Molecular Imaging: Biomarkers for Oncology

Steven M. Larson, M.D
Nuclear Medicine Svc, Department of Radiology
MSKCC, NY NY
Molecular Imaging in Oncology

Imaging the key molecules or molecular based events that are fundamental to the malignant state
Biomarkers

• Biomarkers are biologic indicators of disease or therapeutic effects, which can be measured through dynamic imaging tests, as well as tests on blood, tissue and other biologic samples.

• (Oncology Biomarker Qualification Initiative (OBQI), a joint enterprise of US FDA, NCI and CMS)
Why Now, Why Biomarkers?

• The search for biomarkers as endpoints of clinical trials to help reduce the growing cost of obtaining new drug approvals.

• Dissatisfaction with the classical anatomic based imaging methods for assessing treatment response assess such as WHO criteria, or RECIST;

• For Imaging, PET/CT and FDG in oncology, and the major role of FDG, as a measure of glycolysis, in cancer management
Oncology Biomarker Qualification Initiative (OBQI)

• “Biomarkers are indicators of disease or therapeutic effects, which can be measured through dynamic imaging tests, as well as tests on blood, tissue and other biologic samples.”
• NCI, FDA, CMS memorandum of understanding
• Cooperate closely with industry
• http://www.fda.gov/oc/mous/domestic/FDA-NCI-CMS.html
Potential Benefit of Biomarkers in Clinical Trials

• Determine if patient’s tumor is likely to respond at all to specific treatments
• Assess after 1 or 2 treatments if a tumor is dying, even if it is not shrinking in size.
• Determine which patients are at high risk for their patient recurring after surgery
• Efficiently evaluate whether an experimental therapy is effective for tumor treatment
The 1997 FDAMA Act and key FDA approvals made possible PET FDG Reimbursement in oncology and cardiology

Spurred major technologic development over the last decade, including PET/CT and many new molecular imaging agents.
PET/CT in Cancer Care:
Combines 2 high resolution diagnostic imaging methods

Positron Emission Tomography (PET)
Biochemistry and Function
Computerized Tomography (CT)
Anatomy and Structure
Discovery ST
PET-CT
PET FDG as Biomarker

Current Candidate Biomarker

• 2-Flouro-2-D-deoxy glucose
  – [18F]FDG is a positron emission tomography (PET) drug used in diagnostic imaging. On March 10, 2000, FDA announced [18F]FDG to be safe and effective for certain indications when produced under conditions specified in approved applications (see Federal Register, Vol. 65, No. 48, 12999-13010).
Current Candidate Biomarker

- 2-Flouro-2-D-deoxy glucose
  - [18F]FDG is indicated in positron emission tomography (PET) imaging for (1) assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer; (2) patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging, for the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function; and (3) patients for the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.
Imaging Treatment Response: tyrosine kinase inhibitors

$^{18}$F-FDG in GIST tumors treated with Glivec, an bcr/abl,c-kit,PDGFR kinase inhibitor
GI Stromal Tumor (Pre-therapy with STI-571)

Feb 26, 2001

686140
GI Stromal Tumor (Post-therapy STI-571)

June 7, 2001 (CT May 4, 2001)
SUV

Activity per unit volume

Injected Activity/Body Wt*

*also, lean body mass, BSA, etc
PET imaging and Tumor Response
920 citations in medline*

- Breast Cancer
- NSCLC
- Lymphoma
- Esophageal
- Gastric
- Head and Neck
- Brain Tumor
- Etc.
PET/CT Function/Structure
Exploratory IND

Phase 0 testing
Exploratory IND*

• Determine whether a mechanism of action defined in experimental systems can also be observed in humans (a binding property of inhibition of an enzyme)
• Provide important information on PK
• Select the most promising compound from a group of candidates designed to interact with a particular therapeutic target in humans based on PK or PD properties.

*Guidance for Industry, Investigators and Reviewers.. Jan 2006
Exploratory IND

- Studies can be performed at “Microdose” levels, ie <1/100\(^{th}\) of a pharmacologic dose, or <100 µgms, for biologicals, <30 nM
- Toxicity studies in animals should be 100X the dose in humans administered on a BSA basis
  - observe for 14 days, weight, chem, heme
  - Necropsy @ 2 days for histopathology
HSP 90 : a target for chemo

Critical Chaperone Function

  e.g. Her 2, AR, AKT
Ansamycins bind to the ADP/ATP switch site in Hsp90

Geldanamycin (GM)

17-AAG
HER2+ Breast cancer with active sites of disease including the lung and bone. Previously treated with 3 different trastuzumab-containing combinations, progressing on bevacizumab plus trastuzumab prior to enrollment on the trial. Confirmed PR by RECIST.

