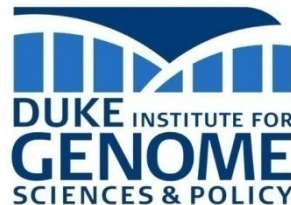


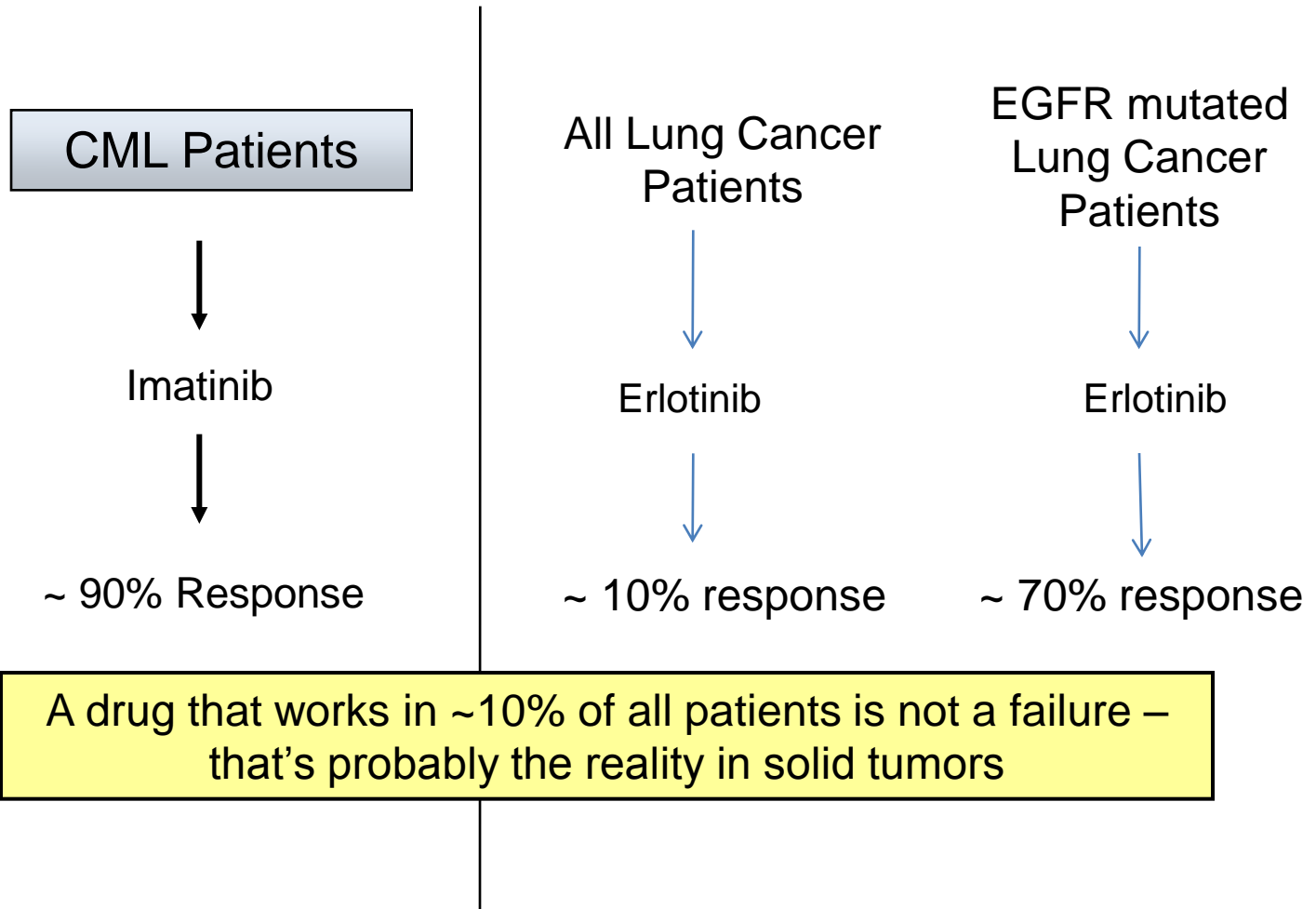
Rationale for Genomic Guided Molecular Therapy in Lung Cancer

