48th Annual Hampton Lecture
Aubrey O. Hampton (1900-1955)

Precision Medicine
New Horizons in Oncologic Imaging
48th Annual Hampton Lecture
Aubrey O. Hampton (1900-1955)

Precision Medicine

2015 President Obama’s Precision Medicine Initiative Launched with a $215 million investment in the President’s 2016 Budget
Precision Medicine

Personalized, Molecularly Tailored, Biomarker Driven, Evidence-Based Medicine

• Tools employed in Precision Medicine include molecular diagnostics, imaging and analytics/software.
The Precision Medicine in Oncology

Challenges/Conundrum

- Because of the significant spatial and temporal heterogeneity of cancer (key to treatment failure & the development of drug resistance), Precision Medicine in Oncology requires both *in vitro* and *in vivo* (spatially and temporally resolved), biomarkers of tumor biology

- **unprecedented opportunities for Imaging** -

*The Precision Medicine Conundrum: Approaches to Companion Diagnostic Codevelopment; CCR Focus Section (#20), March 2014*
Precision Medicine & Imaging

Rembrandt’s King Beshazzar’s Feast (1635)
A trunk-branch model of intratumoral heterogeneity*

Why is in-vivo Imaging essential for Implementing Precision Medicine

Four Types of Genetic Heterogeneity - Relevant to Tumorigenesis*

- Intratumoral heterogeneity within a primary tumor
- Intermetastatic heterogeneity between two metastases
- Intrametastatic heterogeneity within metastatic lesions
- Interpatient heterogeneity

*B. Vogelstein et all: Cancer Genome Landscapes: Science 2013
Companion Diagnostics: Pathway to Value
Cetuximab as the first-line treatment of mets. Colorectal Ca

- Cetuximab (anti-EGFR antibody) costs ~ $61,279
- ~36% of pts did not respond
- Pts who have the k-ras gene mutation do not respond to anti-EGFR antibody

In USA, testing for k-ras mutation (companion diagnostics approved in August 2009) will save ~ $600 millions in drug costs alone*

* Economic Analysis: Oncology Times 2009
Precision Medicine: Companion Diagnostics

The first Companion Diagnostics - Herceptin and HercepTest were approved together in 1998

Biology driven Precision Biopsy

HER2 Amplified Gene Copies

HER2 Normal Gene Copy

Investigational: MSKCC
Breast Cancer Metastasis

Intermetastatic Heterogeneity

18F-FDG PET/CT April 5, 2013

18F-FDG PET/CT July 18, 2013

Treatment Follow-up - Mixed Tumor Response

Investigational: MSKCC
Mixed Tumor Response

Metastatic Breast Ca – Response to Tx

- 70 pt. metastatic breast Ca
- $^{18}$FDG PET/CT Mixed Response Definition:
  - a decrease of FDG uptake by > 30% in one lesion and
  - increase of FDG uptake by > 30% in another lesion

Mixed response in 33% of patients

Precision Medicine

Targeted Therapy/Targeted Imaging

Metastatic Breast Cancer – Therapy: ES receptor antagonist

18F-FES PET/CT
Baseline 9-12-13

18F-FES PET/CT
Post Therapy 10-22-13

Investigational: MSKCC
Prostate Cancer: Imaging Metastatic Disease

Frontiers of Diagnostic Imaging

$^{99}$Tc – Bone Scan

$^{18}$FDG PET/CT

Glycolysis

Hricak H.: Oncologic Imaging: A Guiding Hand of Personalized Cancer Care; Radiology 2011

$^{18}$FDHT PET/CT

Androgen Receptor
Intra/Inter-Tumoral Heterogeneity

Challenges for In vitro Diagnostics

• Which lesion to biopsy?
• How many biopsies? - Intra-Tumoral Heterogeneity
• Total Tumor Burden?
• Continuous Tumor De-differentiation – Re-biopsy?

Imaging*

The greatest promise for Interrogating Molecular Pathogenesis of Cancer

* B. Vogelstein et al: Science 2013
Prostate Cancer
Revealing Heterogeneous Biology of Tumor Metastasis

18F-FDG PET/CT
Glycolysis

18F-FDHT PET/CT
Androgen Receptor

Hricak H.: Oncologic Imaging: A Guiding Hand of Personalized Cancer Care; Radiology 2011
Prostate Cancer
Revealing Heterogeneous Biology of Tumor Metastasis

Hricak H.: Oncologic Imaging: A Guiding Hand of Personalized Cancer Care; Radiology 2011
Prostate Cancer