Modi et al., Abstract 501, ASCO 2006
Metastatic Breast Cancer

A – heart
B – left adrenal metastasis
C – right kidney

Solit, Rosen et al
Herceptin as a Phase 0 Imaging Example.
Phase 0 Trials in Oncology Drug Development

Steven M. Larson, M.D
Nuclear Medicine Svc, Department of Radiology
MSKCC, NY NY
Pharmacodynamics

Targeted Therapies: Inhibition of signal transduction
${^{68}}$Ga (Fab’$_2$) Herceptin

Imaging Biomarker for Her 2 receptor expression in vivo
Imaging Her-2 Expression

• Ansamycins, which target HSP-90, induce Her-2 Degradation
• 15-20% response in Breast Ca with anti-her2 monoclonal antibody, Herceptin
Imaging her-2 expression in vivo

$^{68}$Ga-(Fab’$_2$) herceptin

Virtual Immunohistology (VIH): Non-invasive imaging of tumor antigen expression in the living organism

Targeted Radiopharmaceutical Therapy

- Antibody Forms
  - Intact Antibody
  - Fab’2
  - Fab
  - sFv
  - Diabody (sFv)2
  - Minibody

Courtesy Anna Wu, City of Hope Med Ctr
Quantitation of Antigen In-vivo with $\beta^+$ labeled antibodies

$$\Delta \text{Uptake} = \Delta [\text{Ag}]$$

$^{68}\text{Ga}-(\text{Fab'})_2$

anti-p185HER2 (humanized 4DT: Herceptin)
MicroPET images obtained 3 hours post injection with $^{68}\text{Ga}$-F$(\text{ab})_2$-Herceptin in a mouse with a BT 474 breast tumor.
Gallium-68 herceptin imaging of her-2
Western Blot Analysis of HER2 Protein Expression by Tumors Recovered from Control Animals or Animals Treated with 17AAG.
Effect of 17AAG on HER2 Protein expression by BT474 Breast Cancer Line

**Saturation Binding of DOTA-Herceptin to BT474 cells**

*Control cells*

Data: Data4_E
Model: saturation

- $B_{max}$: 1165000 ± 94000
- $K_d$: 6.55 ± 1.52

*7/31/02 Group 2: 500 nM NSC 17AAG 18 hours*

Data: Data4_E
Model: saturation

- $B_{max}$: 236000 ±5000
- $K_d$: 6.33 ± 0.43

**K_d** unchanged

**$B_{max}$** reduced by 80%
Tumor Uptake of $^{68}$Ga-DOTA-F(ab')$_2$-herceptin following 2 x 100 mg/kg 17AAG 18 and 6 hours Before Scan at Day 1

Tumor Uptake (normalized) vs Time (Days)

Control Group

Treated Group

17 AAG
Example of $^{68}\text{Ga}$-F(ab$'$)$_2$-Herceptin imaging of a CWR22 Prostate Tumor in a Mouse
ROI Analysis of $^{68}$Ga-F(\(ab'\))$_2$-Herceptin Uptake in a CWR22 Prostate Tumor After 17 AAG Treatment.

Formation half-life 1.35 days
Peter Smith-Jones, Ph.D.
Radiochemist
Pt. # 1. Her 2 + Breast Cancer, metastatic to skull

CT: Temporal lytic lesion

PET: Her 2+ Breast
Tumor Response in Skull
Her 2 imaging: IRB #06-090 Akhurst et al.

Pt. # 5. Her 2 + Breast Cancer, metastatic to liver
Nuclear Pharmacies

*Nuclear pharmacy* is a specialty area of *pharmacy* practice dedicated to the compounding and dispensing of radioactive materials for use in *nuclear* medicine.
Nuclear Pharmacies

• Cardinal Health
• Mallincrodt
• PET-NET
• Eastern Isotopes (IBA Molecular)
• A national network of licensed pharmacies
  – USFDA
  – US Pharmacopeia
  – NRC
  – State Boards of Pharmacy
Proposed Regulatory Path for Approval Imaging Biomarkers

• 1997 FDAMA emphasized USP as a basis for radiopharmaceutical formulation by pharmacist under physician order.
  – Specific tested formulations in humans
  – Extensive testing, safety data and QC available
  – cGMP or equivalent facilities

• Recommendation, like FDG, that USP radiotracers be reviewed by USFDA for safety and effectiveness as a biomarker for key metabolism or the presence of key biomolecules, associated with malignancy or relevant pathology
Molecular Imaging Agents as Potential Biomarkers

- **Glycolysis**
  - $^{18}$FDG

- **Hormone Receptor Expression**
  - $^{18}$F-fluorodihydrotestosterone $^{18}$FDHT (AR)
  - $^{18}$F-Flouroestroadiol $^{18}$FES (ER)

- **Proliferation Markers.**
  - $^{18}$F-L-Thymidine $^{18}$FLT
  - $^{124}$I-Iodo-deoxy-uridine (IUDR)

- **Amino acid transporter**
  - $^{18}$FACBC
  - $^{11}$C-methionine

- **Viral and Gene Expression Imaging**
  - $^{124}$I-Flouroiodoarabinosyluridine (FIAU)

- **Hypoxia and aberrant hif-1 alpha expression**
  - $^{18}$FMISO
  - $^{124}$I-cG250 (CA IX)

- **Growth factor expression**
  - *Her 2, $^{68}$Ga-Fab'2 Herceptin*

- **Transporters**
  - $^{124}$I –Nal (NIS)

- **Drugs**
  - $^{18}$F-disatinib
68Ga-(Fab’2) herceptin


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