PET Biomarkers: Beyond FDG

David A. Mankoff
Seattle Cancer Care Alliance and
University of Washington
Seattle, WA, USA

work supported by NIH Grants CA42045, CA72064, MH63641,
CA90771, S10 RR17229
Cautions

- Many of the imaging methods presented are considered investigational
- Discussion of results and possible applications is not a claim of clinical efficacy
Imaging to Direct Cancer Therapy: Outline

• Clinical questions and biologic targets
• Examples of applications to cancer care
  • Assess the therapeutic targets
  • Identify resistance factors
  • Measure early response to treatment
  • Relate treatment response to patient outcome
Existing Paradigm for Cancer Imaging: Find the Cancer

- Established role:
  - Detect cancer
  - Find how far cancer has spread
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
Internal Mammary Nodal Uptake on FDG PET: Locally Advanced Breast Cancer Pre-Therapy

(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
  - Identify targets, predict response
  - Measure tumor response (early!)
  - Pick treatments most likely to prolong survival
Emerging Cancer Imaging Paradigm: Measure Factors Affecting Response Variable Levels in Tumor

- Surface Receptors
  - Octreotide
- Proliferative Rate
  - Thymidine & Analogs
- Glycolytic Rate
  - FDG
- 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

PET/CT Fusion

FDG PET

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

Region-of-Interest Analysis

- Time-Activity Curves
- Tumor
- Ventricle

Kinetic Modeling

Parameter Estimates

Inject Tracer

Static Image

- Static Uptake Measure (SUV)
Imaging and Clinical Trials

Choices for Imaging Approaches
Specific Examples of PET Imaging to Direct Cancer Therapy

- Assess the therapeutic target
- Identify resistance factors
- Measure early response
- Relate response to outcome
Identifying Therapeutic Targets using Imaging: Why?

- Imaging can measure the level of expression
  - Heterogeneity - spatial and temporal
  - Especially for advanced disease
- Imaging can measure the *in vivo* effect of drug therapy on the target. Examples:
  - Target antagonism
  - Change in target expression
- Imaging is quantitative
- Complementary to in vitro assay
[F-18]-Fluoroestradiol (FES): PET Estrogen Receptor (ER) Imaging

FES

Estradiol

<table>
<thead>
<tr>
<th></th>
<th>RBA</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER</td>
<td>0.9</td>
</tr>
<tr>
<td>SHBG</td>
<td>0.8</td>
</tr>
</tbody>
</table>

(Kieswetter, J Nucl Med, 1984)
Validation: ER+ vs ER- Tumors

FDG

ER-

axial

coronal

ER+

Glucose Metabolism

ER Expression

Liver
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)
FES Uptake Predicts Response of Advanced Breast Cancer to Hormonal Therapy

(LABC or Metastatic Br CA
Primary Tamoxifen Rx)

(Recurrent or Metastatic Br CA
Aromatase Inhibitor Rx)

(Mortimer, J Clin Onc, 2001)  (P < .01 for both)  (Linden, J Clin Onc, 2006)
FES PET Measures Fulvestrant ER Antagonism *In Vivo*

Pre-Rx
- Liver: SUV = 7.4
- Uterus

1 month
- Post-Fulvestrant 250 mg qm
  - (Stable Dz, No Response)
  - SUV = 3.1

5 Months
- Post-Fulvestrant 500 mg qm
  - (Dz Progression)
  - SUV = 3.2

(FES PET, Coronal Slices)

(Linden, SABCS, 2005)
Imaging Androgen Receptor (AR) Blockade
Dehdashti, EJNMMI 32:344, 2005
$^{18}$F-fluorodihydrotestosterone (FDHT)

Pre-Flutamide

Post-Flutamide
Specific Examples of PET Imaging to Direct Cancer Therapy

- Assess the therapeutic target
- Identify resistance factors
- Measure early response
- Relate response to outcome
Agents for Identifying Tumor Resistance Factors

- Hypoxia
  - $^{18}$FMISO, $^{60}$Cu-ATSM, $^{18}$FIAZA, $^{18}$F-EF5
- Drug transport/efflux (p-gp)
  - $^{11}$C-verapamil, $^{11}$C-colchicine, $^{11}$C-or $^{18}$F-paclitaxel, $^{94m}$Tc-sestamibi
Imaging Hypoxia as the Accumulation of a Radiopharmaceutical

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

Nitroreductase enzymes

Radical Anion

covalent bonding to macromolecules

[F-18]-fluoromisonidazole

University of Washington
KA Krohn
Tumor Hypoxia Quantified by PET Predicts Survival

FMISO PET
Brain Tumor
(Spence, UW)

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

Cu-ATSM PET
Cervical Cancer
(Dehdashti, Int J Radiat Oncol Biol Phys, 2003)
Imaging to Direct Hypoxia-Specific Treatment

- Advanced H & N Ca
- Randomized to
  - XRT + Cisplatin/5-FU
  - XRT + Cisplatin/Tirapazamine (TPZ)
- FMISO PET (observational only)
Resistance Due to altered Drug Transport: PET to Measure P-gp Drug Transport

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

P-gp susceptible drug

$^{11}$C-Verapamil

Other P-gp RPs:
- Sestamibi
- F-paclitaxel

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

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

MRI

Pre-CsA

Post-CsA

88% +/- 12% increase in Verap. AUC post- vs pre-CSA

(N= 12, P < .01)

