Modeling molecular diversity in cancer

Integrating "omics", mathematical models and functional cancer biology

Integrative Cancer Biology Program

$$\frac{\partial n}{\partial t} = D_n \nabla^2 n - \chi \nabla \cdot (n \nabla f)$$

Modeling molecular diversity in cancer

Identifying and understanding "omic" determinants of therapeutic response in breast cancer

- A collection of cell lines as a model of molecular and biological diversity
- Three integrative biology examples
  - Associating pathways and markers with response
  - Modeling MEK signaling diversity using pathway logic
  - Bayesian network models of AKT signaling

Modeling molecular diversity in cancer

Identifying and understanding "omic" determinants of therapeutic response in breast cancer

- A collection of cell lines as a model of molecular and biological diversity
- Three integrative biology examples
  - Associating markers with response
  - Modeling MEK signaling diversity using pathway logic
  - Bayesian network models of AKT signaling

Model requirements

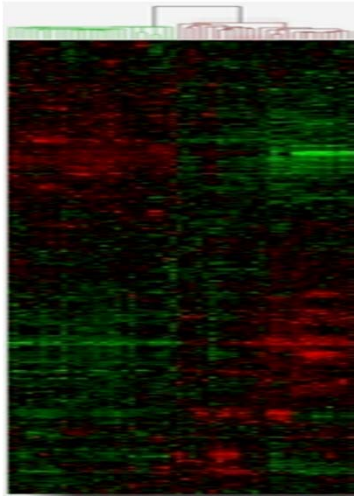
Identifying and understanding "omic" determinants of therapeutic response

- The molecular abnormalities that influence drug response in primary tumors must be functioning in the model
- The panel must have sufficient molecular diversity so that statistical analyses will have the power to identify molecular features associated with response

Cell lines as models of primary breast tumors

A collection of 50 cell lines retain important transcriptional and genomic features of primary tumors

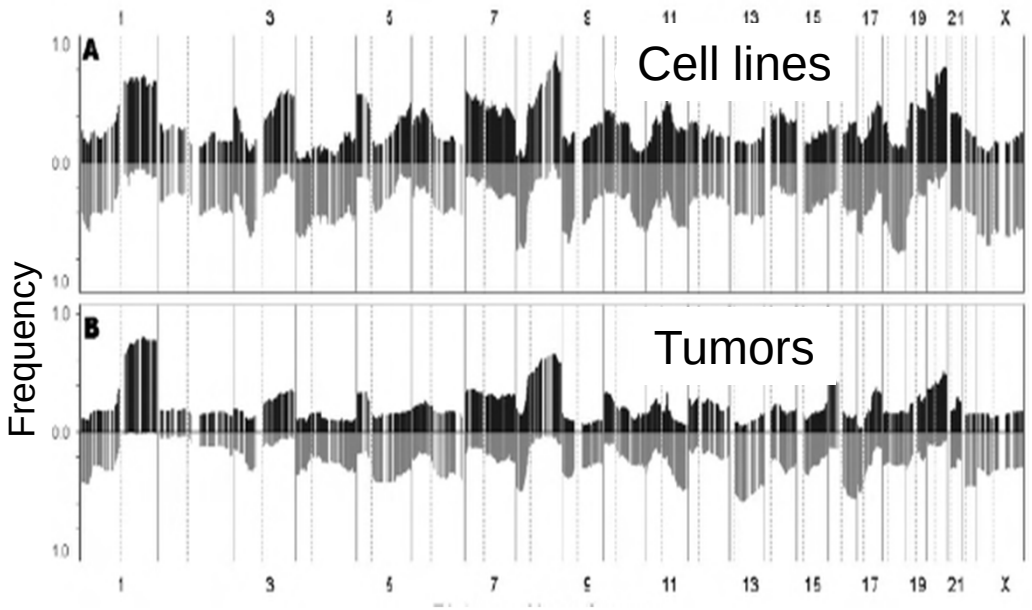
Expression



Luminal

Basal

Copy number



Genome location

Neve et al, *Cancer Cell* 2006
Chin et al, *Cancer Cell,* 2006

Modeling molecular diversity in cancer

Integrating "omics", mathematical models and functional cancer biology

- A collection of cell lines as a model of molecular and biological diversity
- Three integrative biology examples
  - Associating markers with response
  - Modeling MEK signaling diversity using pathway logic
  - Bayesian network models of AKT signaling