Target and Pathway Identification

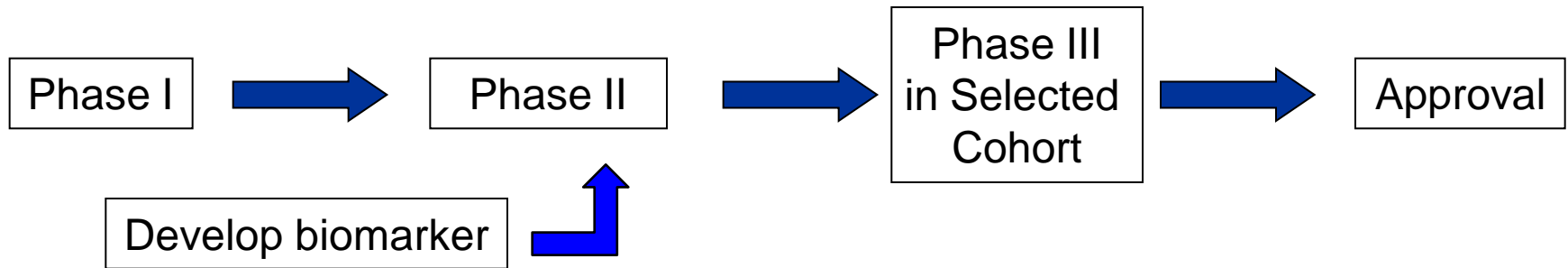
Neal Ready MD, PhD
Institute for Genome Science and Policy
Division of Oncology,
Duke University



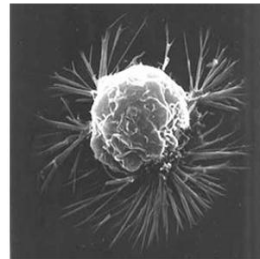
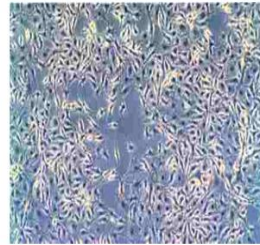
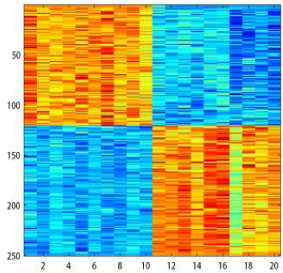
CML and Lung Cancer