(Sosangko, Clin Pharm Ther, 2005)
Specific Examples of PET Imaging to Direct Cancer Therapy

• Assess the therapeutic target

• Identify resistance factors

• Measure early response

• Relate response to outcome
Response of GIST to Imatinib Measured by FDG PET

Pre-Rx 48 hrs

Biologic Events in Response to Successful Cancer Therapy

Rx

↓ Cellular Proliferation
or
↑ Cell Death

↓ Viable Cell Number

↓ Tumor size
Cell Proliferation Imaging Agents

- Gold standard - thymidine
  - Methyl or $^{11}$C-Thymidine
- Analogs with minimal metabolism
  - $^{18}$FLT
  - $^{18}$FMAU
- Analogs with longer half-life
  - $^{124}$IUdR
Small Cell Lung Cancer: PET Imaging Pre-and Post One Cycle of Rx

Thymidine (proliferation)

FDG (Glucose Metabolism)

Pre-Rx

Post-Rx

Tumor

Marrow (with mets)

7 days

(Shields, J Nucl Med, 1998)
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)

FLT PET Images of Lung Cancer

(Shields AF, from Mankoff, Shields, and Krohn, Rad Clin N Amer 43:153, 2005)
Early Response of Breast Measured by FLT PET
Kenny, EJNMMI 34:1339, 2007

Pre-FEC  1 wk Post-FEC

FLT Uptake Reproducibility: 10% -15%

Response

No-Response
FLT Brain Tumor Imaging to Measure Response: Proliferation or BBB Breakdown?
Muzi, J Nucl Med, 2006

Kinetic model:  Parametric Imaging:

\[
\text{Flux}_{\text{FLT}} = \frac{K_1^{\text{FLT}}}{k_2^{\text{FLT}} + k_4^{\text{FLT}}} \]


<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-RT</th>
<th>Post-RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flux</td>
<td>0.030</td>
<td>0.017</td>
</tr>
<tr>
<td>K1</td>
<td>0.066</td>
<td>0.059</td>
</tr>
</tbody>
</table>
Specific Examples of PET Imaging to Direct Cancer Therapy

- Assess the therapeutic target
- Identify resistance factors
- Measure early response
- Relate response to outcome
A Mismatch Between Tumor Metabolism and Perfusion Predicts Poor Response

15O-water and FDG PET

15O-Water (30 - 60 sec)

F = 0.28 mL/min/g

FDG (30 - 60 minute)

MRFDG = 17 μmole/min/100g


DCE MRI and FDG PET

MRI Transfer Constant

FDG PET SUV

(Semple, Annals Oncol, 17: 1393, 2006)
Blood Flow and Metabolism Patterns of Change with Neo-Adjuvant Chemotherapy
Altered Metabolic Phenotype with Rx

Changing Metabolic Phenotype in Resistant Br CA Treated with Neo-Adjuvant Chemotherapy

Balanced Metabolism

Substrate Use
Substrate Delivery

Aberrant Metabolism

↓ ‘d Glucose Metabolism

↓ ‘d Blood Flow

↑ ‘d Blood Flow

Balanced Metabolism

Substrate Use
Substrate Delivery

ChemoRx
PET Biomarkers Beyond FDG: Summary

- Imaging ideally suited to testing new targeted drugs
- Imaging can help targeted drug testing and clinical practice by:
  - Better patient selection:
    - Identifying the therapeutic target
    - Identifying possible resistance factors
  - Better assessment of efficacy
    - Early measure of response
    - Relating response to patient outcome
  - *In vivo* assessment by imaging is complementary to *in vitro* molecular assay of biopsy material
Acknowledgements:
UW PET Cancer P01
P01CA42045, Ken Krohn, PI

• Project 1 - Brain Tumors
  • Alex Spence

• Project 2 - Lymphoma
  • Janet Eary, Ollie Press

• Project 3 - Head and Neck Cancer
  • Joseph Rajendran

• Project 4 - Breast Cancer
  • David Mankoff, Hannah Linden

• Project 5 - Sarcoma
  • Chappie Conrad, Janet Eary

• Project 6 - Endocrine Tumors
  • Jeanne Link, Gary Mann

• Core A - Radiochemistry
  • Jeanne Link

• Core B - Physics
  • Tom Lewellen, Paul Kinahan

• Core C - Data analysis
  • Mark Muzi, Finbarr O’Sullivan

• Core D - Molecular Pathology
  • Jonathan Tait, Kevin Yagle
UW PET Cancer Imaging Research: Key Collaborators

**Pharmaceutics**
- Jashvant Unadkat

**Radiology**
- William Eubank
- Connie Lehman

**Pathology**
- Thomas Lawton
- Jonathan Tait
- Peggy Porter (FHCRC)
- Allen Gown (Phenopath)

**Biochemistry**
- Philip Petra

**Cardiology/Bioengineering**
- James Bassingthwaite
- James Caldwell

**Biostatistics**
- William Barlow (CRAB)
- Brenda Kurland

**Neurology**
- Alex Spence

**Surgery/Orthopedics**
- David Byrd
- Earnest Conrad
- Gary Mann

**Oncology**
- Georgiana Ellis
- Julie Gralow
- Hannah Linden
- Robert Livingston
- Ollie Press
- Jennifer Specht
- Lavanya Sundararajan

**Radiation Oncology**
- Janet Rasey
- Jeffrey Schwartz
- Michelle Yao