Associating molecular markers with response to lapatinib

Univariate predictors

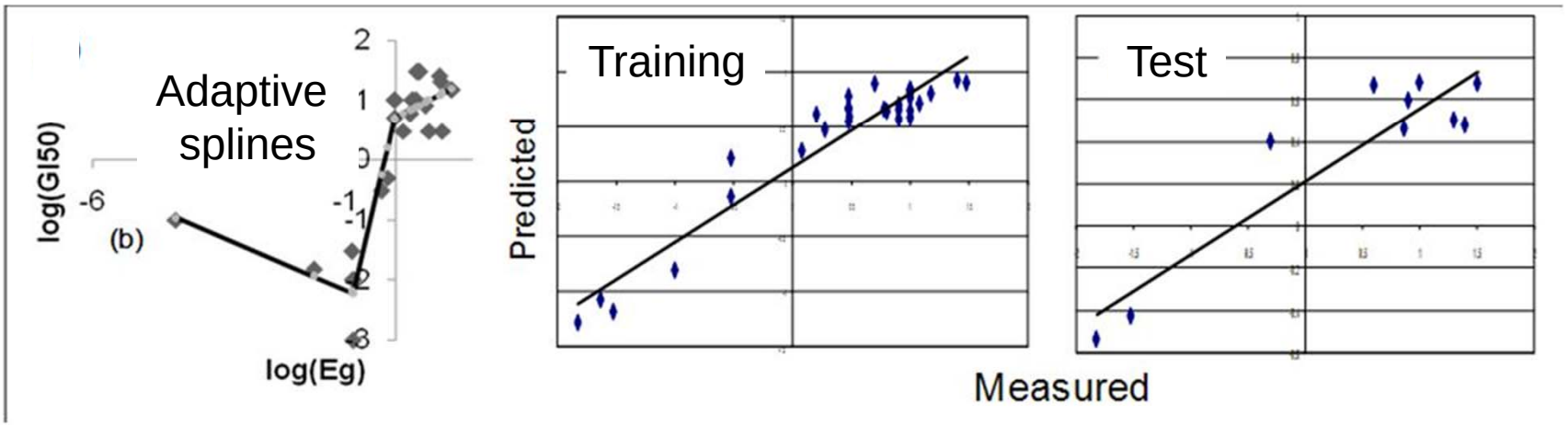
Array CGH

mRNA Expression

Protein Expression

Weighted Voting Methods

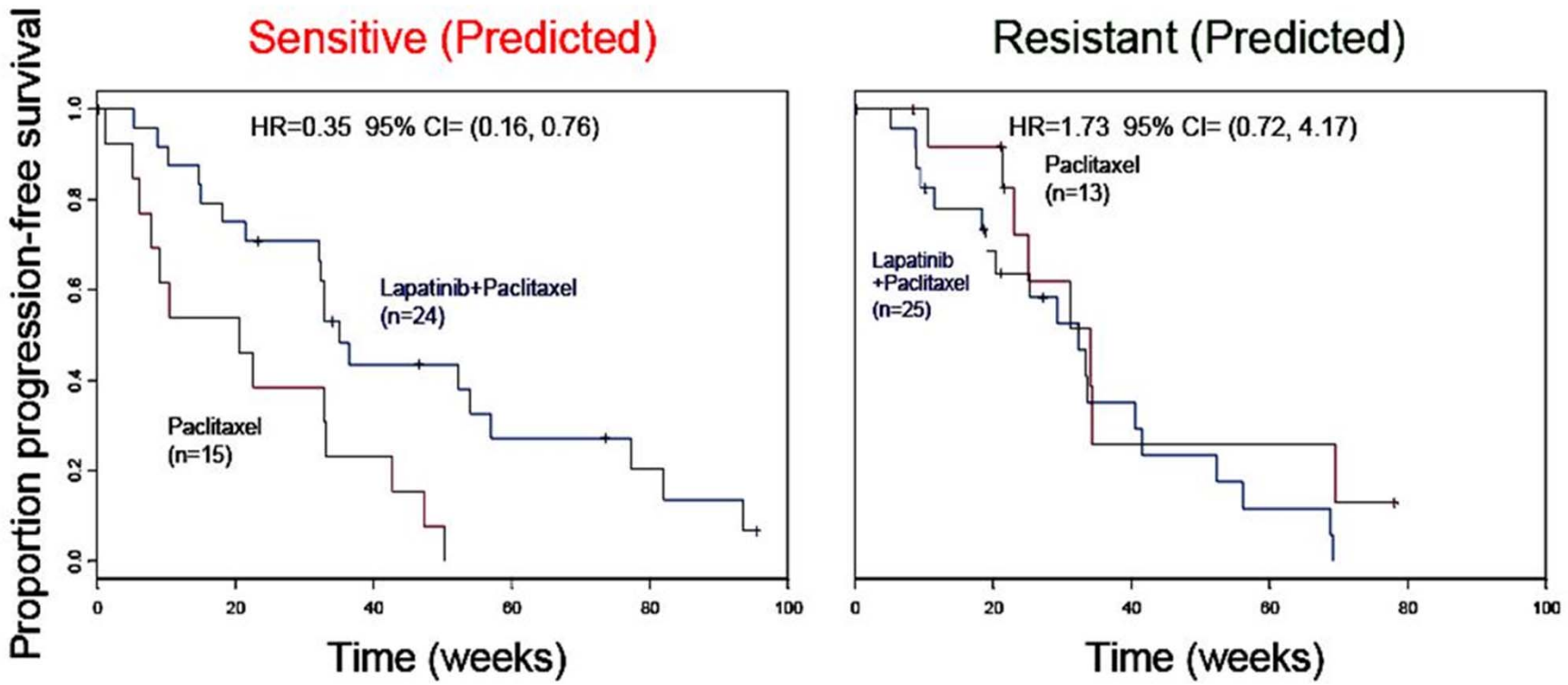
Prediction: Molecular markers and networks associated with sensitivity and resistance will predict clinical response



Debo Das, 2007

Test: Cell line markers predict response in HER2 positive patients

EGF30001: A randomized, Phase III study of Paclitaxel + Lapatinib vs. Paclitaxel + Placebo
HER2, GRB7, CRK, ACOT9, LJ31079, DDX5



GSK-LBNL collaboration

Integrative Cancer Biology Program

Modeling molecular diversity in cancer

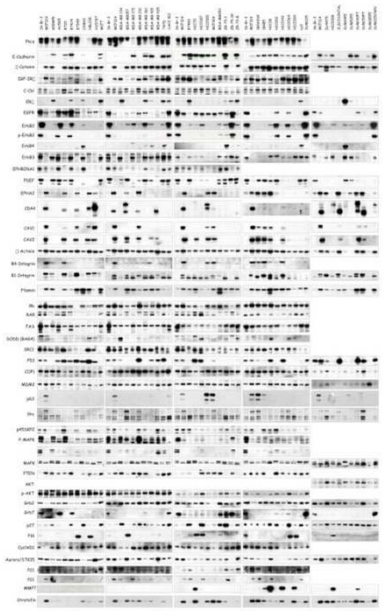
Identifying and understanding "omic" determinants of therapeutic response in breast cancer

