Imaging in Translational Research
An Introduction

Katarzyna J. Macura, MD, PhD, Associate Professor of Radiology
The Russell H. Morgan Department of Radiology and Radiologic Science

kmacura@jhmi.edu
Disclosure

- Research Grant from Siemens Medical Systems
Outline

- What is translational research
- What is quantitative imaging (QI)
- Imaging as a biomarker
- Role of imaging in translational research
  - Examples of projects implementing imaging in translational research
What is Translational Research

- From “the bench” level with basic research (disease at a molecular or cellular level)
- To the clinical, patient level “bedside.”

*Nature Reviews Drug Discovery 2008*
Radiologists involvement

• Development of agents or devices
  – Laboratory level pre-clinical, animal research
  – Significant expertise needed in multiple domains

• Validation and feasibility testing
  – Imaging expertise needed

• Clinical trials
  – Testing innovations in experimental clinical setting
  – Clinical trial methodologies

• Technology assessment
  – Systematic reviews, meta-analysis, guidelines development

• Implementation assessment
  – Practice-based research
  – Outcomes
What is QI

- Extracting quantitative measurements from medical imaging vs. qualitative assessment
Which imaging parameters are quantitative?

- **Morphology**
  - Volume, 3D techniques
  - Cellularity/density/composition of tissues

- **Function**
  - Perfusion (DCE-MRI)
  - Metabolic activity (PET)
  - Metabolite concentration (H1 spectroscopy, Na23)
  - Molecule movement, e.g. water molecule (DWI)
“A characteristic that is **objectively measured** and evaluated as an **indicator** of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. “

- Imaging provides quantifiable parameters non-invasively

MRI

Spectroscopy

Sodium Images

Final Histology

Complete response

Tumor

Baseline

1st cycle

4th cycle

Before surgery

M. Jacobs et al
JHU
DCE – MRI: Kinetic Curve

R. El-Khouli et al, JHU - NIH
Compartmental Modeling

- Volume transfer constant ($K^{\text{trans}}$) between the blood plasma and EES (permeability)
- Volume of EES per unit volume of tissue ($v_e$)
- Flux rate constant between EES and plasma ($k_{ep}$)

$$k_{ep} = \frac{K^{\text{trans}}}{v_e}$$
DCE - MRI

Pre-treatment

Post-treatment

4 cycles of chemotherapy

Volume

Permeability

EVF

10th Percentiles 50th Percentiles 90th Percentiles

Volume Comparison

Studies

Studies

Studies
Imaging Human Tumor Models

Subcellular and Receptor Imaging

Imaging from Bench to Bedside

Imaging Human Tumor Models

Arvind P. Pathak
JHU, ICMIC
Clinical Trial

Disease

Intervention

True Clinical Outcome

Time
Clinical endpoint

- A characteristic or variable that reflects how a patient feels, functions, or survives
- Used in the assessment of the benefits and risks of a therapeutic intervention in clinical trials
Problem with clinical endpoint

- Clinical trials which evaluate the effect that new interventions have on clinical outcomes of particular relevance to the patient (morbidity or mortality) need to be large and long
- Costly $$$,$$$,$$$,
Clinical Trial

Disease → Intervention → Surrogate End point → True Clinical Outcome

Time
Surrogate endpoint

- A **biomarker** that is intended to **substitute** for a clinical endpoint (clinical status or outcome)
- It is expected to reliably **predict** clinical benefit (or harm, or lack of benefit or harm)
  - Changes induced by a therapy or intervention on a surrogate endpoint are expected to reflect changes on a clinically meaningful endpoint
Biomarkers

Detect Disease

Monitor Progression/Recurrence

Monitor Treatment Compliance

Stage Disease

Determine Treatment

Predict Response to Treatment

Monitor Treatment Compliance

Determine Response to Treatment

Monitor Progression/Recurrence

Detect Disease

Stage Disease

Determine Treatment

Predict Response to Treatment

Monitor Treatment Compliance

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Monitor Treatment Compliance
Why biomarkers are important in clinical trials