Revealing Heterogeneous Biology of Tumor Metastasis

CT

$^{18}$F-FDG PET/CT

Glycolysis

Zr-89 J591
PSMA mAb*

Imaging as a Companion Diagnostics - FDHT

Patient selection and follow-up

Metastatic Prostate Cancer – Therapy: AR receptor antagonist*

*Scher et al
Lancet: 2010

Hricak H.: Radiology 2011
Companion Diagnostics: Asking the right question/selecting the right imaging test & tracer

Jan 2008

Feb 2008

Therapy © Androgen Receptor Inhibitor: AR treatment response


**131I Refractory Metastatic Thyroid Cancer:** 124I scan as a Biomarker - selecting patients for 131I therapy following MEK inhibitor

J. Fagin et al: NEJM 2013

---

**124I PET/CT**
Baseline

**124I PET/CT**
5 wks after MEK Inhibitor

Signal transduction ERK-BRAF pathway

J. Fagin et al: NEJM 2013
**Theranostics:** *Hsp90-targeted imaging & therapy*

48 year old female with breast cancer metastatic to lungs and bones; Hsp90-targeted therapy (STA-9090), induced partial response in lung mass (↑) but progression in spinal lesion (↑); ¹²⁴I-PUh71 shows uptake and retention in the lung lesion but clearance from spinal bone metastasis.

*Investigational MSKCC: M. Dunphy & G. Chiosis*
Radiosynthesis of $^{11}$C compounds ($T_{1/2} = 20.4$ min)

~1975 - "C-glucose was prepared by photosynthesis. It was extracted from mashed up Swiss-chard leaves and a "green solution" was injected into the patient; preparation time ~90 min

2012 - "C-glucose is prepared by a "black box" automated versatile synthesizer producing drugs ready for human use; preparation time ~45min

~2032 - "C-glucose will be prepared by a widely available synthesizer – a 3D printer?

Courtesy J. Lewis: MSKCC
<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>Imaging Target</th>
<th>Cancer Site</th>
<th>Human studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>[18F]-FLT</td>
<td>tumor cell proliferation</td>
<td>Lymphoma, prostate, H&amp;N, NSCLC</td>
<td>MSKCC IND</td>
</tr>
<tr>
<td>[18F]-FES</td>
<td>estrogen receptor status</td>
<td>Breast</td>
<td>MSKCC IND</td>
</tr>
<tr>
<td>[18F]-FDHT</td>
<td>androgen receptor</td>
<td>Prostate</td>
<td>MSKCC IND</td>
</tr>
<tr>
<td>[18F]-FMISO</td>
<td>tumor oxygenation</td>
<td>Head &amp; Neck, Rectal</td>
<td>MSKCC IND</td>
</tr>
<tr>
<td>[18F]-FACBC</td>
<td>amino acid metabolism</td>
<td>Breast, Prostate, Brain</td>
<td>RDRC/GEMS IND</td>
</tr>
<tr>
<td>[18F]-FIAU</td>
<td>gene expression</td>
<td>Prostate</td>
<td>MSKCC IND</td>
</tr>
<tr>
<td>[18F]-ML10</td>
<td>imaging apoptosis</td>
<td>Brain, NSCLC, H&amp;N</td>
<td>Non-MSKCC IND</td>
</tr>
<tr>
<td>[18F]-dasatinib</td>
<td>tyrosine kinases</td>
<td>Prostate, Breast</td>
<td>MSKCC IND</td>
</tr>
<tr>
<td>[18F]-glutamine</td>
<td>tumor metabolism</td>
<td>All solid malignancies</td>
<td>MSKCC IND</td>
</tr>
<tr>
<td>[18F]-choline</td>
<td>cellular membrane phospholipids</td>
<td>Brain</td>
<td>MSKCC IND</td>
</tr>
<tr>
<td>[18F]-MFBG</td>
<td>NET-expressing tumor</td>
<td>Pediatric and Adult Neuroendocrine Malignancies</td>
<td>MSKCC IND</td>
</tr>
<tr>
<td>[64Cu]-ATSM</td>
<td>tumor oxygenation</td>
<td>Uterine Cervix, Rectal</td>
<td>ACRIN</td>
</tr>
<tr>
<td>[124I]-IAZGP</td>
<td>tumor oxygenation</td>
<td>Rectal</td>
<td>MSKCC IND</td>
</tr>
<tr>
<td>[124I]-FIAU</td>
<td>gene expression</td>
<td>Prostate</td>
<td>MSKCC IND</td>
</tr>
<tr>
<td>Na-[124I]</td>
<td>Na Iodide Symporter</td>
<td>Thyroid</td>
<td>MSKCC IND</td>
</tr>
<tr>
<td>[124I]-PUH71*</td>
<td>(theranostic) HSP-90</td>
<td>All solid malignancies and lymphoma (with PUH71 therapy)</td>
<td>MSKCC IND</td>
</tr>
</tbody>
</table>