- A collection of cell lines as a model of molecular and biological diversity
- Three integrative biology examples
  - Associating markers with response
  - Modeling MEK signaling diversity using pathway logic
  - Bayesian network models of AKT signaling

Hierarchical analysis of Pathway Logic states and rules

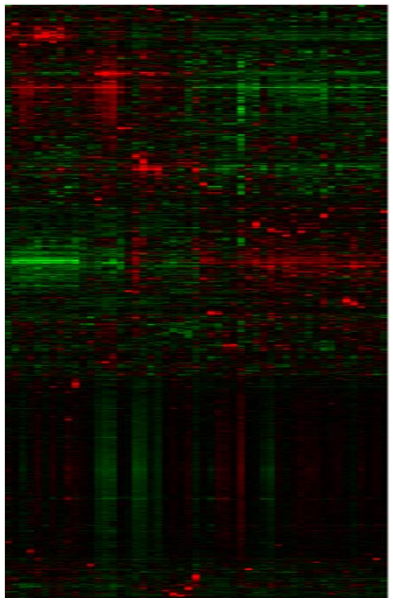
Baseline levels populate PL model states
Rules define predicted pathway activity

Protein abundances



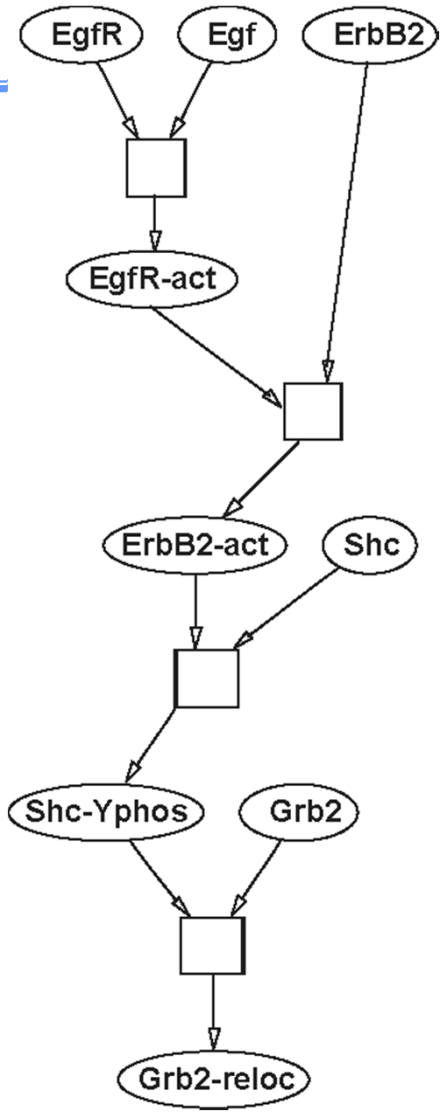
+

Transcript levels



→

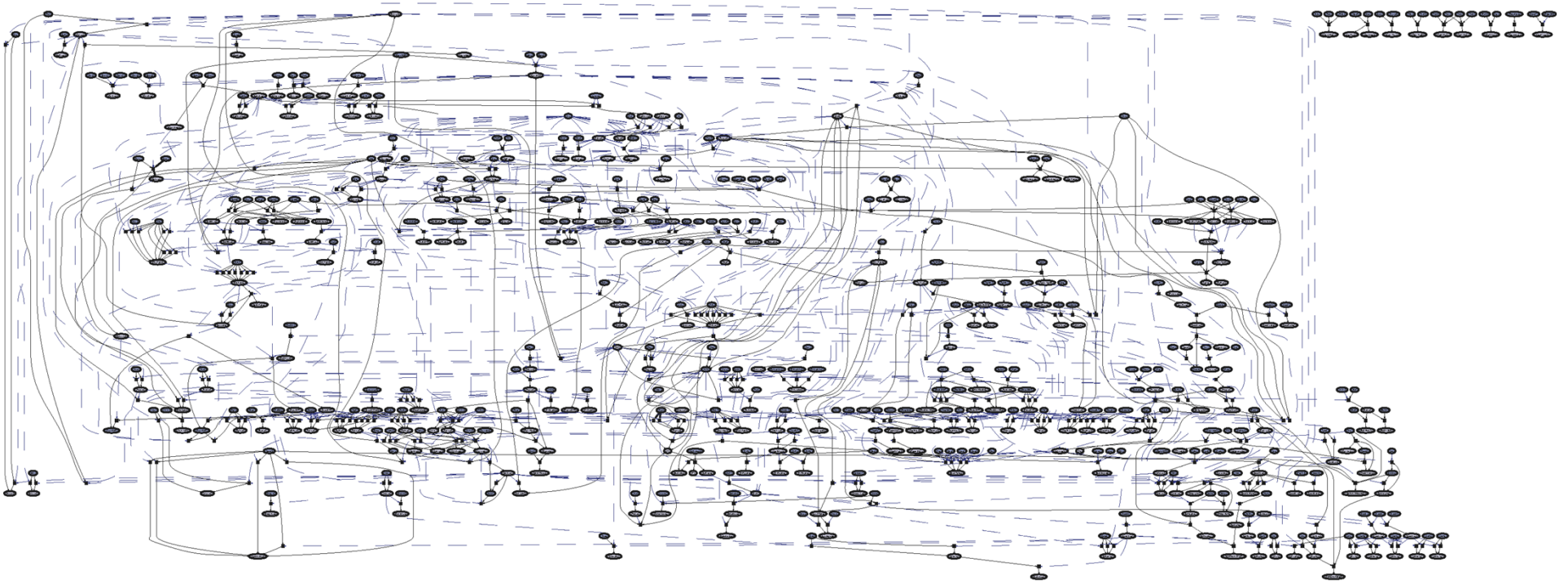
Curated network model



Heiser, Spellman, Talcott, Knapp, Lauderote

Integrative Cancer Biology Program

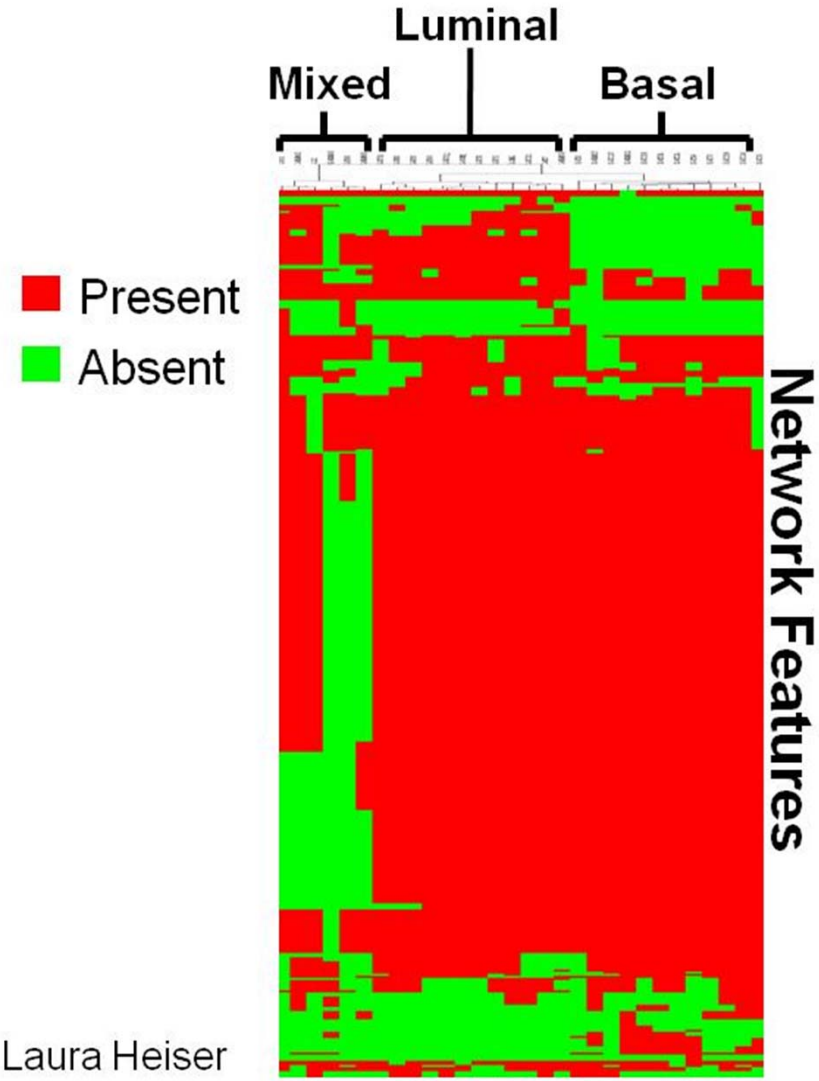
Example network of one cell line



Integrative Cancer Biology Program

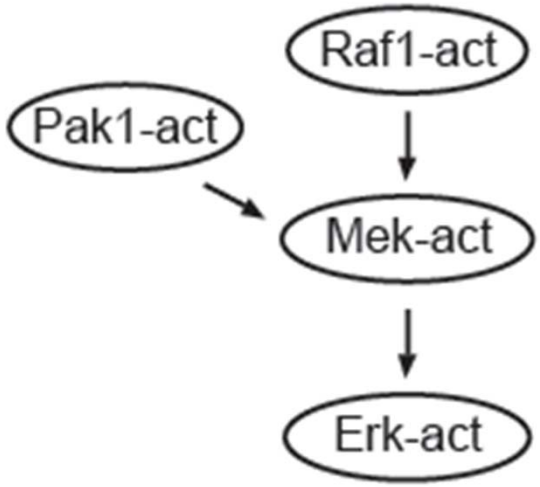
$$\frac{\partial n}{\partial t} = D_n \nabla^2 n - \chi \nabla \cdot (n \nabla f)$$