• FDA approval process very rigorous and lengthy
• Many years and millions of $ for new drug approval
• New candidate compounds are being constantly developed
• Finite $$ resources
• Surrogate end-points can help with implementation of new medical products by replacing large, long, costly studies of clinical outcomes with smaller, faster, and cheaper studies utilizing surrogate end points instead of clinical outcomes
Surrogate endpoint validity

- Surrogate is in the only causal pathway of disease and intervention’s entire effect on true clinical outcome is mediated through its effect on the surrogate.

Examples of translational research implementing imaging
The Role of Imaging in Developing Cell-Based Therapy of Myelin Disease

• Therapeutic effect depends on:
  • survival, migration, appropriate differentiation, and functional integration of transplanted cells within the host
• New myelination by grafted cells works well in young, developing recipients but is more challenging in the adult, disease damaged host
• Non-Invasive monitoring is critical for optimization of cell therapy

We monitor survival and differentiation of grafted cells with bioluminescent imaging

We monitor cell delivery, migration and compact myelin formation with MRI

We monitor axonal conduction with electrophysiology

Piotr Walczak, MD, et al, Institute for Cell Engineering, JHU
From Mice to Man: Imaging Infection with $^{[\text{124}]}$FIAU PET-CT

Catherine A. Foss, Ph.D., et al., SAIRP JHU

Permissive Pathogens Selectively Trap FIAU
(Fialuridine -- nucleoside analogue)

HSV1 tk
EBV tk
KSHV tk
bacteria

(free)

(cell trapped)
Proof of principle: imaging bacterial thymidine kinase (TK)

Radio-FIAU uptake is mechanism-based (substrate for bacterial thymidine kinase)

Bettegowda et al., Proc Natl Acad Sci USA, 2005; 102:1145
Clinical PET-CT images showing bacterial infection in natural and prosthetic joints.

Red arrows indicate the site of infection. A. patient 3 at 2h p.i., infected left hip; B. and C. Patient 4 at 2 and 24h p.i., respectively, infected right knee; D. patient 7 at 2h p.i., infected left ankle; E. patient 8 at 2h p.i., infected right knee.
Prostate Specific Membrane Antigen (PSMA)

- Non-secreted protein
- Functions both as a folate hydrolase and a neuropeptidase
- Highly expressed in prostate cancer
- Associated with tumor aggressiveness and metastatic potential
- It is also expressed in neovasculature of most solid tumors

There are up to $10^6$ PSMA molecules per cancer cell, making it an ideal target for imaging and therapy.
- $^{[18}\text{F}]\text{DCFBC}$, a urea based small molecule ligand of PSMA

- Developed in Martin Pomper’s Laboratory with Ronald Mease, JHU SAIRP.

- Pre-Clinical Studies demonstrate high specific uptake in PSMA expressing tumors.

FDA and IRB Approval for 1st in human study

- Preclinical Toxicology – NCI DCIDE 8/2007
- Precursor Validation
- Radiosynthesis GMP
- FDA exploratory IND - approval 6/25/2010
  - 30 day safety review
- Human Subjects Research approval
  - Institutional Cancer Center Review
  - Institutional IRB review
    - Includes Clinical Radiation Research Committee Review

Steve Y. Cho, JHU
Clinical Protocol

To determine \(^{18}\text{F}\)-DCFBC radiation dosimetry, pharmacokinetics, and biodistribution in patients with advanced prostate cancer.

To evaluate \(^{18}\text{F}\)DCFBC PET/CT for detection of prostate cancer in patients with advanced metastatic prostate cancer.

