Precompetitive Collaboration in Oncology: Imaging Science

Institute of Medicine

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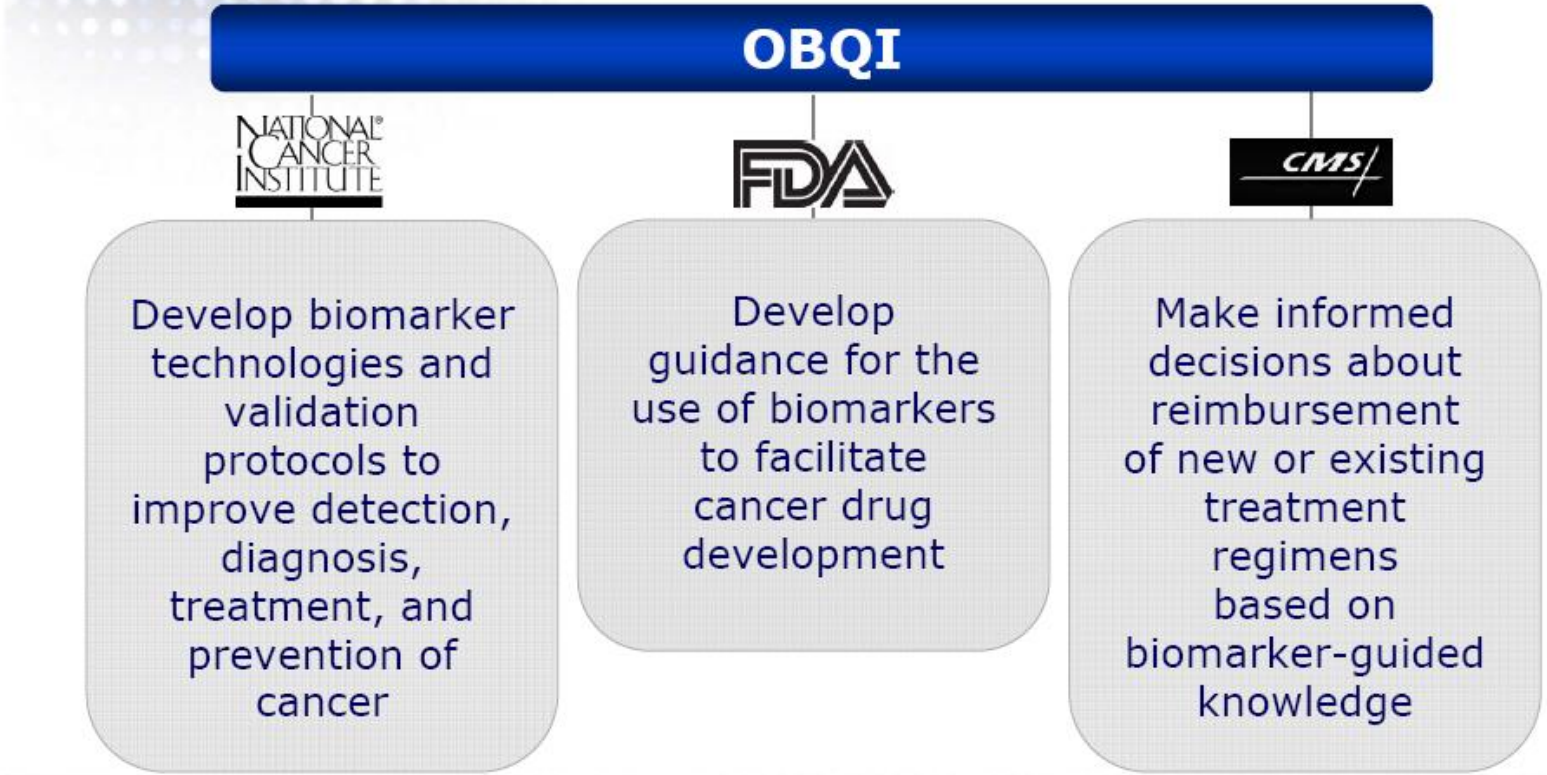
National Cancer Institute

OBQI: Unique HHS Partnership

The Oncology Biomarkers Qualification Initiative (OBQI) is a new and innovative collaboration among NCI, FDA, and CMS designed to qualify biomarkers for use in clinical trials – and ultimately speed better agents to cancer patients*

*Tri-partite MOU signed 01/23/2006

OBQI Coordinates Cross-HHS Goals for Biomarker Validation and Clinical Use



Value Proposition/Benefit for Partners in Public Private Partnership (PPP)

- Patients: Better Clinical Data, More Effective Treatment/Management
- FDA: Provides for Evidence-Based Regulatory Policy
- Pharma: More Efficient Drug Development and Approval Path, Better Early Response Criteria
- Device Industry: Larger Market for PET/CT and PET/MRI Scanners
- CMS: Helps Define Reasonableness and Need
- Academia/NCI: Better Clinical Data, More Effective Treatment/Management

FNIH Biomarkers Consortium Cancer Steering Committee Validation/Qualification of Imaging-Based Biomarkers

Improved Imaging-Based Biomarkers:

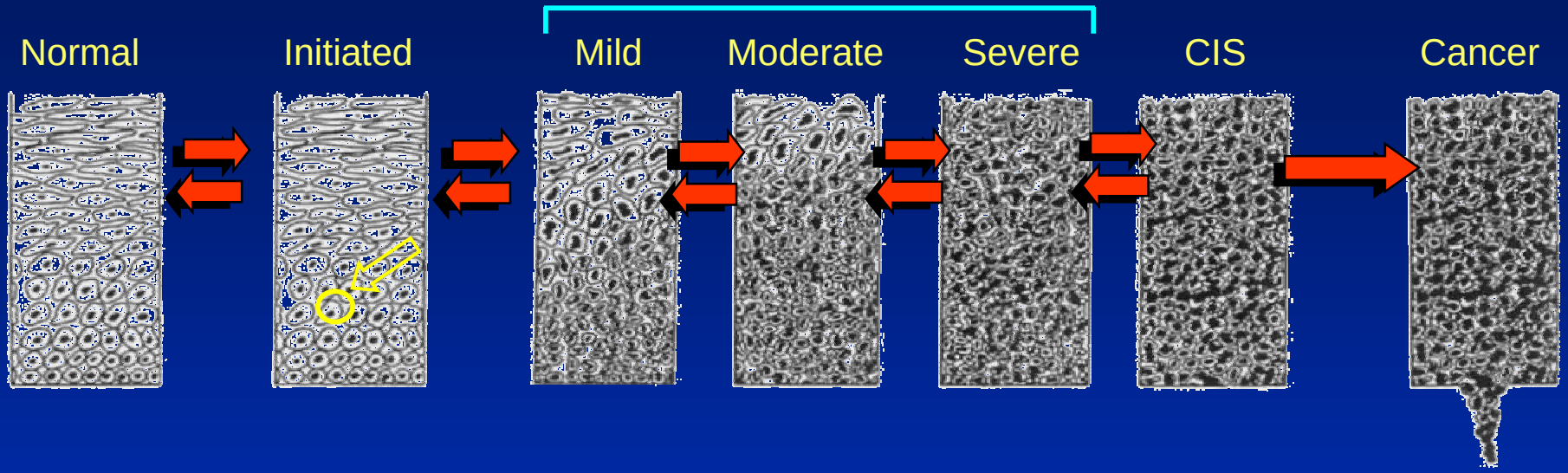
- FDG-PET as a Predictive Marker of Tumor Response and Patient Outcome: Prospective Validation in NSCLC
- Evaluation of FDG-PET Imaging as a Prognostic Marker in Non-Hodgkin's Lymphoma
- Qualification of DCE-MRI To Predict and Monitor Patient Response to Cancer Therapy