Hierarchical analysis of network features

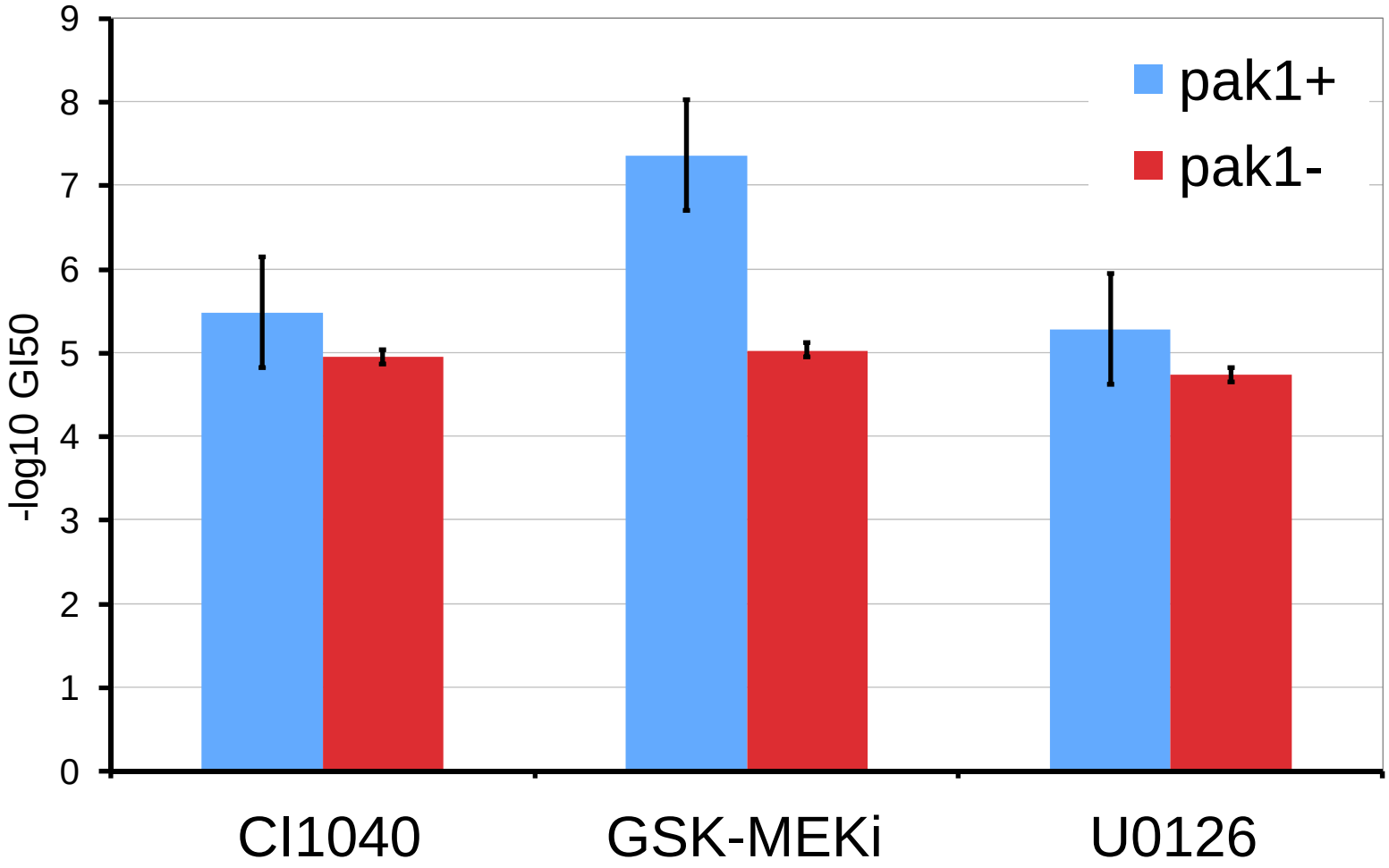


Laura Heiser

Prediction: PAK1 is required for network activation of MEK/ERK cascade in luminal cell lines