Biomarker-Driven Drug Development



Developing Pathway Signature Targeted Therapy



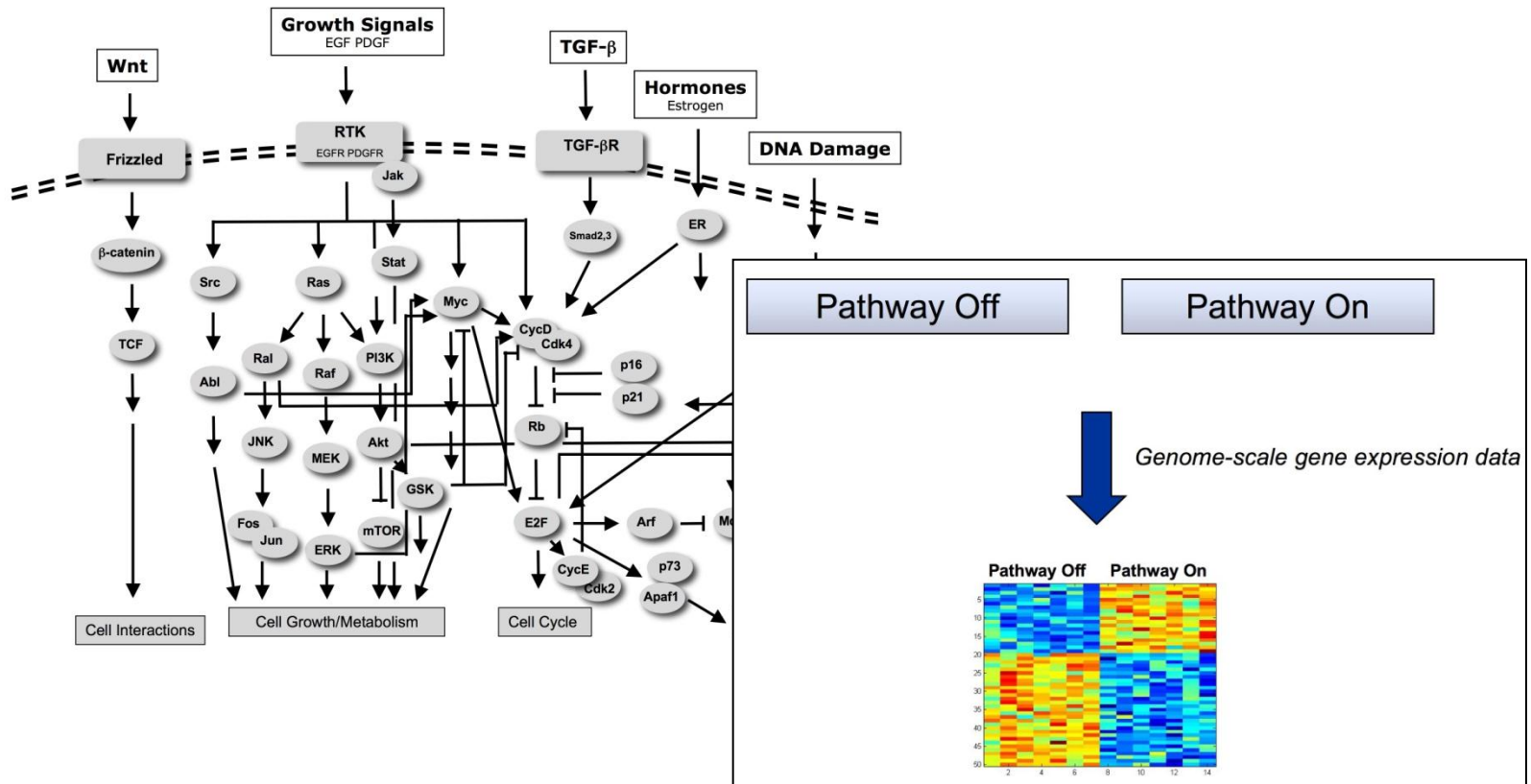
Discovery:

1. *In vitro* experiments
2. Mouse models
3. Human tumors

Validation:

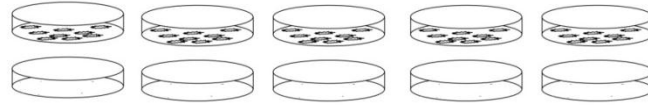
1. Retrospective analysis
2. Undirected clinical trials
3. Directed therapy clinical trials

Signatures To Predict Pathway Activation



Approach Used to Generate Pathway Signatures

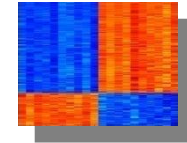
Quiescent HMEC/HBEC's expressing oncogene or control