Multiplex Projects with New Biomarkers and New Trial Designs in Combination with Measurable Endpoints (*e.g.*, MR Volume):

- I-SPY TRIAL-2:An Adaptive Breast Cancer Trial Design in the Setting of Neoadjuvant Chemotherapy

Human Carcinogenesis is a Multi-Year Process

Dysplasia=Intraepithelial Neoplasia (IEN)

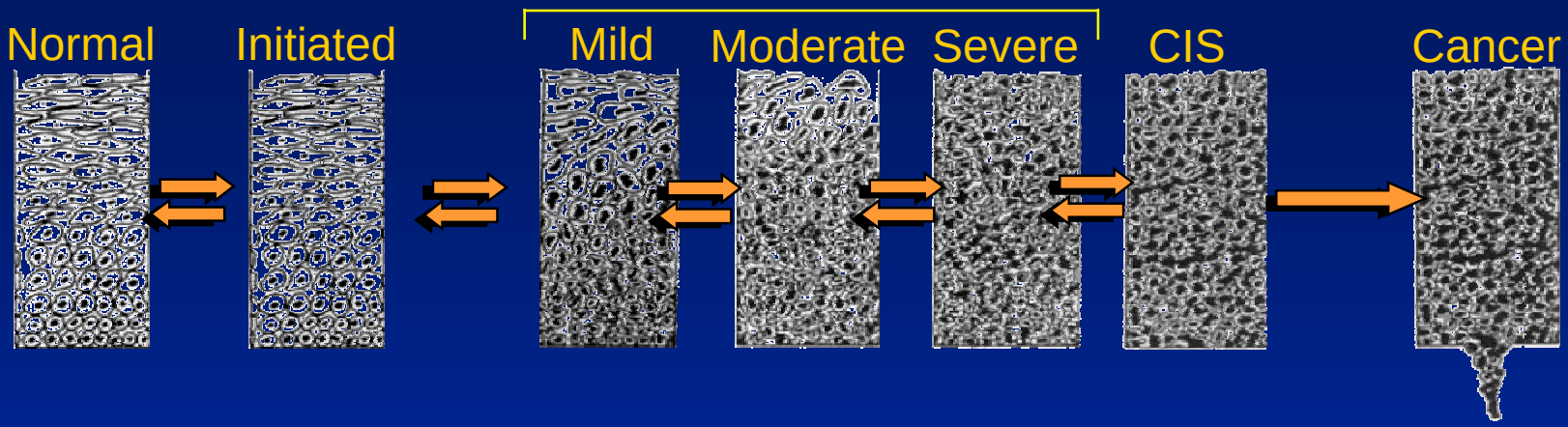


Colon	5–20 yrs	ADENOMA	5–15 yrs			
Head & Neck		TOBACCO USE 4 –10 yrs		DYSPLASTIC ORAL LEUKOPLAKIA	6–8 yrs	
Esophagus	BARRETT'S	est. 9–13 yrs		SEVERE DYSPLASIA	est. 3–4 yrs	
Cervix		9–13 yrs		CIN III/CIS	10–20 yrs	
Lung (Smokers)	20–40 pack-yrs					
Skin (Non-Melanoma)	30 –40 yrs	ACTINIC KERATOSIS	»10 yrs			
Breast	ATYPICAL HYPERPLASIA	14–18 yrs		DCIS	6–10 yrs	
Prostate	20 yrs	PIN	≥10 yrs	LATENT CANCER	3–15 yrs	
Bladder	20 yrs			TIS	<5 yrs	

Adapted from Kelloff *et al.* Oncology 10: 1471–81, 1996; Kelloff, Adv Cancer Res 278: 199–334, 2000,;O'Shaughnessy*et al.* Clin Cancer Res 8: 314-346, 2002

Molecular Biomarkers of Carcinogenesis

Dysplasia = Intraepithelial Neoplasia (IEN)



Prostate	AR, SRD5A2, CYP17, GSTP1 Polymorphisms Genetic Susceptibility to Infection	↑AR, ↓GSTP1, ↑TERT, ↑NKX3.1, ↓8p, 13q, ↓10q, ↓16q, ↑7p, ↑7q, ↑Xq, ↑DNA Ploidy, ↑IGF, ↑EGFR, ↑HER-2, ↑PCNA, ↑Ki67		↓p53, ↑VEGF, ↑FGF, ↓Cadherins, ↑MMPs, ↑PSA		
Colon	↓APC, ↑BCL-2, ↑*c*-MYC Hypomethylation		↑RAS, ↑COX-2		↑SMAD 2, ↑SMAD 4, ↑DCC, ↑STAT3	↓p53, ↓p16, 7q, ↑VEGF, ↑Cyclin D1	p15, Bub1, 22q, CD44	8p, ↑tPA, ↑MMP, ↑CEA, ↓E-Cadherin
Breast	E_2 Metabolism, Cyt P450, ↑ER, ↑PR, ↓DNA Repair	↑DNA Adducts, Genomic Instability, ↓Thrombospondin		↓p53, ↑Cyclin D1, ↓BRCA1, 2, ↑IGF, ↑Aneuploidy		↑ERB-B2, ↑EGFR, ↑VEGF, ↑RXR, ↑NM23		↑Angiogenesis, ↑Collagenase, ↑FGF
Lung		↓3p, ↓9p, ↓13q, ↓5p, ↓P16			↑53, ↑K-RAS, ↑*c-myc*, ↓22q, ↓18q, ↑β-Catenin			
Head & Neck		↓3p, ↓9p, ↓p53, ↓FHIT, ↓p16, ↓p19			↑Cyclin D1, ↑EGFR, ↑COX-2		↓6p, ↓8p23, ↓4q26-q28	
Esophagus		↓p16, ↓p53, ↑DNA Content ↑EGFR, ↑VEGFR, ↑Cyclin D1, ↓APC, ↑TGFα, ↑VEGF, ↑Cadherin						
Liver	HBV, HCV, Carcinogen/ DNA Adducts		↑TGF, ↑IGF-2, ↑TNF-2, IL6, Genomic Instability		Telomerase, *c*-MYC, ↓p53, ↓Rb, ↑IGF2-R, ↓PTEN, ↑DLCI, ↓p73, ↓E-Cadherin, Cyclin D, Cyclin E, p16, p21, p27, Aberrant Methylation			

Genome Initiatives Contributing to Oncology Drug Development

The Cancer Genome Atlas (TCGA) —NCI, NHGRI

A comprehensive and coordinated effort to accelerate our understanding of the molecular basis of cancer through the application of genome analysis technologies, including large-scale genome sequencing. The pilot project is evaluating lung, brain, and ovarian cancers.

