Innovations in Breast Molecular Imaging and Targeted Therapy

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Disclosure

No relevant financial relationships with commercial interests.

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Molecular Imaging and Contrast Agent Database (MICAD)

• The Molecular Imaging and Contrast Agent Database (MICAD) is a freely accessible online source of information on in vivo molecular imaging agents

• MICAD includes agents developed for imaging modalities such as positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), ultrasound, computed tomography, optical imaging, and planar gamma imaging.

• 454 agents currently listed under “breast cancer” (Last update: 27 June 2013)
Precision Medicine

*Tailoring of medical treatment* to the individual characteristics, needs, and preferences of a patient during all stages of care, including prevention, diagnosis, treatment, and follow-up.
Cancer is Heterogeneous

“As advances in genomic medicine have captured the interest and enthusiasm of the public, an unintended consequence has been the creation of unrealistic expectations”  Genomic medicine: too great expectations? PP O'Rourke

Unrealistic Expectations
Companion Imaging Tool for Patient Selection

Molecular Imaging Technologies
Cancer is Heterogeneous – Possible Imaging Outcomes

Courtesy of Professor E.G.E. de Vries, Groningen
Detection of HER2+ Gastric Cancer - Monitoring Afatinib Therapy

Pre-therapy
\(^{89}\text{Zr}-\text{trastuzumab PET/CT}\)

Post-therapy
\(^{89}\text{Zr}-\text{trastuzumab PET/CT}\)

Afatinib daily

Janjigian, Carrasquillo et al.
Intra/Inter Tumoral Heterogeneity – Can we/should we biopsy each and every lesion?

\[ ^{18}\text{F-FDHT PET/CT} \]

Invisible Man is a suspended sculpture made of 864 syringes
- Daniel Joshua Goldstein

Courtesy of H. Hricak
Discordant Receptor Status
Primary BCa vs Metastasis


Courtesy of Professor E.G.E. de Vries, Groningen
18F-FACBC is an unnatural L-leucine analog

- Uptake is mediated by sodium-independent, “L”-type large amino acid transport system (LAT)

- LAT proteins are over-expressed in e.g., breast cancer

- Little renal excretion compared to 18F-FDG

18F-FACBC PET/CT in Newly Diagnosed Invasive Ductal and Invasive Lobular BCa

Glucose vs amino acids for tumor detection

FDG PET
(Fluorodeoxyglucose)

FACBC PET
(18F labelled 1-amino-3-fluorocyclobutane-1-carboxylic acid )

Ulaner GA et al., Initial results of a prospective clinical trial of 18F-Fluciclovine PET/CT in newly diagnosed invasive ductal and invasive lobular breast cancers. Journal of Nuclear Medicine, in press, 2016.
18F-FACBC PET/CT in Newly Diagnosed Invasive Ductal and Invasive Lobular BCa

- Patients with IDC or ILC & plan for neoadjuvant chemotherapy. Exclude age <18, pregnancy, lactation.
- Baseline FACBC PET/CT
- Neoadjuvant systemic therapy
- Repeat FACBC PET/CT
- Surgical management of locoregional disease. Compare imaging findings to pathology

Ulaner GA et al., Initial results of a prospective clinical trial of 18F-Fluciclovine PET/CT in newly diagnosed invasive ductal and invasive lobular breast cancers. Journal of Nuclear Medicine, in press, 2016.
Ulaner GA et al., Initial results of a prospective clinical trial of $^{18}$F-Fluciclovine PET/CT in newly diagnosed invasive ductal and invasive lobular breast cancers. Journal of Nuclear Medicine, in press, 2016.
FACBC PET/CT detected unsuspected extra-axillary lymph node metastases

Ulaner GA et al., Initial results of a prospective clinical trial of $^{18}$F-Fluciclovine PET/CT in newly diagnosed invasive ductal and invasive lobular breast cancers. Journal of Nuclear Medicine, in press, 2016.
18F-FACBC PET/CT in Newly Diagnosed Invasive Ductal and Invasive Lobular BCa

Preliminary results suggest FACBC PET/CT can demonstrate therapy response

FACBC PET/CT prior to systemic therapy

FACBC PET/CT following systemic therapy

Pathologic Complete Response.