**Antibodies and Fragments (Imaging)**

<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>Imaging Target</th>
<th>Cancer Site</th>
<th>Human studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>[68Ga]-Her2 (F(ab')</td>
<td>HER2</td>
<td>Breast</td>
<td>MSKCC IND</td>
</tr>
<tr>
<td>64Cu-DOTA-trastuzumab</td>
<td>HER2</td>
<td>Breast</td>
<td>MSKCC IND</td>
</tr>
<tr>
<td>[124I]-A33</td>
<td>A33 antigen</td>
<td>Colon</td>
<td>MSKCC IND</td>
</tr>
<tr>
<td>[124I]-3F8</td>
<td>disialoganglioside GD2</td>
<td>Neuroblastoma (pediatrics)</td>
<td>MSKCC IND</td>
</tr>
<tr>
<td>[124I]-8H9</td>
<td>8H9 antigen</td>
<td>Multiple tumors e.g. Leptomeninges (pediatrics)</td>
<td>MSKCC IND</td>
</tr>
<tr>
<td>[124I]-G250</td>
<td>CA9 antigen</td>
<td>Renal</td>
<td>MSKCC IND</td>
</tr>
<tr>
<td>[89Zr]-DFO-huP591</td>
<td>PSMA</td>
<td>Prostate</td>
<td>MSKCC IND</td>
</tr>
<tr>
<td>[89Zr]-DFO-Trastuzumab</td>
<td>HER2</td>
<td>Breast</td>
<td>MSKCC IND</td>
</tr>
<tr>
<td>[89Zr]-DFO-MSTP2109A</td>
<td>PSMA</td>
<td>Prostate</td>
<td>MSKCC IND</td>
</tr>
<tr>
<td>[89Zr]-Df-IAB2M</td>
<td>PSMA</td>
<td>Prostate</td>
<td>ImaginAb/MSKCC IND</td>
</tr>
<tr>
<td>111In-DOTA-cG250</td>
<td>CA9 antigen</td>
<td>Renal</td>
<td>LICR IND</td>
</tr>
</tbody>
</table>

**Antibodies and Fragments (Therapy)**

<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>Imaging Target</th>
<th>Cancer Site</th>
<th>Human studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>90Y-DOTA-cG250</td>
<td>CA9 antigen</td>
<td>Renal</td>
<td>LICR IND</td>
</tr>
<tr>
<td>131I-8H9</td>
<td>8H9 antigen</td>
<td>Multiple tumors e.g. Leptomeninges (pediatrics)</td>
<td>MSKCC IND</td>
</tr>
<tr>
<td>131I-3F8; 131I-hu3F8</td>
<td>disialoganglioside GD2</td>
<td>Neuroblastoma (pediatrics)</td>
<td>MSKCC IND</td>
</tr>
<tr>
<td>225Ac-lintuzumab</td>
<td>Anti-CD33</td>
<td>Acute Myeloid Leukemia</td>
<td>MSKCC IND</td>
</tr>
</tbody>
</table>

**Nanoparticles (Imaging)**

<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>Imaging Target</th>
<th>Cancer Site</th>
<th>Human studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>[124I]-Cdot nanoparticles</td>
<td>αvβ3</td>
<td>Melanoma</td>
<td>MSKCC IND</td>
</tr>
</tbody>
</table>

**IND Enabling Stage for 2015:** [68Ga-DOTA-RM2; 68Ga-DOTA-JR11; 111In-DOTA-JR11; [89Zr]-DFO-transferrin; [89Zr]-DFO-SB1; [89Zr]-DFO-MLY44789A| [11C agent: choline, acetate, thymidine, glucose]
Molecular Imaging: Developing Tumor Biomarkers for Precision Medicine - Oncology

Validation, Approval (FDA & CMS) and Dissemination of Imaging Biomarkers lags behind advances in targeted therapy

- Needs Assessment (clinical & financial)
- EGAPP framework for Imaging Biomarkers
  - Analytical performance
  - Clinical validity
  - Clinical utility
NEXT GENERATION SEQUENCING IMAGING

QUANTITATIVE, BIG DATA AND MOLECULARLY DRIVEN

- **Imaging Tumor Biology**: molecular imaging (new tracers & PET, CT, MRI, optical)

- **Radiomics**: quantitative, high throughput, “automated,” large data analysis – building decision support systems

- **Radiogenomics**: defining relationships, *association maps*, between image features (including Radiomics) and molecular markers (OMICS)

Hricak H: RSNA 2014 AAPM Planner Session
Radiomics

Images are data!