International HapMap Project—US, Canada, China, Japan, Nigeria, UK

The HapMap is a catalog of common genetic variants that occur in human beings. It describes what these variants are, where they occur in our DNA, and how they are distributed among people within populations and among populations in different parts of the world. The International HapMap Project is not using the information in the HapMap to establish connections between particular genetic variants and diseases. Rather, the Project is designed to provide information that other researchers can use to link genetic variants to the risk for specific illnesses, which will lead to new methods of preventing, diagnosing, and treating disease.

Complexity of Genomic/Proteomic Analysis

Genes (23,000)

ß **(3-5x)**

Allelic Variants

ß **(3-5x)**

mRNA Splicing Variants

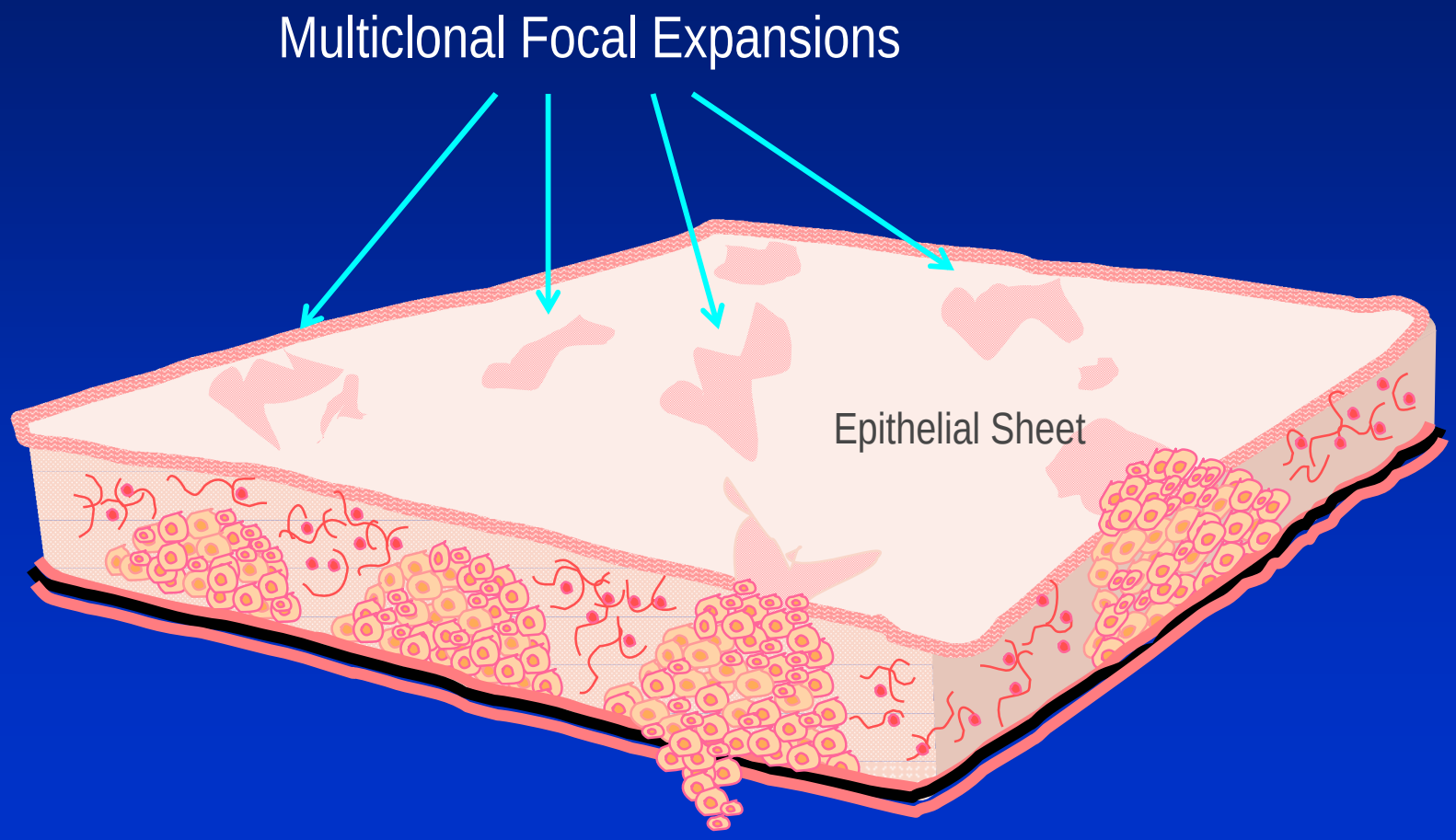
ß **(3-5x)**

Protein Post-translational Modifications

ß **(>10^6)**

Protein-Protein Interactions

“Field Cancerization”



