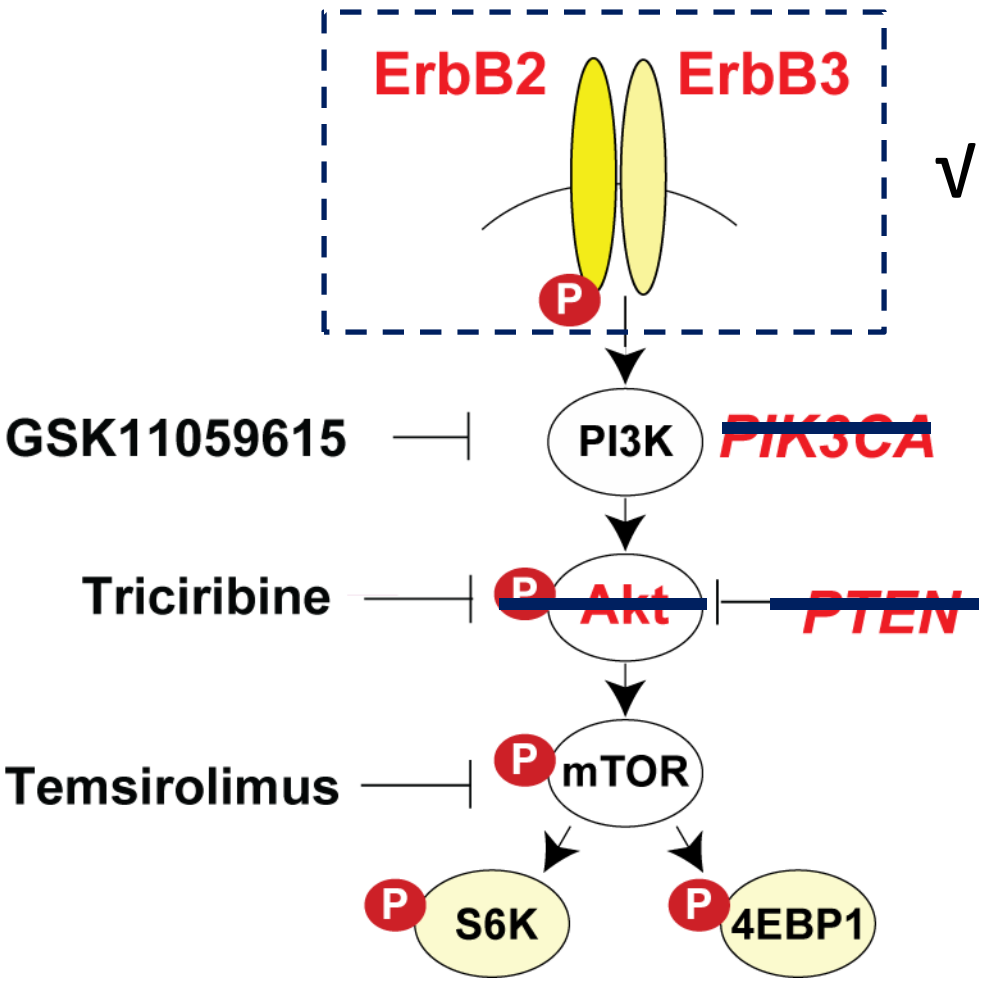
Building a hybrid predictor for Triciribine using biochemical and genomic data