Gene expression analysis

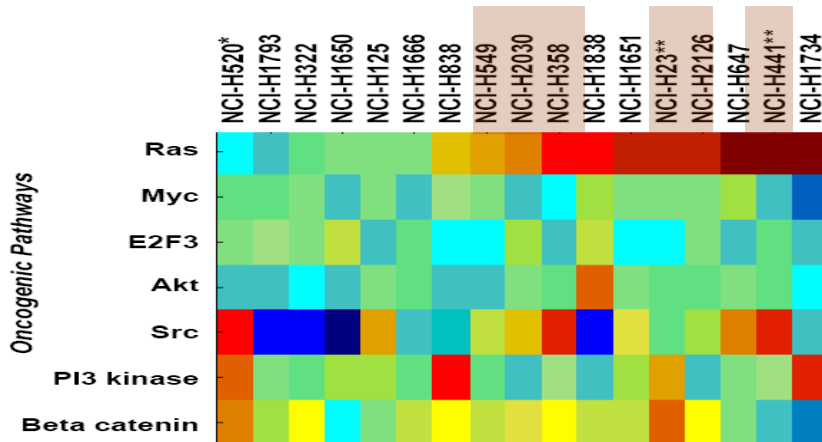
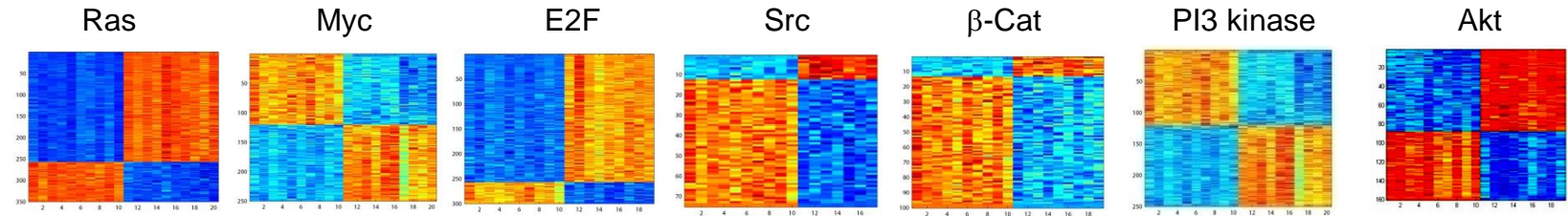