Beyond Detection: Imaging as Cancer Biomarker Tissue *vs* Imaging Biomarkers

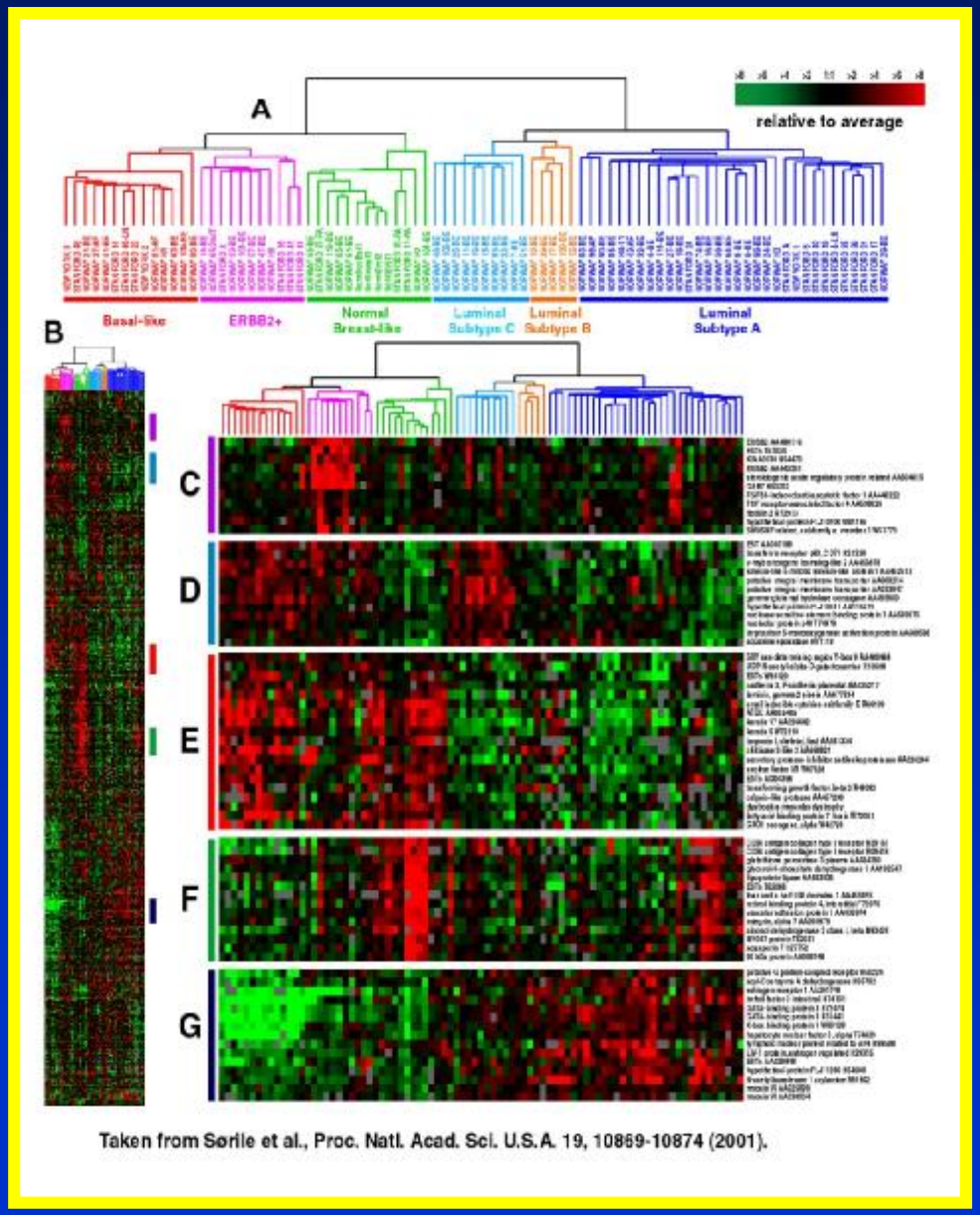
Tissue/Blood Biomarker

- **Can probe many features**
- Single location, limited sampling
- **Variable cost**
- Invasive (tissue)
- Serial assay challenging
- **Widely available — central assay**

Imaging Biomarker

- Probes 1-2 features
- **Tissue volume, full tumor burden sampling**
- Often expensive
- **Non-invasive**
- **Serial assay possible**
- Less widely available—local assay

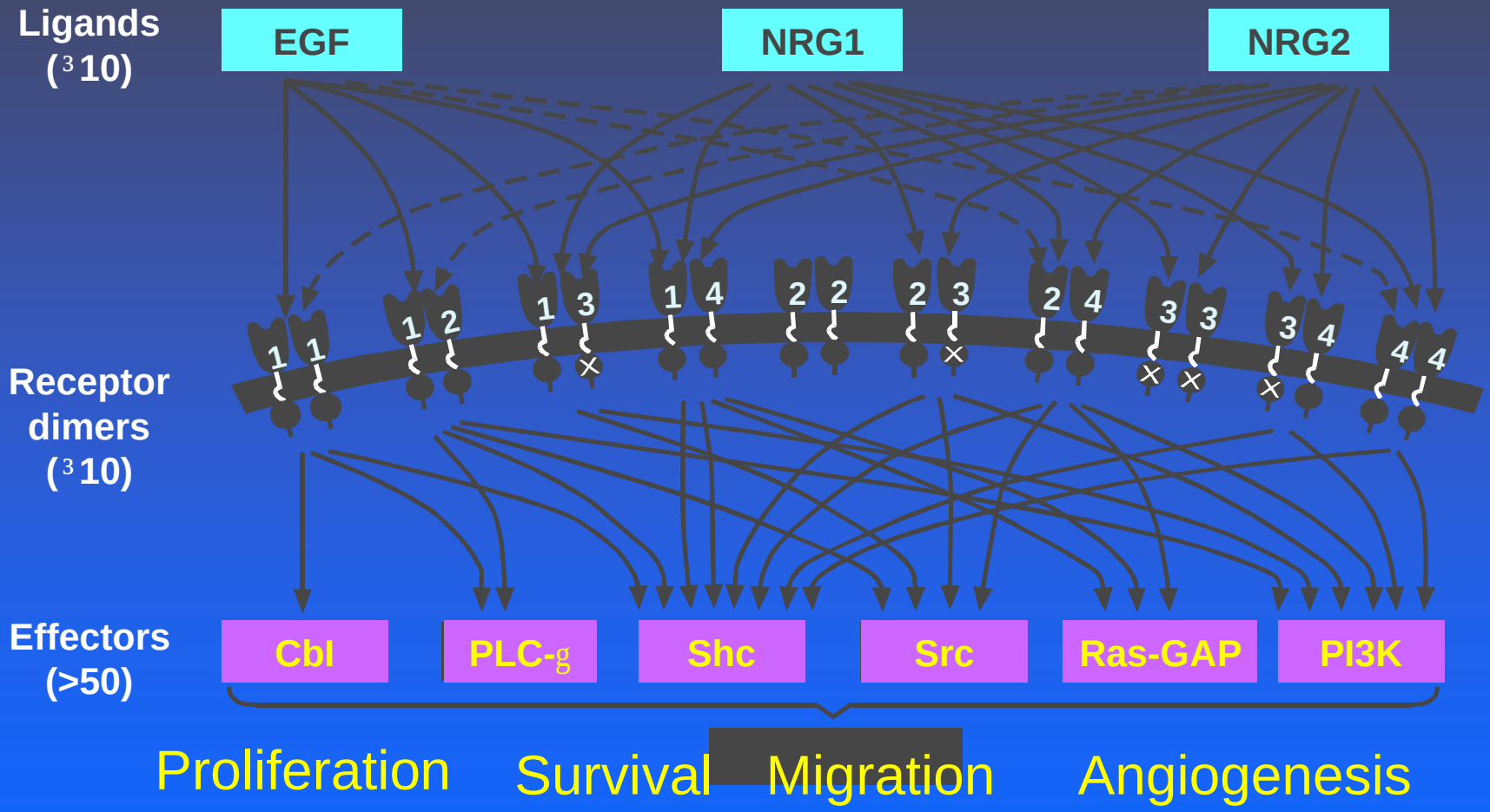
Gene Expression Profile in Breast Cancer



Taken from Sørlie et al., Proc. Natl. Acad. Sci. U.S.A. 19, 10869-10874 (2001).

