Molecular Imaging as a Cancer Biomarker: Imaging to Guide Targeted Cancer Therapy

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- Discussion of investigational drugs
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Molecular Imaging as a Cancer Biomarker: Outline

- Clinical/biological questions and methods to address them
- Cancer biomarker imaging
  - Prognosis
  - Targeting/Resistance
  - Early response
Anatomic versus Functional Imaging

- **Anatomic Imaging**
  - Relies on tumor size, shape, density
    - e.g., mammography, CT
  - Measures response by changes in size

- **Functional/molecular imaging**
  - Relies on in vivo tumor biology: perfusion, metabolism, molecular features
    - e.g., MRI, PET
  - Measures response by changes in functional/molecular processes
Functional Imaging Modalities

- Magnetic Resonance (MR)
  - Magnetic Resonance Imaging (MRI)
  - Magnetic Resonance Spectroscopy (MRS)
- Radionuclide imaging
  - Positron Emission Tomography (PET)
  - Single-Photon Emission Computed Tomography (SPECT)
- Ultrasound (U/S)
- Optical imaging
Why Radiotracer Imaging?
Answer: To achieve tracer conditions

- Example: Estrogen Receptor Imaging
  - Tracer specific activity: 1000 mCi/umol
  - Injected activity dose: 5 mCi
  - Injected molar dose: 5 nmol
  - Peak blood concentration: 1 nM
    (Typical estradiol blood concentration is nM)
  - Radiographic, MR, or optical agents require mM (factor of $10^6$ difference!)
  - Therefore - can image biochemical processes without disturbing them
Existing Cancer Imaging Paradigm:
Targets for Detecting Tumor Cells
Higher in Tumor than Normal Tissue

Protein Synthesis
Amino Acids

DNA Synthesis
Thymidine & Analogs

Energy Metabolism
FDG, Acetate

Membrane Synthesis
Choline, Acetate

Blood Flow
Water, Sestamibi
FDG PET Detects Internal Mammary Nodal Metastases in Locally Advanced Breast Cancer

(Bellon, Am J Clin Oncol, 2004)
A New Paradigm for Cancer Imaging: Help Direct Cancer Treatment

- **New 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

- Proliferative Rate
  - Thymidine & Analogs
  - Glycolytic Rate
    - FDG

- Surface Receptors
  - Octreotide
- Nuclear Receptors
  - FES, FDHT
- Angiogenesis
- Water
  - RGD Peptides

- Hypoxia
  - FMISO, ATSM

- Drug Transport
  - MIBI, Verapamil, F-Paclitaxel
Imaging Requirement for Biomarker Imaging: Simultaneously Localize and Characterize Disease Sites

Functional/Anatomic Imaging

FDG PET

PET/CT Fusion

Functional Imaging Combinations

FDG

Glucose Metabolism

Estradiol Binding

FES
**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

![Diagram of imaging protocols and analysis](image)

- **Dynamic Imaging**
  - Time
  - Region-of-Interest Analysis
  - Kinetic Modeling
  - Parameter Estimates

- **Static Image**
  - Static Uptake Measurement (SUV)

- **Time-Activity Curves**
  - Tumor
  - Ventricle
  - Blood

- **Inject Tracer**
Guiding Cancer Therapy: Imaging Goals

**Diagnosis**

- **Goal 1 - Prognosis**
  - Prognosis: Predict Tumor Behavior
  - Hypoxia

- **Goal 2 - Prediction**
  - Identify Target/
  - Predict Response
  - Tumor Receptors
  - Hypoxia

**Therapy**

- **Goal 3 - Response**
  - Measure Response
  - Proliferation

**Outcomes**

- **Path Response**
- **DFS**
- **OS**

**Goal 4 - Research**

- Elucidate Cancer Biology
Prognostic Markers - Why Imaging?

• Tumor clinical behavior varies considerably
  • Need to match aggressiveness of treatment to aggressiveness of tumor
• Prognostic tissue biomarkers predict clinical behavior and help direct therapy, examples:
  • Ki-67 (proliferation) - lung, breast, brain, others
  • Gene expression profiles - breast
• In vivo tumor biology is complementary to in vitro assay and adds prognostic information, examples:
  • Glycolysis (FDG PET)
  • Hypoxia (FMISO PET, other probes)
FDG Predicts Survival in Recurrent Thyroid Cancer
Robbins, J Clin Endo Metab 91:498, 2006

$^{131}$I-

FDG PET

High TG, Neg Scan L Cervical LN

Surviving Fraction

FDG-

FDG+

$\text{p<0.001}$

Months from PET Scan

FDG - (n=180)

FDG + (n=219)
Imaging Hypoxia as the Accumulation of a Radiopharmaceutical

$\text{H}_2\text{O}_2 \rightarrow \cdot\text{OH} \rightarrow \cdot\text{O}_2^- \rightarrow \text{O}_2^- \rightarrow \text{R-NO}_2^- \rightarrow \text{R-N}=\text{O} \rightarrow \text{R-NH}_2$

\textit{Radical Anion}

\textit{Nitroreductase enzymes}

\textit{Covalent bonding to macromolecules}
Tumor Hypoxia Quantified by PET Predicts Survival

**FMISO PET**
- **Brain Tumor**: (Spence, Clin Can Res, 2008)

**FMISO PET**
- **H & N Cancer**: (Rajendran, Clin Can Res, 2007)

**Cu-ATSM PET**
- **Cervical Cancer**: (Dehdashti, Int J Radiat Oncol Biol Phys, 2003)
Guiding Cancer Therapy: Imaging Goals

**Goal 1 - Prognosis**
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- Identify Target/Predict Response
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**Goal 4 - Research**
- Elucidate Cancer Biology