Ulaner et al., unpublished data
Visualization of ER

- Good correlation FES uptake & ER expression immunohistochemically
- FES tumor uptake predictive for response to anti-hormone therapy. Low FES uptake no response

Linden HM et al, J Clin Oncol 2006
Van Kruchten et al, Lancet Oncol 2013

Courtesy of Professor E.G.E. de Vries, Groningen
Patients with a ER+ BCa History: A Diagnostic Dilemma

• 33 patients

• Number of lesions:
  – FES-PET: n = 398
  – Conventional imaging: n = 319

• FES-PET effect for patients
  – In 88% improved diagnostic understanding
  – In 48% change in therapy
  – 100% positive predictive value

MRI Suspicion of Metastases
4 y Earlier Small Primary ER+ Breast Tumor

MRI
FES-PET
FES-PET/MRI

Pathologic processes suspected in C6 and T4

Monitoring Fulvestrant Effects on Tumor ER

Courtesy of Professor E.G.E. de Vries, Groningen
Monitoring Fulvestrant Effects on Tumor ER

- Fulvestrant blocks and degrades tumor ER-expression
- Optimal fulvestrant dose unclear
  - 250 mg → 500 mg im/4 weeks + ‘loading dose’ day 14
- Trial with serial FES-PET before and during fulvestrant (days 0, 28 and 84)
Monitoring Fulvestrant Effects on Tumor ER

Van Kruchten et al, Cancer Disc 2015
Monitoring Fulvestrant Effects on Tumor ER – Heterogeneous Response
Changes in Tumor FES-Uptake
Before & During Fulvestrant (Day 28) of all Patients

Van Kruchten et al, Cancer Disc 2015
18F-FES PET/CT: GDC-0810 (ARN-810)

Imaging of Estrogen Receptors

Courtesy of Drs. Ulaner, Dickler, et al.,
GDC-0810 (ARN-810) – an orally bioavailable selective estrogen receptor degrader

Confirmed full target occupancy ~20 hours post dose

Courtesy of Drs. Ulaner, Dickler, et al.,
FES PET versus FDHT PET in a BCA patient

AR overexpression in 75-80% of breast cancers and in 30% of triple negatives

18F-FES PET

18F-FDHT PET

Courtesy of Professor E.G.E. de Vries, Groningen
Whole Body Molecular Imaging
Signature in Metastatic Breast Cancer Patient

Immunohistochemistry os ilium/SI joint right: ER+ (10%), PR+ (5%), HER2+ (3+)

Courtesy of Professor E.G.E. de Vries, Groningen
Ongoing Metastatic Breast Cancer trial

Baseline
- Biopsy of metastasis

Treatment
- Biopsy: HER2+ and/or ER+
- PET: either status
- Biopsy: HER2- and ER-
- PET: HER2+ and/or ER+

2 weeks
- Early treatment response
- Targeted therapy according to standard clinical care
- Targeted therapy as investigational strategy

8 weeks
- Treatment response
- FDG-PET
- CT

All other patients
- Standard chemotherapy
- CT

Patient numbers are based on assumptions on primary tumor characteristics
Zephir TDM-1 study

Pre treatment
- Biopsy
- CT
- FDG-PET
- $^{89}$Zr PET

Treatment
- T-DM1 treatment (every 21 days)
- 2x FDG-PET early and late in treatment

Follow-up until progression

NCT01565200
89Zr-Trastuzumab Tumor Accumulation Associates with T-DM1 Clinical Benefits

- 56 Her2+ (IHC/FISH) metastatic breast cancer patients with 89Zr-trastuzumab & FDG PET

Gebhart G et al., Ann Oncol 2016
Molecular imaging as a tool to investigate heterogeneity of advanced HER2-positive breast cancer and to predict patient outcome under trastuzumab emtansine (T-DM1): the ZEPHIR trial
Discordant Receptor Status
Primary BCa vs Metastasis


Courtesy of Professor E.G.E. de Vries, Groningen
Detection of HER2+ Metastases in Patients with HER2- Primary BCa

1. Confirm HER2-negative status of the patient’s archived primary breast malignancy

2. $^{89}$Zr-trastuzumab PET/CT to identify patients with $^{89}$Zr-trastuzumab positive foci suspicious for HER2-positive metastases

3. If suspicious $^{89}$Zr-trastuzumab foci on research PET/CT, then perform research biopsy to confirm HER2-positive malignancy

4. If research biopsy demonstrates HER2-positive malignancy, then refer for HER2-targeted therapy, which is performed off protocol

Ulaner GA et al., Detection of HER2-positive metastases in patients with HER2-negative primary breast cancer using $^{89}$Zr-DFO-trastuzumab PET/CT, Journal of Nuclear Medicine, in press, 2016.
Ulaner GA et al., Detection of HER2-positive metastases in patients with HER2-negative primary breast cancer using $^{89}$Zr-DFO-trastuzumab PET/CT, Journal of Nuclear Medicine, in press, 2016.
Clinical Translation of *HP* MR

- IRB protocol for HP pyruvate **approved** (#14-205 PI: Keshari, Co-PI: Hricak)
- IND **acknowledged** for sterile compounding of pyruvate onsite (#11259470, PI: Keshari, Co-PI: Hricak)
- First patients utilizing GE SpinLab Hyperpolarizer and Quality Control unit