*Bob Gillies

• Curating and mining data for incorporation into decision-support systems may help radiologists determine diagnoses and prognoses

• Potential to reduce uncertainty in diagnostics
  - Facilitating dissemination of “Best Practice”
  - Enhancing continuous education

• Improved detection of Intratumoral Heterogeneity/Tumor Characterization
  - Facilitating Precision Biopsy

Hricak H: RSNA 2014 AAPM Planner Session
MR Imaging: Radiomics

Texture Analysis
Compared to T2WI & DWI, there is further improvement in PCa detection, visualization of tumor heterogeneity & characterization.

Radiomics

Bladder Cancer: Reveling Tumor Heterogeneity

Vargas H., Veeraraghavan H., et al: MSKCC Investigational
Radiogenomics - *Radiation Therapy*

The link between Germ line genetic variations and *normal tissue response to radiation therapy*, with the long term goal to identify patient at risk for radiation toxicity based on genetic variations.

Radiogenomics - *Imaging*

An association between Imaging features and *Genetic & Epigenetic signatures*; a link between diagnostic imaging & molecular diagnostics.
Convergent Evolution
Genotype & Phenotype

INTEGRATED DIAGNOSTICS
Convergence of “omics,” molecular pathology, laboratory medicine & imaging
Radiogenomics in Imaging

• Radiogenomics - defines relationships, association maps, between image features (including Radiomics) and molecular markers (OMICS)

• A Radiogenomic correlation does not imply causation!!!

• Pilot studies include both big data analysis and candidate genes/descriptive findings: GBM, HCC, Breast Ca, Lung Ca & Kidney Ca


ALK Molecular Phenotype in Non–Small Cell Lung Cancer: CT Radiogenomic Characterization

Yamamoto S, at al: Radiology, August 2014
Halpenny DF, at al: Lung Cancer, Epub Sep 2014

ALK positive lung adenocarcinoma & CT
ALK is commonly associated with larger volume & multifocal thoracic lymphadenopathy

Personalized Therapy: Crizotinib
(FDA approved in August 2011)
Clear Cell RCC: Phenotypic Heterogeneity

Contrast enhanced CT

Courtesy O. Akin; MSKCC
Radiogenomics

Association between CT features (8 descriptive & 5 quantitative) & Clear-Cell RCC genetic mutations

<table>
<thead>
<tr>
<th>CT Parameter</th>
<th>VHL</th>
<th>PBRM1</th>
<th>BAP1</th>
<th>SETD2</th>
<th>KDM5C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Vein Invasion</td>
<td>0.194</td>
<td>1.000</td>
<td>0.030</td>
<td>0.391</td>
<td>0.030</td>
</tr>
<tr>
<td>Lobulated Tumor Enhancement Pattern</td>
<td>0.166</td>
<td>0.010</td>
<td>1.000</td>
<td>0.743</td>
<td>0.747</td>
</tr>
<tr>
<td>Low Nephrographic Phase Enhancement</td>
<td>0.737</td>
<td>0.394</td>
<td>0.101</td>
<td>0.023</td>
<td>0.445</td>
</tr>
<tr>
<td>Collecting System Invasion</td>
<td>0.031</td>
<td>1.000</td>
<td>0.059</td>
<td>0.168</td>
<td>0.209</td>
</tr>
</tbody>
</table>

*Cluster mutations in clear-cell RCC
*N=232*

*C. A. Karlo et al: Radiogenomics of clear-cell renal cell carcinoma: Associations between CT imaging features and mutations; Radiology 2014*
Ovarian Cancer: Radiogenomics
Enhancing Continuous Education

Is there association between CT imaging findings and prognostically relevant gene signatures (TCGA) in HGSOC?

Oncologic Imaging/Precision Medicine – the Next 10Y
Convergence of the Life Science, Physical Science & Engineering

Opportunities are Unprecedented

• Imaging Tumor Biology – molecular imaging probes to interrogate in-vivo tumor biology
• Molecular Precision with Image-guided Bx
• Companion Diagnostics - convergence of “omics,” molecular pathology, laboratory medicine & imaging as essential driving forces in precision medicine
• Theranostics & Pharmacokinetics/Pharmacodynamics
• Bioinformatics/Computational Biology/Images are Data – Mechanistic Imaging
Thank you!