ACRIN Trials with IND-Based Imaging Probes: Outline

- Introduction - Mankoff
  - Motivation - cancer biomarker imaging
  - ACRIN Goals and Experimental Imaging Sciences Committee (EISC)
  - Current IND-based PET studies
- Regulatory considerations - Jacobs
  - When do you need an IND
  - Components of an IND
  - Practical considerations - probe supply and other issues
- Discussion and questions - Mankoff/Jacobs/Schubert
A Biomarker Paradigm for Cancer Imaging: Help Direct Cancer Treatment

- Role for imaging:
  - Guide cancer treatment selection
  - Evaluate early treatment response
Imaging and Targeted Therapy
Help Match Therapy to Tumor Biology

- **Goals in cancer treatment**
  - Characterize tumor biology pre-Rx
  - Individualized, specific therapy
  - Static response may be acceptable

- **The implied needs for cancer imaging**
  - Characterize in vivo tumor biology - predict behavior
  - Identify targets, predict response
  - Identify resistance mechanisms
  - Measure tumor response (early!)
Emerging Cancer Imaging Paradigm: Measure Factors Affecting Response Variable Levels in Tumor
Imaging Requirement for Biomarker Imaging: Simultaneously Localize and Characterize Disease Sites

Functional/Anatomic Imaging

PET/CT Fusion

FDG PET

FDG PET/CT Fusion

Functional Imaging Combinations

FDG
Glucose Metabolism

FES
Estradiol Binding
**Imaging Requirement for Biomarker Imaging: Image Acquisition and Quantitative Analysis**

- **Dynamic protocols**
  - Allows kinetic modeling
  - Full range of analysis options
  - But … not for everyone

- **Static protocols**
  - Clinically feasible, robust
  - But … only simple quantification possible

**Dynamic Imaging**
- Time
- Region-of-Interest Analysis
  - Tumor
  - Ventricle
- Parameter Estimates

**Kinetic Modeling**
- Time-Activity Curves
  - Tissue
  - Blood

**Inject Tracer**
- Static Uptake Measure (SUV)
- Static Image
ACRIN Experimental Imaging Sciences Committee (EISC)
EISC Framework for Study Development

Identify Clinical Need

- Match Scientific Rationale to Imaging Method
- Identify Possible Centers
- Identify Regulatory Barriers
- Determine Technical Needs

New Imaging Methods

Disease Site Committees

Core Lab

Outcomes
Advocacy
Informatics

BDMC

Finalize Concept and Design
EISC: Progress Overview

- **Current trials open**
  - Cervical hypoxia (almost)

- **Protocols**
  - Brain Tumor Hypoxia
  - Prostate bone met. response

- **Concept Development**
  - Breast optical imaging
  - FLT Head and Neck response
  - FLT Brain

- **Concepts on hold**
  - Pediatric Brain Tumor MRSI

- **Other protocols**
  - FLT Breast (NCI)

- **Other**
  - Study design workshop and “white papers”
  - Discussions with SNM re: PET studies and collaborations

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ACRIN Trials with Novel PET Imaging Probes

- Opened or opening
  - ACRIN 6682 - $^{64}$Cu-ATSM and cervical hypoxia (Dehdashti, PI)
  - ACRIN 6684 - $^{18}$F-FMISO and brain tumor hypoxia (Sorenson, PI)
  - ACRIN 6687 - $^{18}$F- and prostate bone metastasis response to Rx (Yu, PI; collaboration with DOD consortium)
  - ACRIN 6688 - $^{18}$F-FLT and breast cancer response (Bear/Jolles, Kostakoglu, PI; collab with VCU/CIP Phase I/II)

- Under development
  - ACRIN 6690 - MRI and $^{18}$F-FLT to evaluate glioblastoma response to XRT, chemotherapy, and cedarinib (Sorenson, collaboration with RTOG)
  - ACRIN 6689 - $^{18}$F-FLT to evaluate response of H/N Cancer to XRT (Shields, possible collaboration with SNM)
Imaging Hypoxia as the Accumulation of a Radiopharmaceutical

\[ \text{H}_2\text{O}_2 \xrightarrow{\cdot \text{OH}} \cdot \text{O}_2^- \xrightarrow{\cdot \text{O}_2^-} \text{R-NO}_2 \xrightarrow{+ e^-} \text{R-N=O} \xrightarrow{+ 4e^-} \text{R-NH}_2 \]

Nitroreductase enzymes

Radical Anion

\([F-18]\)-fluoromisonidazole

covalent bonding to macromolecules

University of Washington

KA Krohn
Tumor Hypoxia Quantified by PET Predicts Survival

- FMISO PET
  - Brain Tumor
    - (Spence, Clin Can Res, 2008)
  - H & N Cancer
    - (Rajendran, Clin Can Res, 2007)

- Cu-ATSM PET
  - Cervical Cancer
Biologic Events in Response to Successful Cancer Therapy

Rationale for Measuring Early Response by Cell Proliferation Imaging

Rx

↓ Cellular Proliferation
  or
  ↑ Cell Death

↓ DNA Synthesis

↓ Viable Cell Number

↓ Tumor size
Thymidine Analogs for PET Cell Proliferation Imaging
Clinically Feasible Isotope and Imaging Protocol

$^{18}$F-Fluoro-L-thymidine (FLT)

(Shields AF, from Mankoff, Shields, and Krohn, Rad Clin N Amer 43:153, 2005)

FLT PET Images of Lung Cancer

(Grierson, Nucl Med Biol 27:143, 2000)

(Shields AF, from Mankoff, Shields, and Krohn, Rad Clin N Amer 43:153, 2005)
Early Response of Breast Cancer Measured by $^{18}$F-fluorothymidine (FLT) PET

Pre-Rx 1 wk Chemo Clinical Response: (Later)

Response

No Response

$^{18}$F-Fluorothymidine (FLT)

(Grierson, Nucl Med Biol 27:143, 2000)

(Kenny, EJNMMI 34:1339, 2007)

$^{18}$F-Fluorothymidine (FLT)

(Grierson, Nucl Med Biol 27:143, 2000)

(Kenny, EJNMMI 34:1339, 2007)
FLT Brain Tumor Imaging to Measure Response: Kinetic Analysis
(Muzi, J Nucl Med, 2006; Spence, Mol Imag Biol, 2009)

Kinetic model: Parametric Imaging:

\[
\text{Flux}_{\text{FLT}} = \frac{K_{1_{\text{FLT}}} \cdot k_{3_{\text{FLT}}}}{k_{2_{\text{FLT}}} + k_{3_{\text{FLT}}}}
\]

(Muzi, J Nucl Med, 2005)
RA Considerations for ACRIN Trials with IND-Based Probes

- Opening the trial
  - Needs for IRB review
  - Documentation - forms, etc.
- Running the trial
  - Supply of the imaging probe
  - Safety monitoring
  - Reporting