> **Injection in patient (20 s)**

> **Metabolic Conversion and Dynamic Imaging (40 - 60 s)**

> **1-2 minutes**
HP Pyruvate Breast Patient #2
- invasive ductal carcinoma (w/Liz Morris)

- 53 yr old, moderately differentiated, nuclear grade II/III
Summary

• HER2 status
  - $^{89}$Zr-DFO-trastuzumab
  - $^{68}$Ga-nanobodies

• ER Status
  - $^{18}$F-FES

• AR Status
  - $^{18}$F-FDHT

• Metabolism
  - $^{18}$F-FACBC
  - $^{13}$C-pyruvate (MRI)

• HSP90 status
  - $^{124}$I-PUH71

• Progesterone Status
  - $^{18}$F-FFNP

• uPAR
  - $^{68}$Ga-NOTA-AE105

• Proliferation (Sigma-2)
  - $^{18}$F-ISO-1
  - $^{18}$F-FLT
Conclusions

• New molecular imaging technologies allow for the imaging of heterogeneity in primary and metastatic cancer

• “Personalized” imaging allows for the rapid and effective monitoring of therapy effectiveness – prior to standard measurement of response

• Imaging technologies can be effectively deployed in the study of new breast cancer therapies.
Thank You!
Memorial Sloan Kettering Cancer Center.
Patterns of HER2 Expression Revealed by HER2 PET/CT imaging n=52

- All or most of the tumor load is seen on $^{89}$Zr-Trastuzumab PET/CT (39%)
- Minority of tumor load or no lesions are seen on $^{89}$Zr-Trastuzumab PET/CT (29%)
- 16%

**89Zr-HER3 Antibody PET Scan in BCa**

- HER3 overexpression: EGFR+ or HER2+, or ER-tumors (68%, 63% and 59%)
- ER-+, or EGFR- or HER2- tumors (37%, 38% and 44%).

subcutaneous metastases, day 4 scan

Bensch et al, ASCO 2014
Hsp90 Inhibition by PU-H71

- HER2/neu is a client protein of heat shock protein 90 (Hsp90)

- PU-H71 - synthesized by Dr Gabriela Chiosis and co-workers
  - Chemistry – Dr Tony Taldone
  - Biology / Biochemistry – Dr Eloisi Caldas-Lopez

Affinity-based proteomics reveal cancer-specific networks coordinated by Hsp90
Rationale for $^{124}$I-PU-H71 Imaging

- Tumor response to PU-H71 is dose-dependent
- Plasma PK ≠ Tumor PK
- $^{124}$I-PU-H71 is chemically identical to PU-H71
- $^{124}$I-PU-H71 has a decay half life of 4d, and can be used to determine intratumoral uptake over long periods of time
- Tracer radiometabolites are present in liver but not in tumor
  - Therefore tumor $^{124}$I-signal = intact PUH71
- $^{124}$I-PU-H71 can be injected alone or co-injected with PU-H71 to estimate intratumoral concentrations of different doses of PU-H71
$^{124}\text{I}}$-PU-H71 PET Accurately Predicts Intratumoral Concentrations of PU-H71: “theranostic”
Microdose Evaluation of $^{124}$I-PU-H71: Retention of PU-H71 in Tumors for over 48h post-administration

I-124 PUH71 PET-CT of a patient with recurrent breast cancer in biopsy-proven lung metastases. Imaging 24 h post-injection. Top: PET MIP image of chest showing multiple abnormal foci of tracer-uptake. Bottom: CT (left), PET (right), and PET-CT fusion (middle) transaxial images demonstrate tracer-avidity of subcentimeter pulmonary nodule; and subcentimeter left internal mammary and mediastinal lymph nodes.

Mark Dunphy, John Gerecitano, Gabriella Chiosis et al.
Patient #1: Breast Cancer

FDG PET

PUH71 PET (Phase 1)

4h p.i.

24h p.i.

5 d prior to PUH71 PET

Mark Dunphy, John Gerecitano, Gabriella Chiosis et al.
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 (↓); $^{124}$I-PUh71 shows uptake and retention in the lung lesion but clearance from spinal bone metastasis.

Investigational MSKCC: M. Dunphy & G. Chiosis
Combined Tumor Characterizations
Combined Tumor Characterizations

Radiomics

Molecular Omics
Cancer is Heterogeneous


Detection of HER2+ Metastases in Patients with HER2- Primary BCa

Ulaner GA et al., Detection of HER2-positive metastases in patients with HER2-negative primary breast cancer using $^{89}$Zr-DFO-trastuzumab PET/CT, Journal of Nuclear Medicine, in press, 2016.