Test: PAK1^{+} luminal cell lines are more sensitive to MEK inhibitors

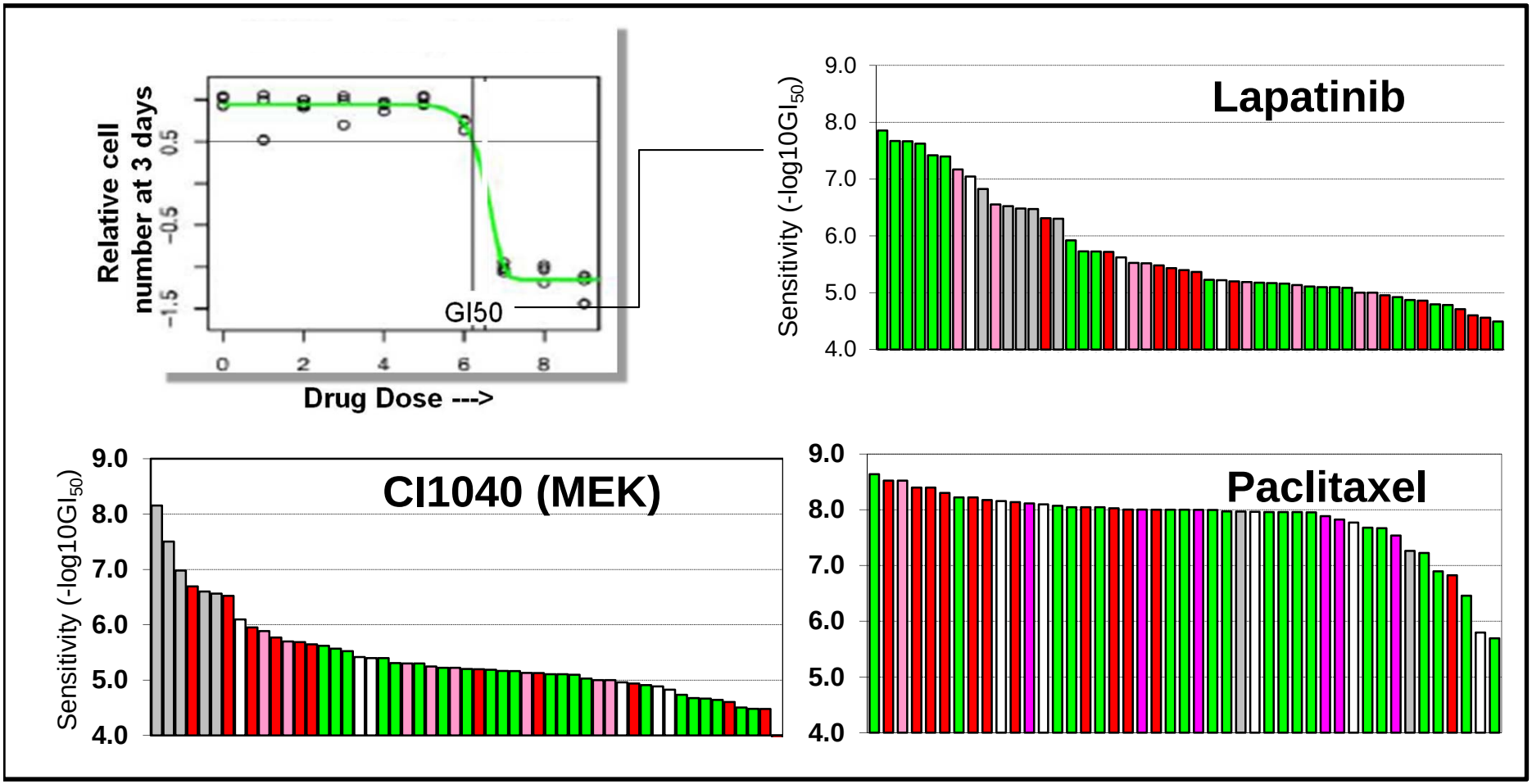


Modeling molecular diversity in cancer

Identifying and understanding "omic" determinants of therapeutic response in breast cancer

- A collection of cell lines as a model of molecular and biological diversity
- Three integrative biology examples
  - Associating pathways and markers with response
  - Modeling MEK signaling diversity using pathway logic
  - Bayesian network models of AKT signaling

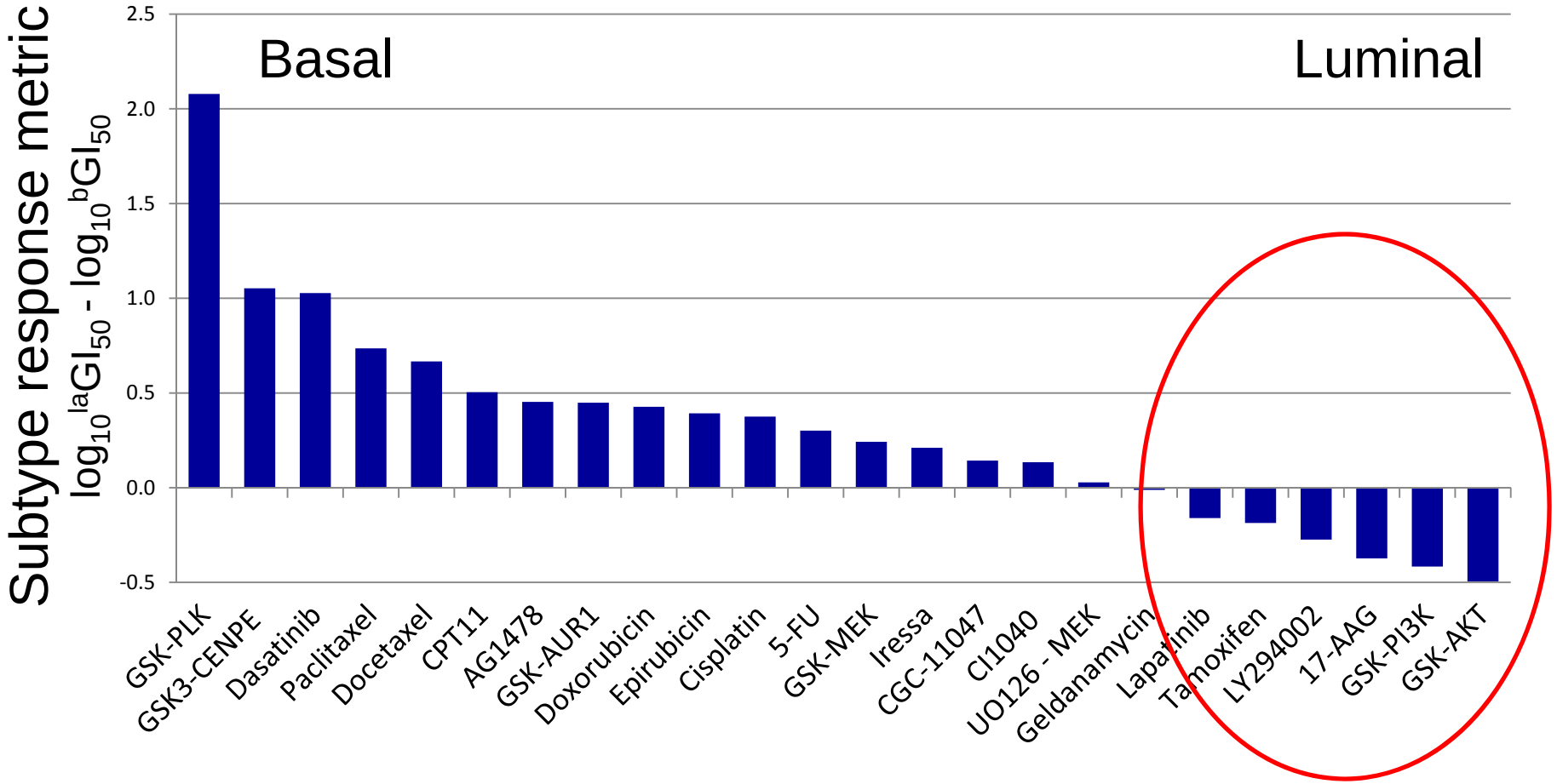
Therapeutic agents show strong luminal subtype specificity