Patterns of gene expression correlated
to oncogenic pathways

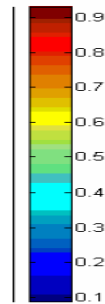


Apply models to identify pathway status in tumors

Mapping Pathway Status to Lung Cancer Cell Lines

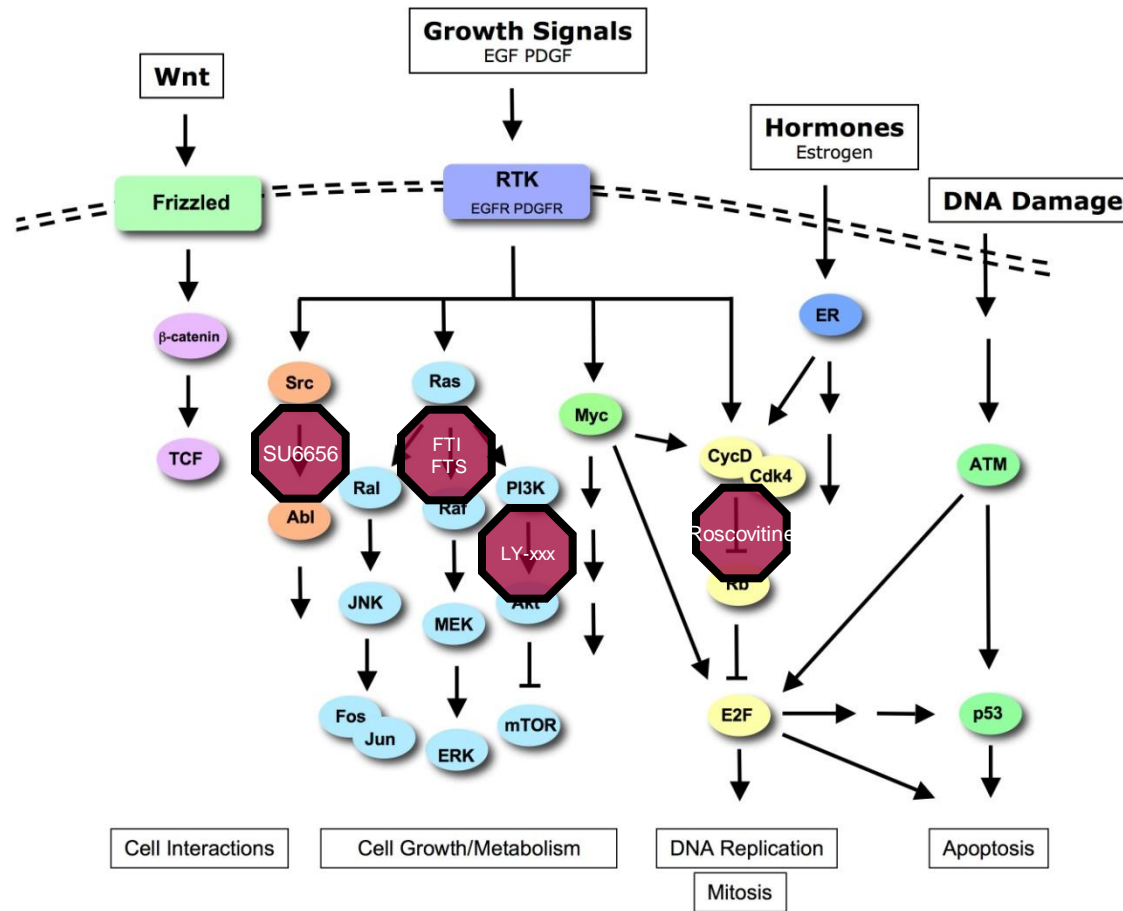