Troester and Perou, Strategies for Cancer Chemoprevention, 2005

ErbB Signaling Network



Yarden & Sliwkowski, Nat Rev Mol Cell Biol 2: 127–137, 2001

Promise of Imaging Science

Features of Imaging

- Non-invasive, optical biopsy
- Sequential/multiple sampling
- Quantitative localization
- Molecular target expression
  - Levels
  - Patterns

Applications

- Screening/early detection
- Early diagnosis
- Staging and therapy monitoring
- Drug development tool
  - Molecular target based drug screening
  - Imaging of drug biodistribution, in 3D and within tumor microenvironment
  - Target based validation in animal models
  - Imaging of drug –target interaction *in vivo*
  - Co-register drug distribution with drug target expression
  - Co-register drug distribution with drug effect

Why FDG-PET

- FDG-PET exploits the reliance of tumor cells on glucose and glycolytic metabolism to image cancers (Warburg Effect, strong mechanistic rationale)
- FDG-PET data can be assessed visually, or analyzed semiquantitatively or quantitatively
- FDG-PET is approved for use in the diagnosis, staging, and restaging of a variety of cancer types, and in these applications can significantly impact the clinical management of disease
- In a number of clinical settings (*e.g.*, NSCLC, esophageal cancer, lymphoma), FDG-PET can provide an early measure of response to treatment with approved therapies
- With a few additional studies, FDG-PET could facilitate drug development and patient care by resulting in:
  - Shorter duration of Phase II studies to evaluate new drug/regimen
  - Accelerated approval in Phase III trials, with full approval contingent on evidence of clinical benefit (*e.g.*, PFS, OS) after longer term follow-up
  - Better patient care by ceasing ineffective therapies earlier

Kelloff *et al.* Clin Cancer Res 11: 2785–2808, 2005

Centers for Medicare and Medicaid Services (CMS) Coverage for FDG-PET in Oncology

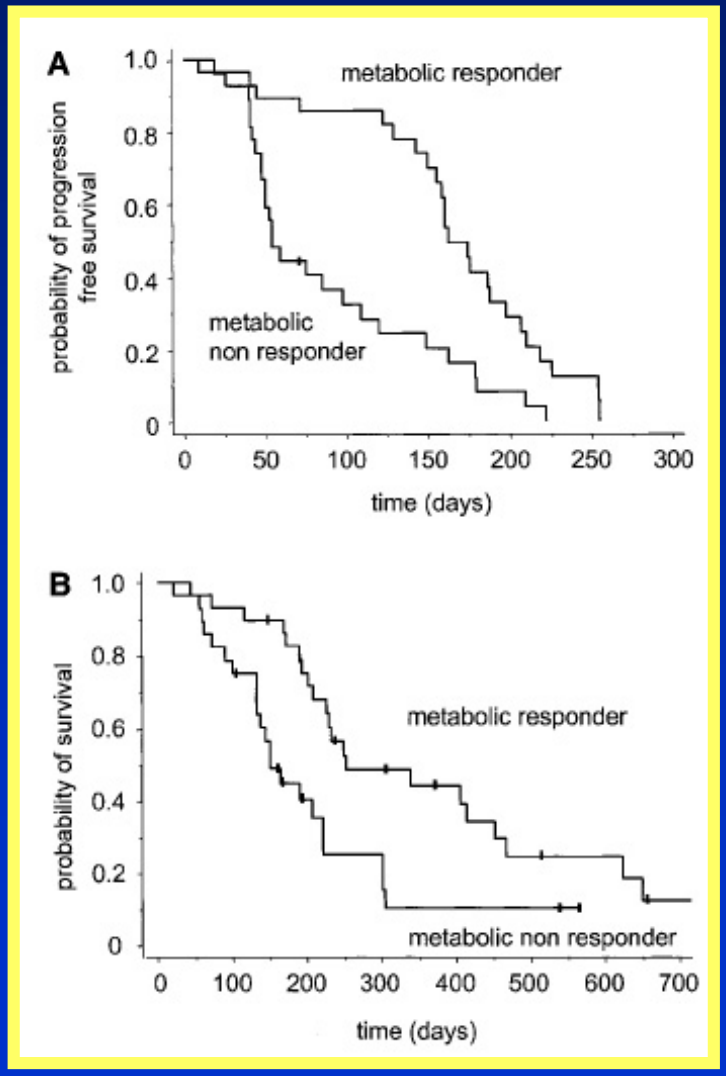
Clinical Condition	Coverage (Effective Date)
Solitary Pulmonary Nodule	Characterization (January 1998)
Lung Cancer (non small cell)	Initial Staging (January 1998) Diagnosis, staging and restaging (July 2001)
Esophageal Cancer	Diagnosis, staging and restaging (July 2001)
Colorectal Cancer	Tumor localization if CEA suggests recurrence (July 1999) Diagnosis, staging and restaging (July 2001)
Melanoma	Evaluating recurrence, as an alternative to Gallium scan (July 1999) Diagnosis, staging and restaging (July 2001)
Lymphoma	Staging and restaging, as an alternative to Gallium scan (July 1999) Diagnosis, staging and restaging of Hodgkin and non-Hodgkin (July 2001)
Head and Neck Cancer (excluding CNS and Thyroid)	Diagnosis, staging and restaging (July 2001)
Breast Cancer	Adjunct for diagnosis, staging, restaging and monitoring response (October 2002); particularly, as an adjunct for staging metastatic disease, restaging locoregional recurrence or metastasis, and for monitoring response of locally advanced and metastatic breast cancer when a change in therapy is anticipated
Thyroid Cancer (follicular cell)	Evaluating recurrent or residual follicular cell tumors (previously treated by throidectomy and radioiodine ablation) when serum thyroglobulin >10ng/ml and I-131 whole body scan is negative (October 2003)

Why FDG-PET in Lung

- Relatively ineffective first line therapy in late stage disease
- Unmet medical need requiring new drugs/therapies
- Existing clinical FDG-PET data for diagnosis and staging
- Existing retrospective data on early response, suggesting criteria for ceasing ineffective therapy and allowing design of trials to evaluate new drugs

PET in NSCLC: Prediction of Response to Chemotherapy

Median TTP and overall survival longer for responders than non-responders (163 *vs* 54 days and 252 days *vs* 151 days, respectively



Weber *et al.* J Clin Oncol 21: 2651–2657, 2003

FDG-PET as a Predictive Marker of Tumor Response and Patient Outcome: Prospective Validation in NSCLC

Patients with advanced NSCLC, who were scheduled to undergo palliative chemotherapy with an a two drug chemotherapy regimen (with or without Avastin)

Registration/Randomization
1:3 ratio

Group A:

- Two (2) PET scans prior to chemotherapy – at least 24 hours between the 2 pre-therapeutic scans
- One PET scan after the first chemotherapy cycle
- Follow-up CT scans per standard of care