Kuo, Guan, Hu, Bayani 2007

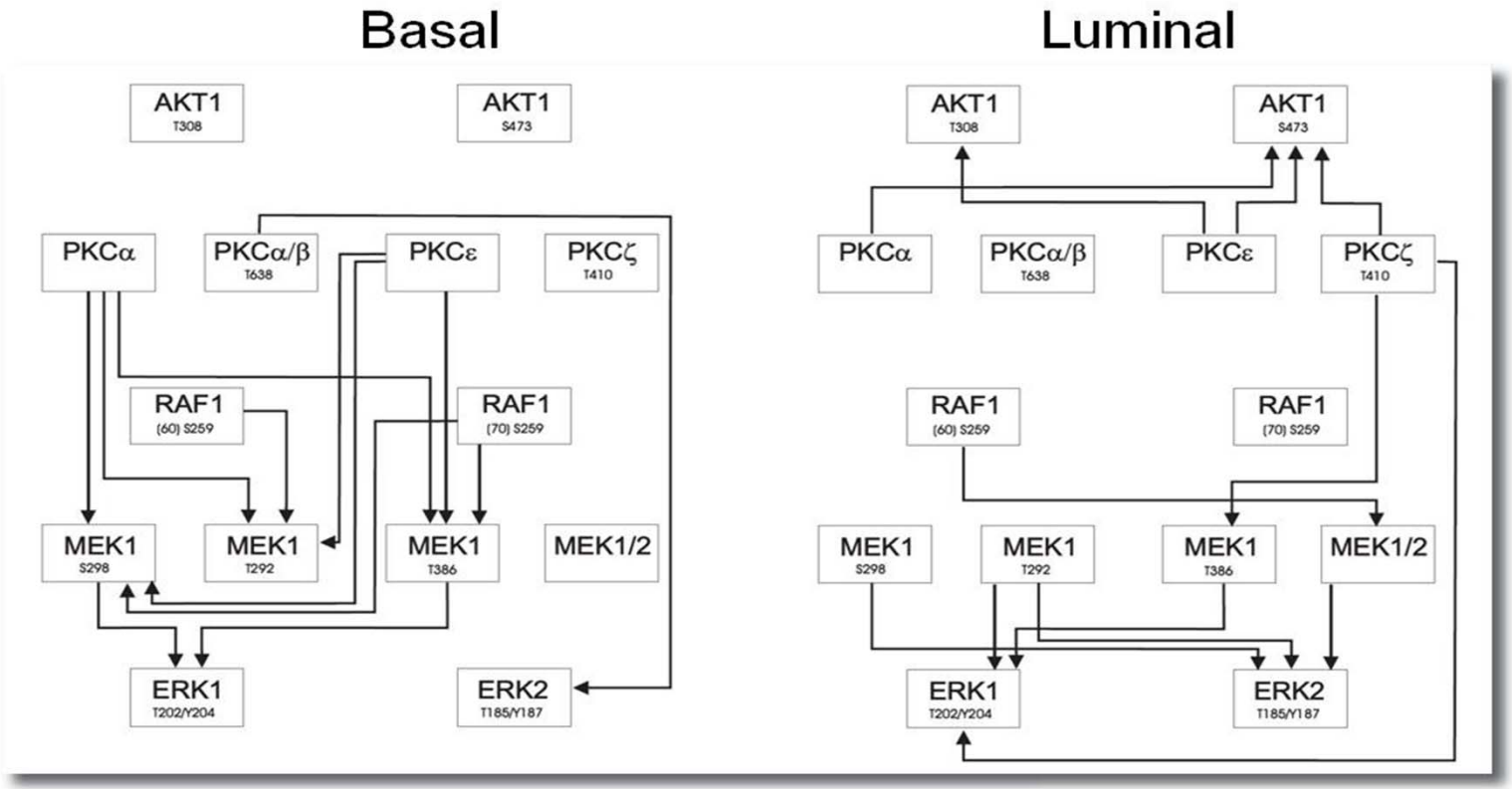
Integrative Cancer Biology Program

AKT pathway inhibitors show strong luminal subtype specificity



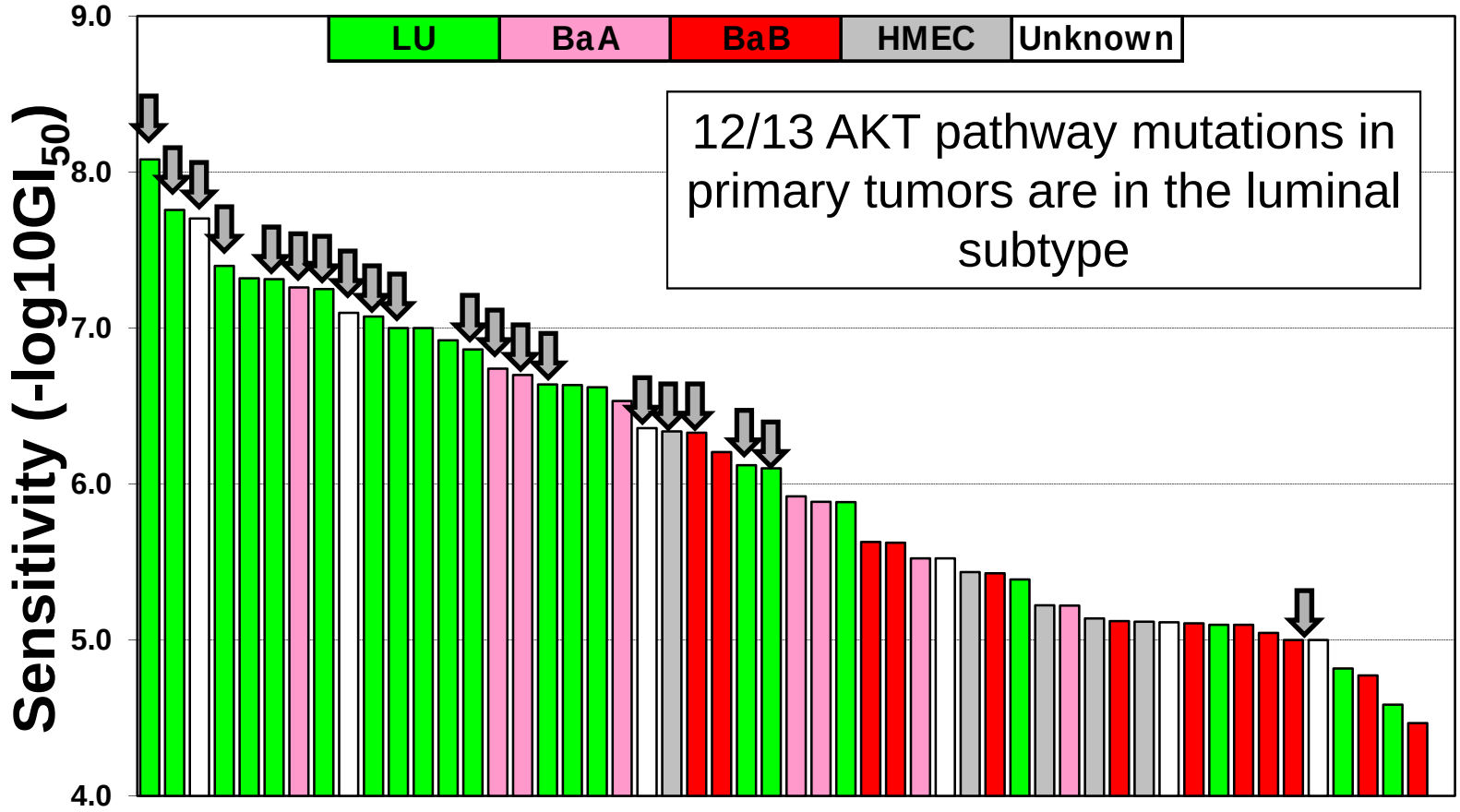
Bayesian network analysis reveals AKT dependent signaling in luminal lines

Prediction: PI3-kinase pathway mutations will occur preferentially in luminal subtype cell lines



Mukherjee , Speed, Neve, et al., 2007

Test: AKT-inhibitor responsive cell lines carry PI3-kinase pathway mutations



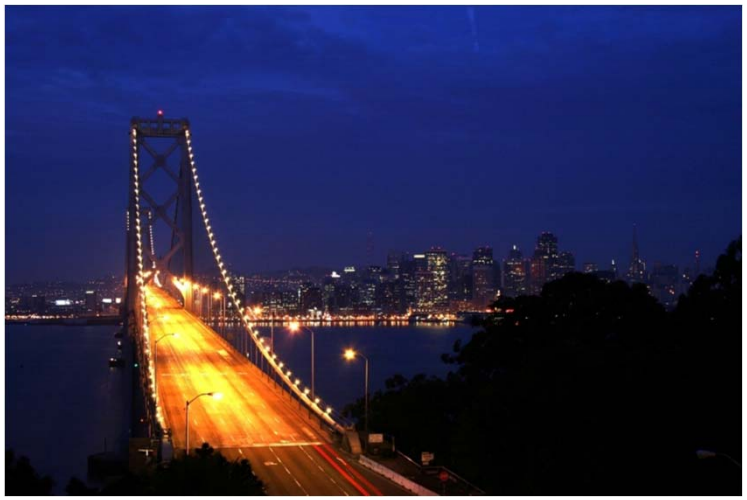
Kuo, Neve, Spellman et al., 2007

Modeling molecular diversity in cancer

Integrating "omics", mathematical models and functional cancer biology

- A collection of cell lines as a model of molecular and biological diversity
- Three integrative biology examples
  - Associating pathways and markers with response
  - Modeling MEK signaling diversity using pathway logic
  - Bayesian network models of AKT signaling

Collaborating Laboratories & Support



Engineering
Earl Correll
Bob Nordmeyer
Jian Jin
Damir Sudar

Surgery/Pathology
Britt Marie Ljung
Fred Waldman
Shanaz Dairkee
Laura Esserman

Exp. Therapeutics
Maria Koehler
Mike Press
Michael Arbushites
Tona Gilmer
Barbara Weber
Richard Wooster

Cell /Genome Biology
Rich Neve
Mina Bissell
Philippe Gascard
Frank McCormick
Mary Helen
Barcellos Hoff
Rene Bernards
Gordon Mills

Comp. Biol
Paul Spellman
Laura Heiser
Keith Lauderote
Merrill Knapp
Carolyn Talcott
Sach Mukherjee
Terry Speed
Jane Fridlyand
Bahram Parvin
Lisa Williams
Steve Ashton

ICBP, SPORE, GSK, Affymetrix, Genentech, Panomics, Cellgate, Cell Biosciences, Komen, Avon, EGF30001 Trial Investigators