Cell lines with K-ras or N-ras or H-ras mutations
H23, H358, H441, H549, H2126, H2030

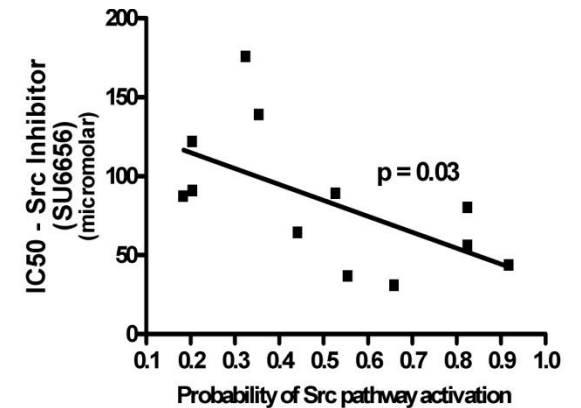
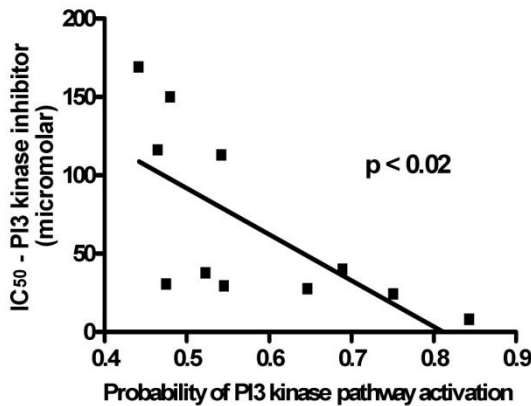
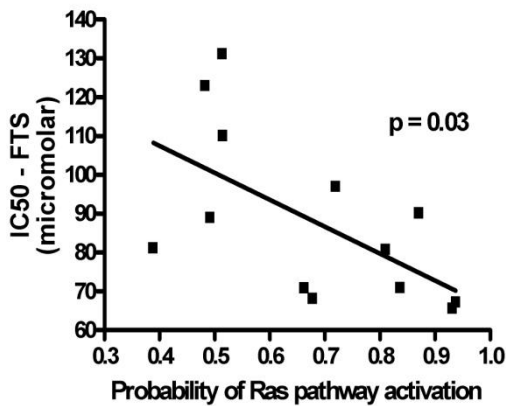
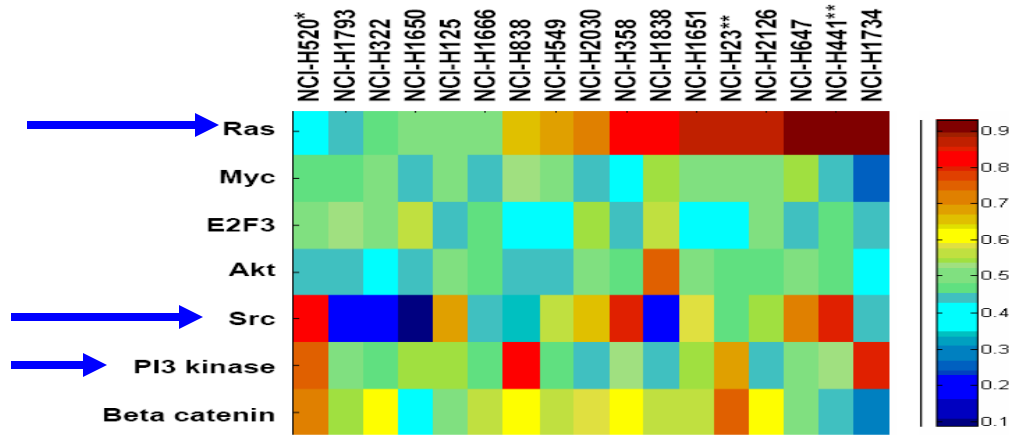