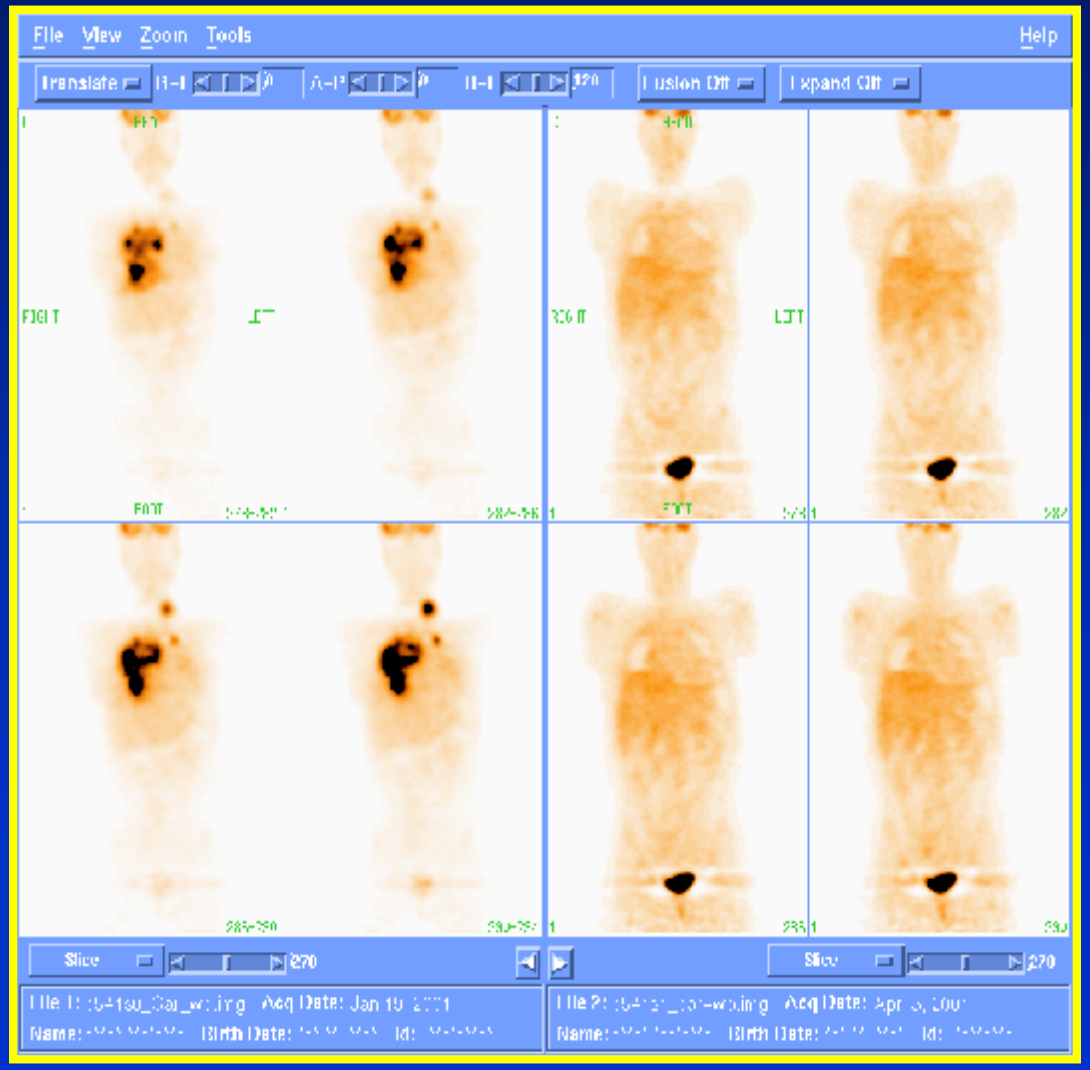
Group B:

- One (1) PET at baseline (pre Cycle 1 of chemotherapy)
- One PET scan after the first chemotherapy cycle
- One PET scan after the second chemotherapy cycle
- Follow-up CT scans per standard of care.

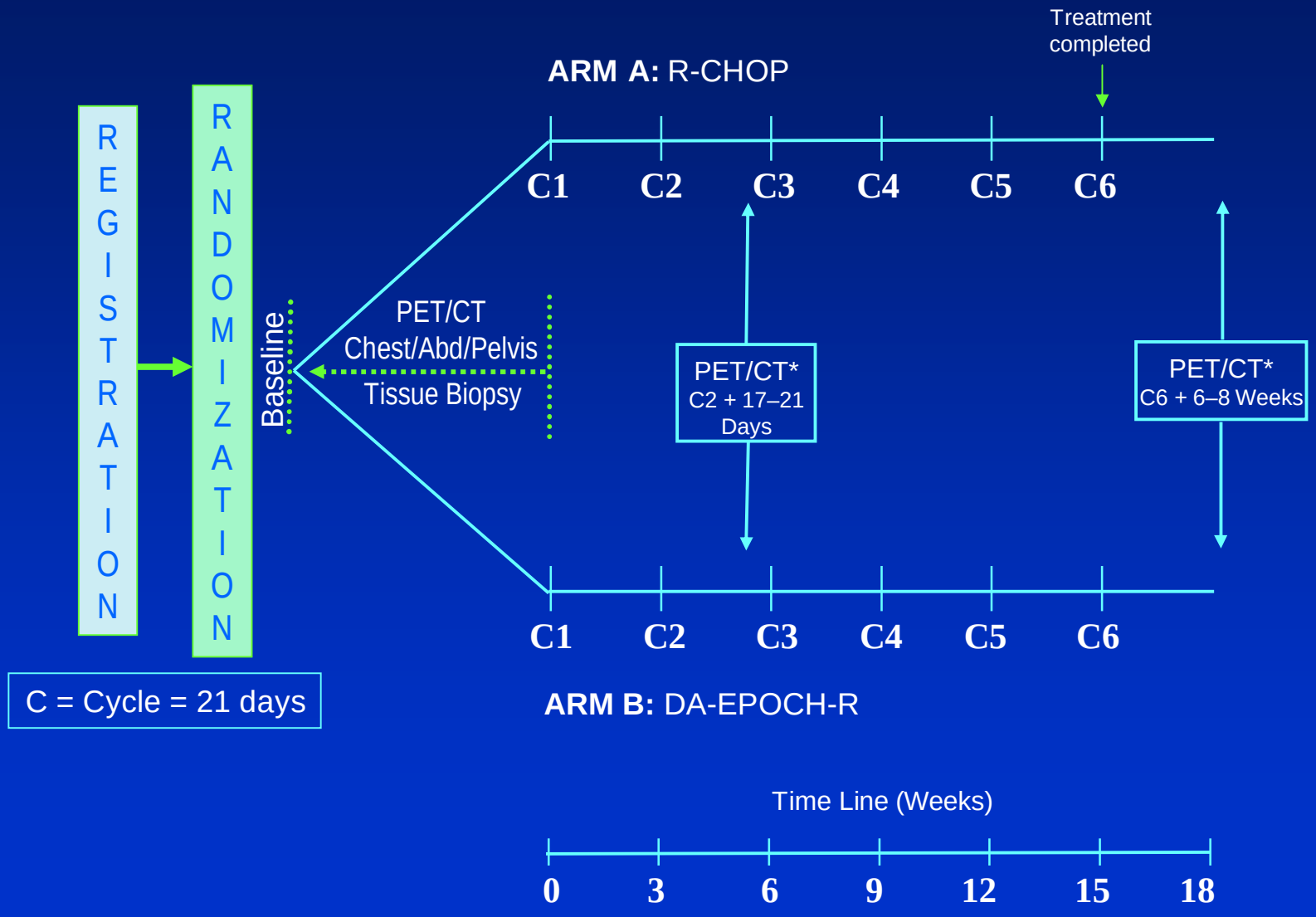
Why FDG-PET in Lymphoma

- Successful clinical management
- Effective drugs
- Existing clinical FDG-PET data for diagnosis and staging
- Established treatment response criteria, that can be refined by FDG-PET

Lymphoma:
Evaluation of Treatment Response



Access to FDG-PET/CT imaging is a requirement for institutions enrolling patients on the F18 FDG-PET validation CALGB 50303 study.