**Outcomes**
- DFS
- OS

**Path**
- Response
Identifying Therapeutic Targets: Why Imaging?

- Imaging can measure the level of expression
  - Heterogeneity - spatial and temporal
  - Especially for advanced disease
- Imaging can measure the \textit{in vivo} effect of drug therapy on the target. Examples:
  - Target antagonism
  - Change in target expression
- Imaging is quantitative
- Complementary to \textit{in vitro} assay
ER Expression and Breast Cancer Endocrine Therapy

- Endocrine therapy for breast cancer
  - SERMs - e.g., tamoxifen
  - Aromatase inhibitors - e.g., letrozole
  - SERDs - e.g., fulvestrant
- ER as predictive assay
  - ER-: Response Rate < 10%
  - ER+: Response Rate 50%
  - ER+/PR+: Response Rate 75%
$^{18}$F-Fluoroestradiol (FES): PET Estrogen Receptor (ER) Imaging Provides a Quantitative Estimate of ER Expression

(Kieswetter, J Nucl Med, 1984)

(Mintun, Radiology 169:45, 1988)

Validation: ER+ vs ER- Tumors

FDG

axial

Glucose Metabolism

ER+

ER-

FES

coronal

ER Expression

Liver (Liv)
FES Uptake Predicts Breast Cancer Response to Hormonal Therapy

Example 1
- Recurrent sternal lesion
- ER+ primary
- Recurrent Dz strongly FES+

Example 2
- Newly Dx’d met breast CA
- ER+ primary
- FES-negative bone mets

University of Washington

(Linden, J Clin Onc, 2006)
## Brain Tumor FDG Uptake vs Survival: Tumor Volumes
- Tralins, J Nucl Med, 2002

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Hypoxia as a Target for Radiotherapy Planning
Head/Neck CA Treatment Planning Including FMISO PET

Imaging to Direct Hypoxia-Specific Treatment

- Advanced H & N Ca
- Randomized to
  - XRT + Cisplatin/5-FU
  - XRT + Cisplatin/Tirapazamine (TPZ)
- FMISO PET (observational only)

Time-to-Locoregional Failure

FDG PET

FMISO PET

Graph showing time-to-local failure rate for different treatment regimens

Hypoxia: Cis-FU vs Cis-TPZ, P = .006
Cis-FU: No vs yes, exact log-rank P =
Resistance Due to altered Drug Transport:

$^{11}$C-Verapamil PET to Measure P-gp Drug Transport

Hypotheses:

- P-gp limits drug transport into the brain
- Inhibiting P-gp will increase brain transport

$^{11}$C-Verapamil

(Hendrickse, Br j Pharmacol, 1998)
Imaging P-gp Activity *in vivo* in Humans

$^{[11]C}$-Verapamil images pre- and post-cyclosporine (CSA)

88% +/- 20% increase in verapamil AUC (N= 12, P < .001)

(Sasongko, Clin Pharm Ther, 2005)
Guiding Cancer Therapy: Imaging Goals

**Diagnosis**

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Prognosis: Predict Tumor Behavior
Hypoxia

**Goal 2 - Prediction**
Identify Target/
Predict Response
Tumor Receptors
Hypoxia

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Measure Response
Proliferation

**Outcomes**

**Path Response**

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**Goal 4 - Research**
Elucidate Cancer Biology
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)

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

(Shields AF, from Mankoff, Shields, and Krohn, Rad Clin N Amer 43:153, 2005)
Thymidine Incorporation Pathways
Imaging Tumor Proliferation

(Mankoff and Eary, Clin Cancer Res 14: 7159, 2008)
Early Response Measured by $^{18}$F-fluorothymidine (FLT) PET

Breast CA, ChemoRx (Kenny, EJNMMI 34:1339, 2007)

Lung CA, Genfitinib Rx (Sohn, Clin Cancer Res 14: 7423, 2008)

Pre-Rx  1 wk Rx

PET  PET-CT

Day 0  Day 7

A  B

Responders  Nonresponders

![Graphs showing SUV max over time for responders and nonresponders.]

- **Responders**: SUV max decreases significantly from Day 0 to Day 7 ($p < 0.001$).
- **Nonresponders**: SUV max remains relatively constant with a slight increase.

R, NR

- **R**: Tumour.
- **NR**: Tumour and vertebra.
FLT Brain Tumor Imaging to Measure Response
Kinetic Analysis
(Muzi, J Nucl Med, 2006; Spence, Mol Imag Biol, 2009)

Kinetic model:
\[
\text{Flux}_{\text{FLT}} = \frac{K_{1_{\text{FLT}}} \times k_{3_{\text{FLT}}}}{k_{2_{\text{FLT}}} + k_{3_{\text{FLT}}}}
\]

Parametric Imaging:

- Pre-RT
- Post-RT

(Muzi, J Nucl Med, 2005)
Imaging as a Cancer Biomarker: Summary

- New paradigm for cancer imaging - beyond cancer detection
  - Requires novel approaches to image acquisition and analysis
  - Matches imaging to clinical questions and cancer biology
- Imaging outcomes match approach to therapy
  - How aggressive? Prognosis
  - What target? Prediction
  - Is it working? Response

... new study designs for cancer imaging research

- Image quantification key
- Complementary to tissue/serum biomarkers
ACRIN Trials with Novel PET Imaging Probes

- Opened or opening
  - ACRIN 6682 - $^{60}$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 (Yu, PI; collaboration with DOD consortium)

- Under Development
  - ACRIN 6688 - $^{18}$F-FLT and breast cancer response (Bear/Jollie, PI; collab with VCU/CIP Phase I/II)
  - Others under discussion for FLT for brain tumors and H/N CA
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