Match with drug
sensitivity

Signaling Pathways Underlying the Oncogenic Phenotype-Identifying Targets



Pathway Signatures Predict Therapeutic Response



Clinical Trials to Validate Biomarkers

- Directed Therapy Clinical Trial When:
 - 1) Retrospective clinical validation data available
 - 2) and/or All Treatments are Standard
 - 3) Example- direct to erlotinib or docetaxel 2nd line
- Simon Two Stage Design, Stage I treat all patients same; Stage II only treat patients with + biomarker when:
 - 1) No retrospective clinical data available
 - 2) and/or One or more of therapies not standard
 - 3) Example-molecular therapy unproven in NSCLC

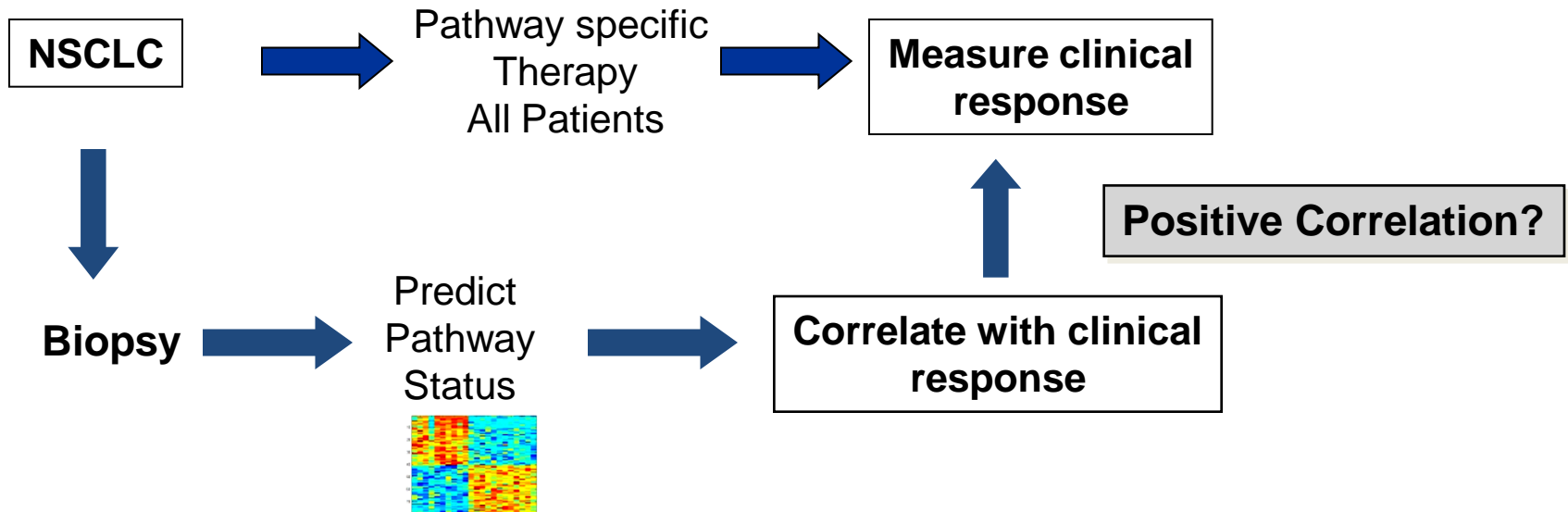
Duke Clinical Trials

Validation of Signatures for Molecular Therapy

- Simon two stage design
 - First clinical trial all patients are treated
 - Second trial select for tumors with biomarker
- Advanced disease trial for previously treated
- “Window of opportunity” early stage disease