Initial Qualification of FDG-PET as a Surrogate Endpoint for Clinical Benefit

Baseline FDG-PET

↓

Treat with Approved Chemotherapeutic Drug (Standard Therapy)

↓

FDG-PET: Metabolic Response (Predetermined Response Level)

↓

Continue Treatment to Clinical Endpoint(s)—*e.g.*, OS, DFS, PFS, OR by Conventional Measurement

Further Qualification (*e.g.*, 2 Different Drugs with Different Mechanisms in a Specific Target Organ) of FDG-PET as a Surrogate Endpoint for Clinical Benefit for Evaluation of New Therapies

Baseline FDG-PET

Treat with New Therapy

FDG-PET: Metabolic Response
(Predetermined Response Level)
If Response Is Met for Predetermined % of Patients, May Support Claim of Clinical Benefit and Accelerated Approval for New Therapy

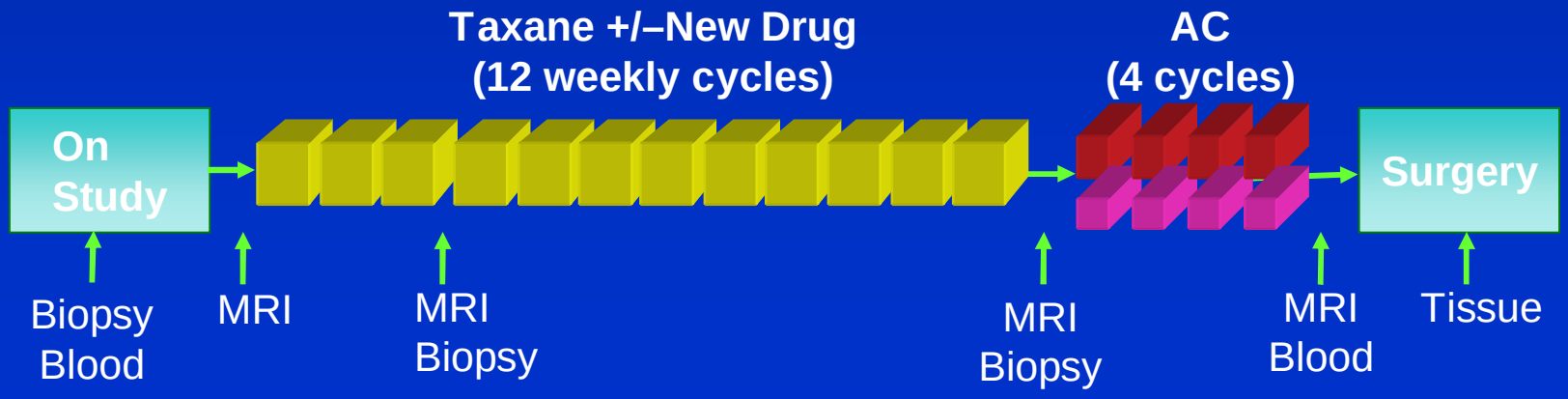
Continue Treatment to Clinical Endpoint(s) OR Carry Out Confirmatory Trial with Clinical Endpoint(s)

Validation of DCE-MRI Derived Biomarkers for Response to Therapy

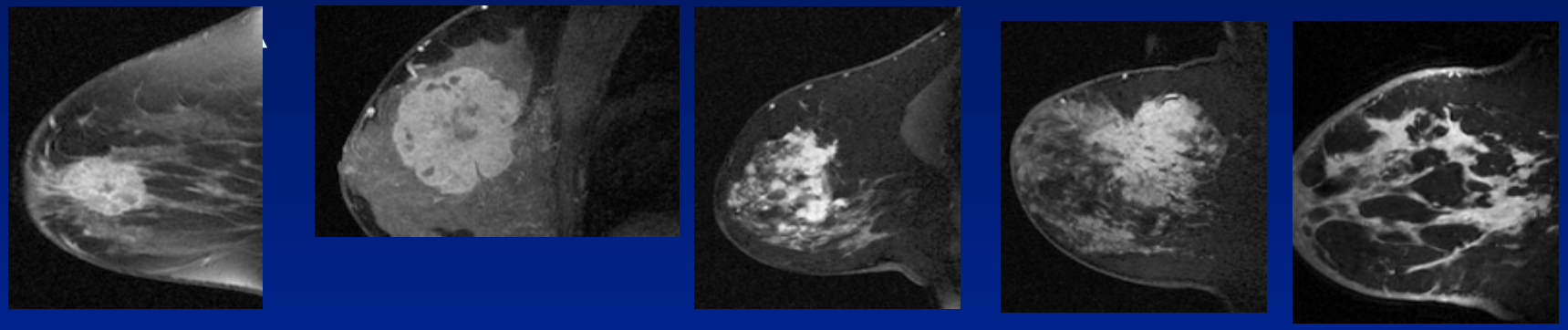
- DCE MRI has been proposed as a means of predicting and monitoring response to cancer therapeutics.
- It measures tumor blood flow and so may be useful for prediction and monitoring of response to treatments that target the tumor vasculature including the VEGF pathway
- Use of DCE-MRI has been limited by lack of standardization, and so this new project is aimed at establishing a rational, standardized approach to DCE MRI
- The initial phase is development of an idealized, standardized DCE MRI data set using prostate cancer as a model to test various analytic approaches and trade-offs in the acquisition protocol that may be needed for broader application. The data will be made available to others interested in testing additional DCE-MRI analytic strategies

Summary of I-SPY 2 Design

- Standard control (taxane-based)
- Balance randomization to new drugs initially
- Build predictive index for each therapy/biomarker combination
- Adaptively randomize
- Evaluate many drugs & combinations
  - Successes graduate to phase 3
  - Underperformers dropped for futility



