Modeling molecular diversity in cancer

Integrating “omics”, mathematical models and functional cancer biology

Lawrence Berkeley National Laboratory
University of California, San Francisco
University of California, Berkeley
SRI International
Netherlands Cancer Institute
MD Anderson Cancer Center
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
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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

Copy number

Frequency

Genome location

Neve et al, Cancer Cell 2006
Chin et al, Cancer Cell, 2006
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Associating molecular markers with response to lapatinib

Prediction: Molecular markers and networks associated with sensitivity and resistance will predict clinical response.
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
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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
Example network of one cell line
Hierarchical analysis of network features

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.
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Therapeutic agents show strong luminal subtype specificity

Kuo, Guan, Hu, Bayani 2007
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

12/13 AKT pathway mutations in primary tumors are in the luminal subtype

Kuo, Neve, Spellman et al., 2007
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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

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