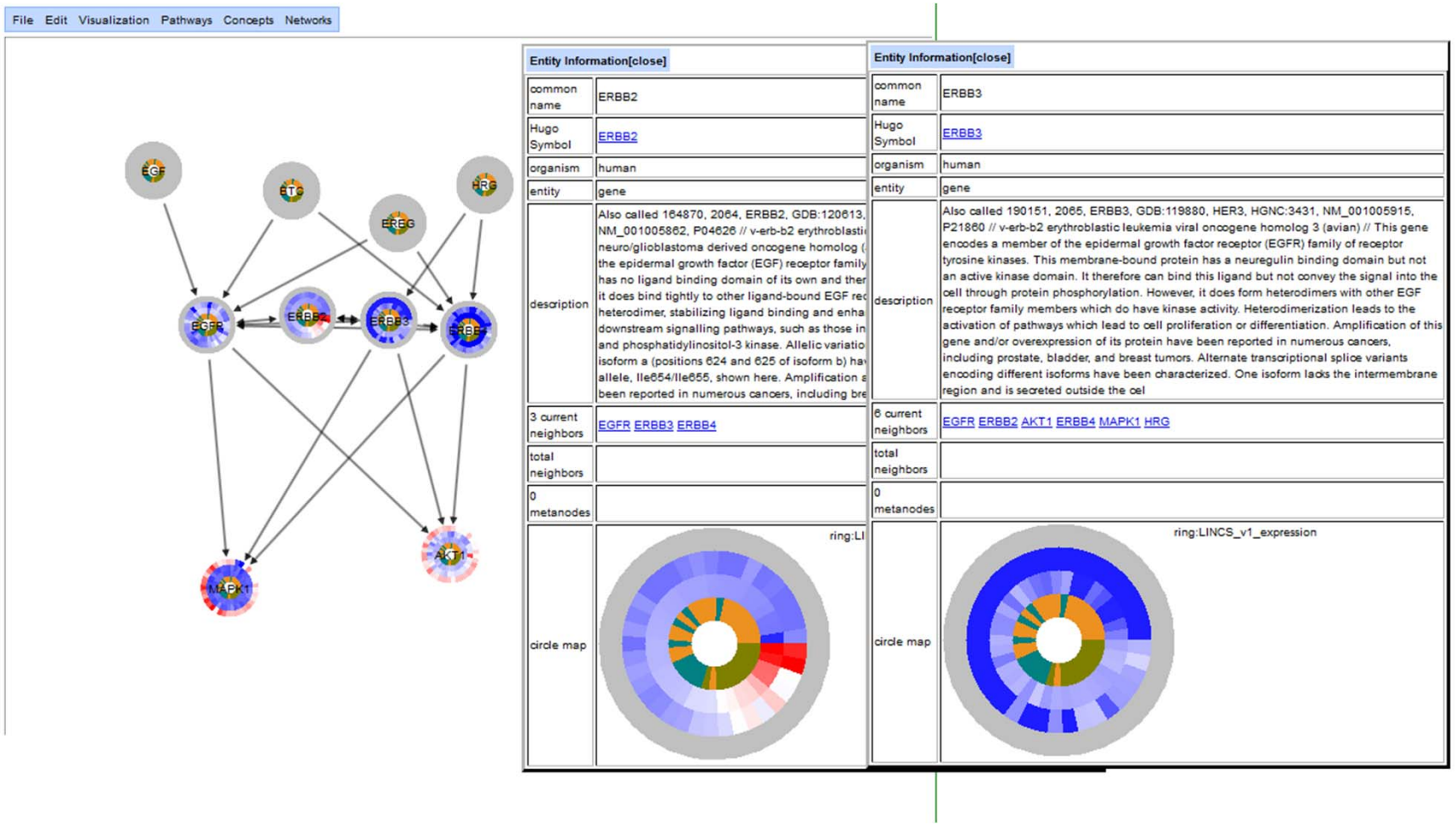
On-line browsing peturbagen response predictors