Validation of the Strategy

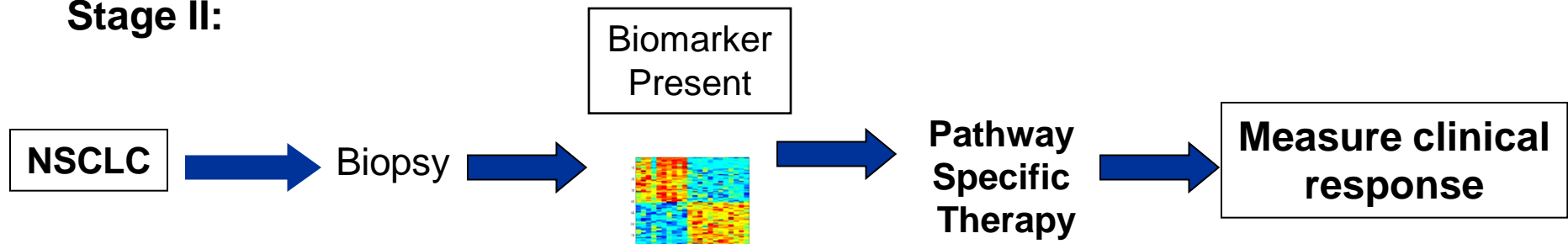
Simon Two Stage Design-Stage I



Validation of the Strategy

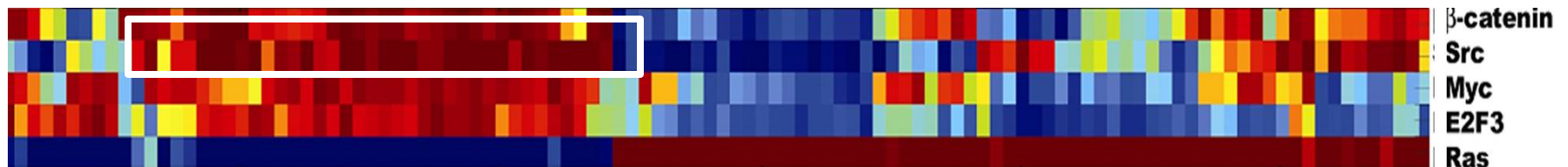
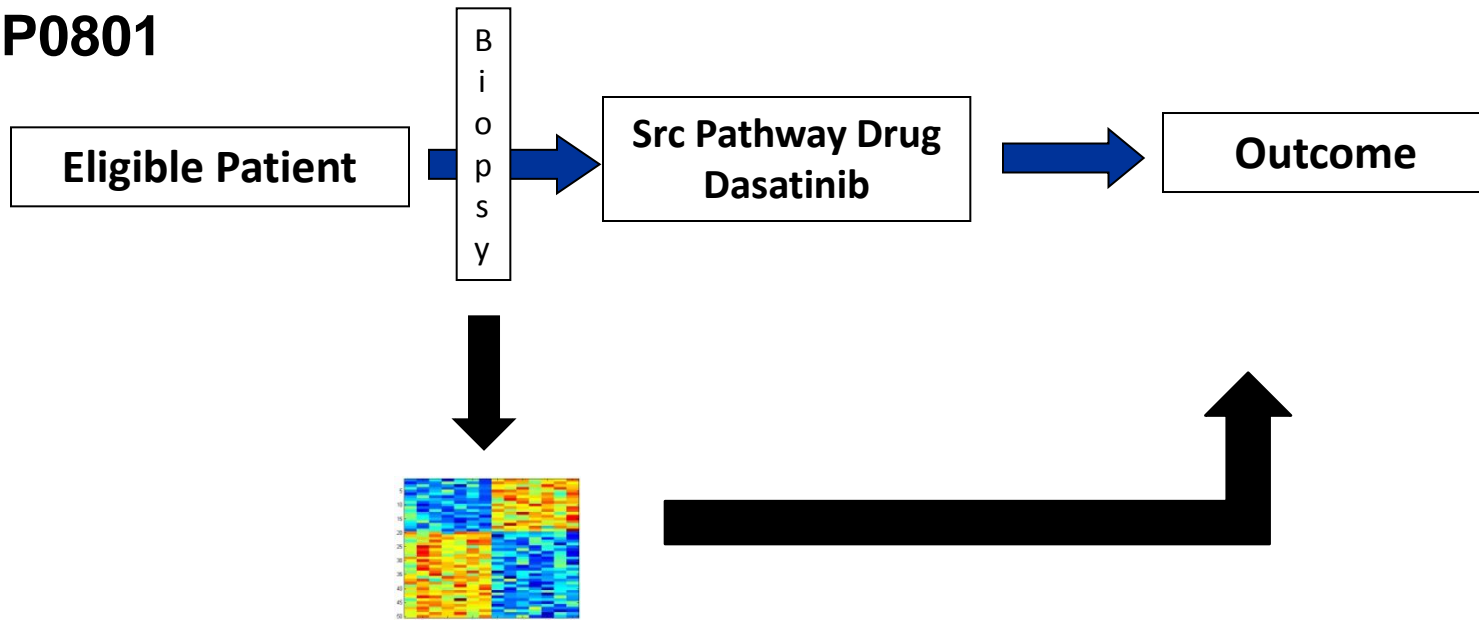
Simon Two Stage Design-Stage II

Stage II:



Validate Gene Signature for Dasatinib In Previously Treated NSCLC TOP 801, Michael Kelley MD

TOP0801



Other Opportunities

Advanced Stage NSCLC

- Everolimus is mTORR inhibitor
- Phase II NSCLC unselected n=85
 - ORR 4.7%
 - ORR+SD 47%
- Robust gene signatures for mTORR and rapamycin
- Clinical trial Simon stage biopsy and treat all
- If biomarker identified 30% most sensitive, ORR 10-15%

Squamous Cell Carcinoma Head and Neck

Identify Gene Signature Biomarker

Panitumumab

TOP 901, Neal Ready

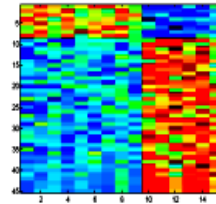
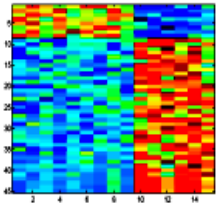
Window of Opportunity Biomarker Development

Locally
Advanced
SCCHN
PET/CT
Biopsy

Pmab
2 weeks

Repeat
PET/CT
Biopsy

Surgery or RT
Pmab
2 Doses During
CRT
or RT



Gene Expression Biomarker Development Challenges in NSCLC

- Changing the culture
- Infrastructure
- Collaboration
- Learning curve biopsy success
surgery>cervical node>liver/adrenal> bronch endo> CT lung>>>bone
- Funding
- What is the alternative if we do not identify biomarkers?