**Inclusion criteria:**

- Histological confirmation of prostate cancer
- Radiologic evidence of new or progressive metastatic disease demonstrated on anatomical imaging (CT, MRI, or ultrasound), bone scintigraphy, \(^{18}\text{F}\)-Sodium Fluoride PET, or \(^{18}\text{F}\)-FDG PET
- PSA ≥ 1.0 ng/mL
First $^{18}$F-DCFBC PET/CT Patient

• Prostate CA s/p prostatectomy 6 year ago
  – Gleason 5+4=9 with extensive extraprostatic extension, bilateral seminal vesicle invasion, and positive margin at the bladder neck
• A year ago, his PSA was 52.5 ng/mL when he was initiated on hormonal therapy on protocol
• Recent PSA of 4.8 at 2 months prior to scan, 1.0 at 5 months ago
• Hormone-refractory Prostate CA

Steve Y. Cho, JHU
MIP of PET1 [immed post-inject] and PET5 [2hr post-inject]
Serial MIP Projection PET Images

PET1

PET2

PET3

PET4

PET5
L4 vertebral body focal uptake – Not seen on bone scan
Focal Intense Sacral and Mild Diffuse Left Iliac Uptake (sacral focus not seen on bone scan)
Sacral Osseous Metastasis
Bilateral Ischial Uptake
(Not seen on bone scan)
Aortic Bifurcation Nodal Metastasis
Aortic Bifurcation Nodal Metastasis – IV contrast CT correlation

Recent
9-20-2010

Prior
9-22-2009
Overview
Development of $[^{18}\text{F}]\text{DCFBC}$

• **Pre-clinical**
  – Biologically Viable Target selection
  – Ligand screen/selection
  – Radiochemistry
  – Preclinical validation in animal model

• **Translation to Patients**
  – Preclinical Toxicology – completed by DCIDE Program
  – CGMP (Current Good Manufacturing Practice) – completed
  – Clinical Design, exploratory IND, IRB approval – completed
  – First-in-human studies – dosimetry, biodistribution, PK, and initial prostate cancer detection assessment
Multi- and interdisciplinary research teams will be required to solve the “puzzle” of complex diseases and conditions.
Clinical and Translational Science Awards (CTSA) Consortium

• Purpose: “assist institutions to forge a uniquely transformative, novel, and integrative academic home for Clinical and Translational Science that has the consolidated resources to: 1) captivate, advance, and nurture a cadre of well-trained multi- and inter-disciplinary investigators and research teams; 2) create an incubator for innovative research tools and information technologies; and 3) synergize multi-disciplinary and inter-disciplinary clinical and translational research and researchers to catalyze the application of new knowledge and techniques to clinical practice.”
Sharing a Common Vision

Working together as a national consortium, CTSA institutions share a common vision to improve human health by transforming the research and training environment to enhance the efficiency and quality of clinical and translational research. The CTSA program is led by the National Center for Research Resources, part of the National Institutes of Health.

National Consortium Strategic Goals

Learn how the goals of the CTSA Consortium are being carried out by the Strategic Goal Committees.

Featured Institution

University of Iowa

Each month, this section highlights the activities of a CTSA at a local level. View this month’s feature and more in our featured institutions section.

http://www.ctsaweb.org/
About the CTSA Imaging Working Group (IWG)

Drawing from experience of the NIH Roadmap for Medical Research and extensive community input, the Clinical and Translational Science Awards (CTSA) program creates an academic home for the discipline of clinical and translational science at institutions across the country.

A major goal of the CTSA initiative is to develop a national consortium of CTSA institutions that will work together to transform the discipline of clinical and translational research across the country. This union fosters the exchange of ideas with the goal of creating an environment in which treatments progress from ideas to therapies in a highly expedited fashion.

The national consortium of medical research institutions funded through Clinical and Translational Science Awards, is working together to improve the way biomedical research is conducted nationwide. The consortium’s website, CTSAweb.org, ensures broad access to CTSA resources, enhances communication and encourages information sharing.

The Imaging Work Group: A consortium

http://www.ctsa-imaging.org/
Thank you!

Questions?