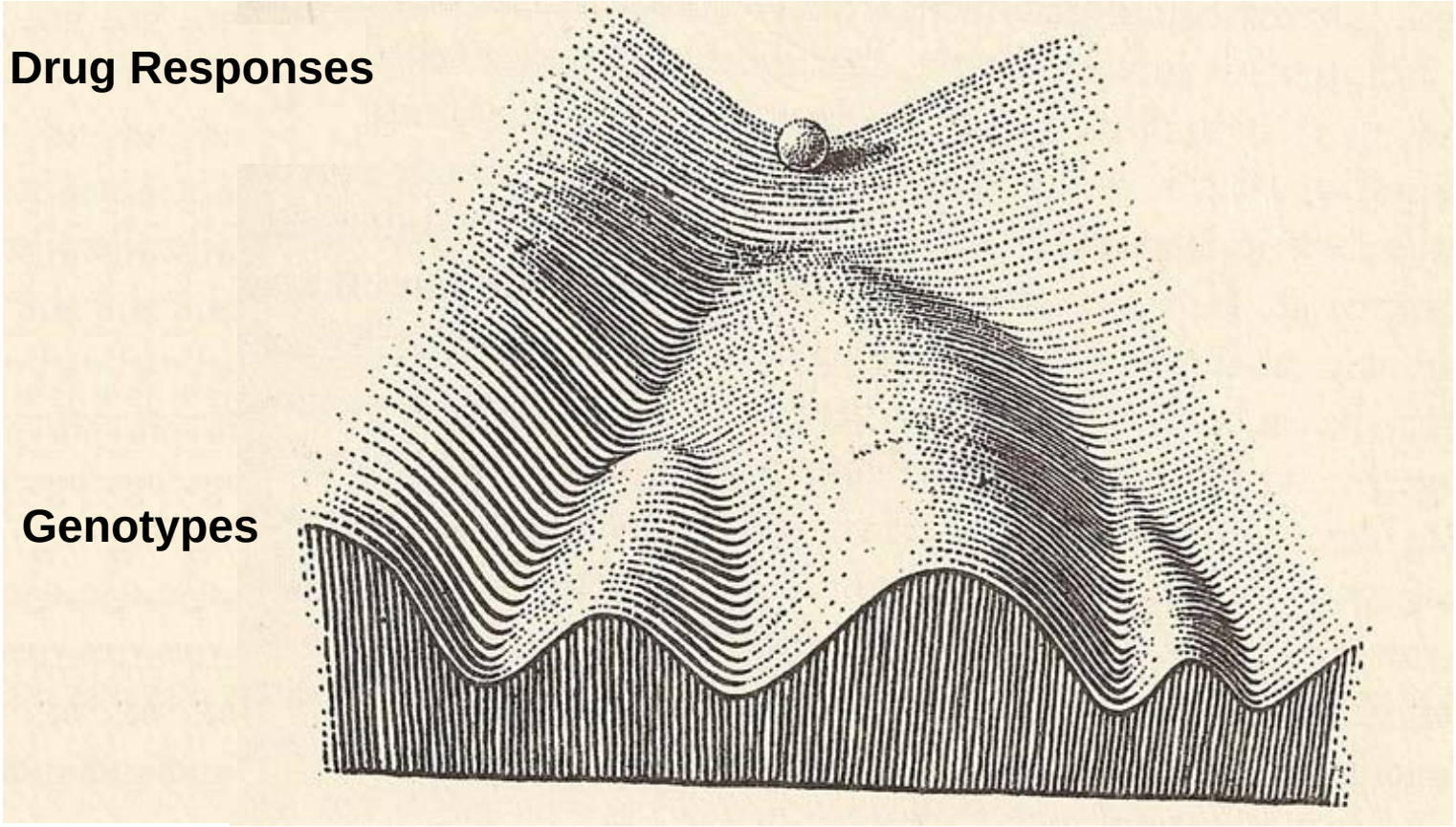
Conclusion: PI3K/Akt Response Predictors (posters 21-22)



Browsing LINCS Data and Models (poster 24)