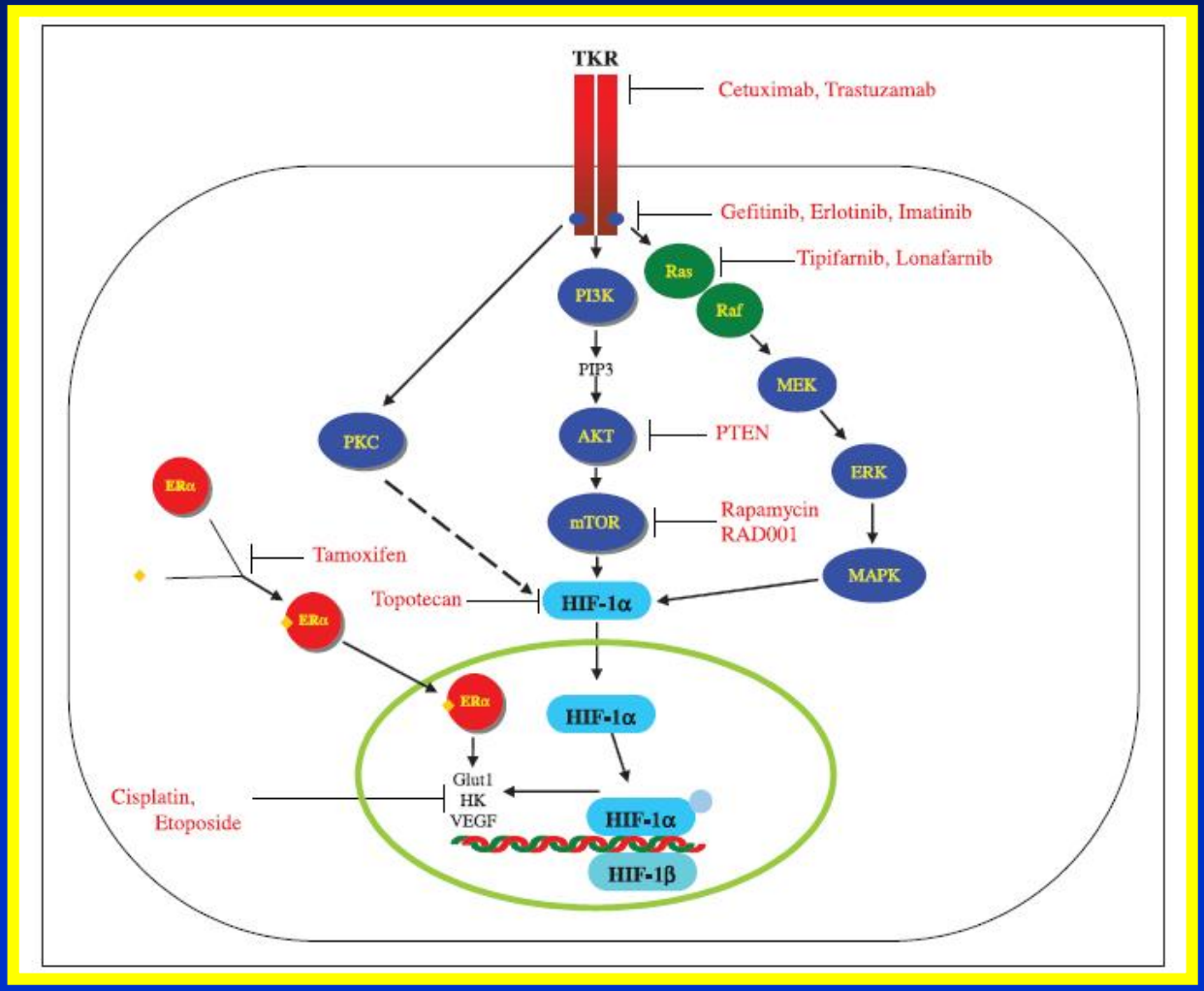
Imaging: Morphologic Pattern, Volume Response from 884 Images (221 Patients)



Morphologic Patterns in Locally Advanced Neoadjuvant Breast Cancer Setting Detected by MR Volume

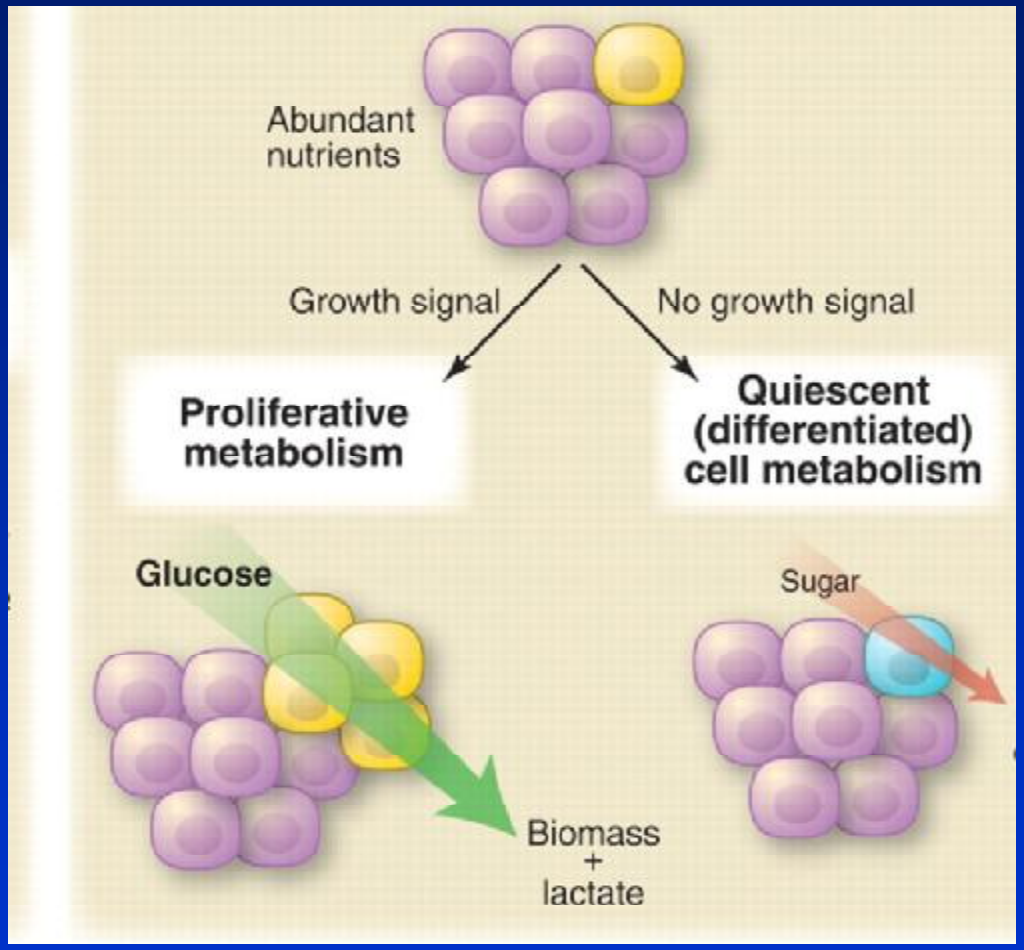
Nola M. Hylton, PhD
(I-SPY Project)

Molecular Targets of Cytotoxic and Cytostatic Drugs in the Pathways Controlling Glycolytic Metabolism



Kelloff *et al.*, Clin Cancer Res 11:2785–808, 2005

Understanding the Warburg Effect: Metabolic Requirements of Cell Proliferation



Adapted from Vander Heiden et al., *Science* 324, 1029 -1033 (2009)

Published by AAAS

Science

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