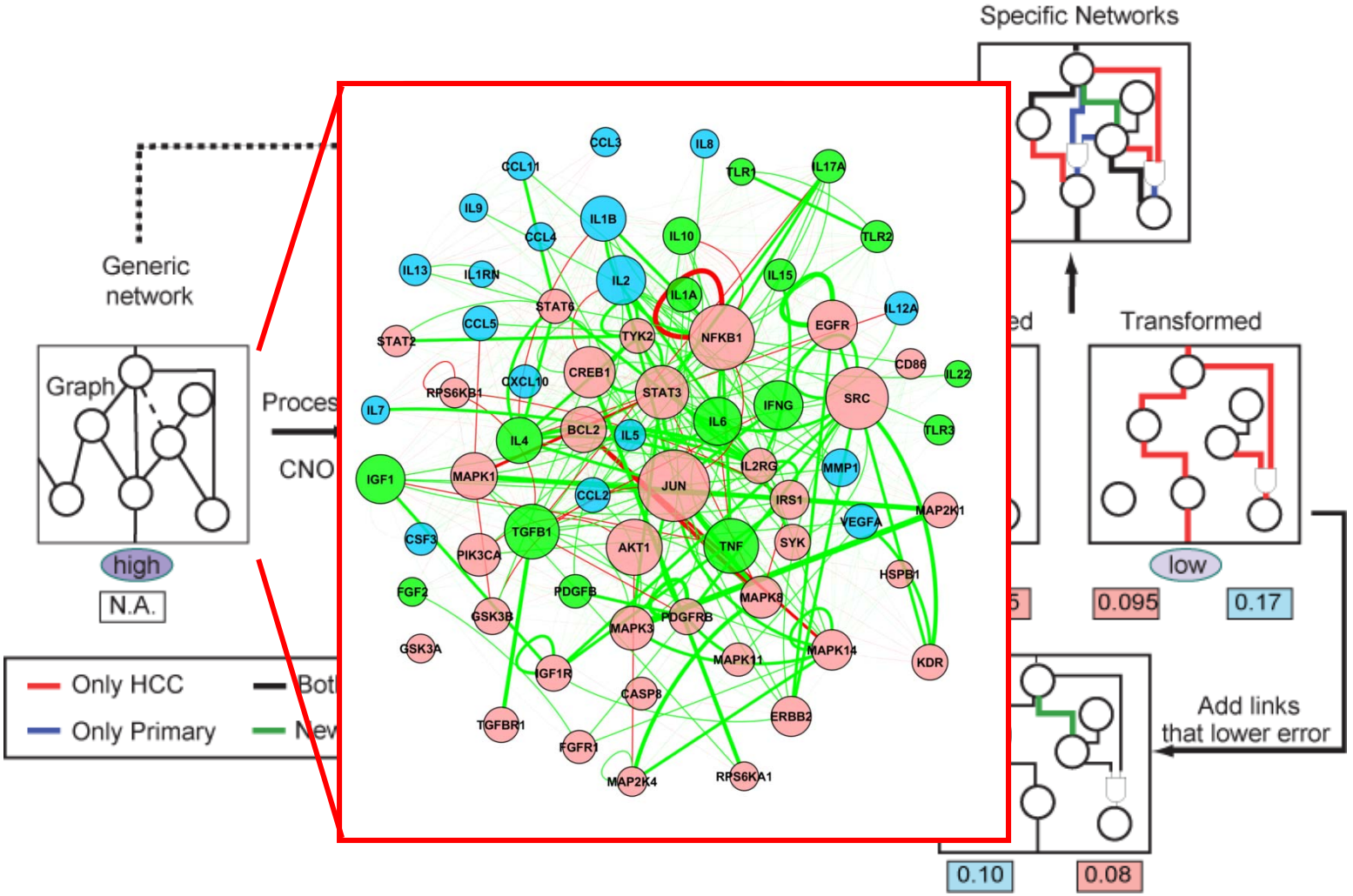


Hypothesis: canalization of drug responses across cell lines: many genotypes map to fewer phenotypes



A genetically canalized developmental system takes development to the same endpoint from many different genetic starting points – Waddington 1952.

Next steps: pathway models of perturbagen response



Modeling polypharmacology – a matrix perturbation of a complex network

LINCS Library of Integrated Network-based Cellular Signatures

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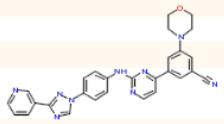
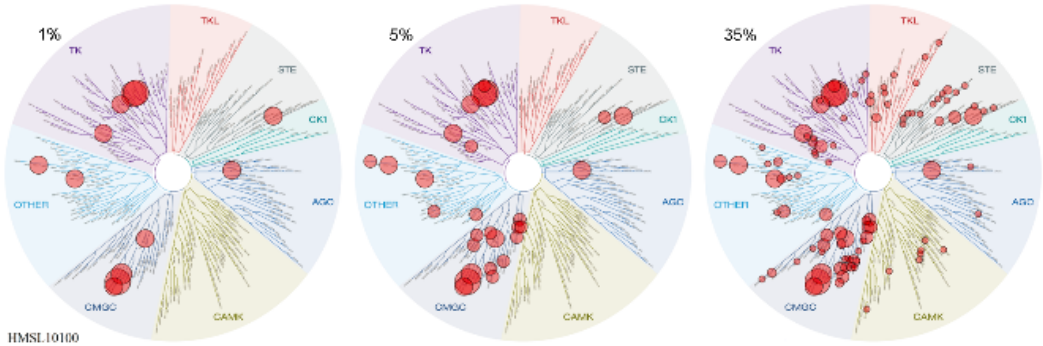
Small Molecule Information

Small Mol HMS LINCS ID:	10100-101
SM Name:	JNK-9L
Alternative Names:	KIN001-204
LINCS ID:	1100
Small Molecule Facility ID:	10100
Salt ID:	101
Molecular Mass:	501.2025564



KINOMEscan Image



Batch Information:

Small Mol HMS LINCS ID	Provider	Provider Catalog ID	Provider Batch ID
10100-101-1	Gray Lab	JNK-9L	JNK-9L-1

Datasets:

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Conflict Statement

- ***I disclose the following financial relationships***

  Consultant for:

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- ***I will not discuss off label use and/or investigational drug use in my presentation*.**