Introduction to Theranostics

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Co-Chair, Clinical Trials Network
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Disclosures

- Eli Lilly/Avid: Consulting, Research support
- GE Healthcare: Consulting
- Blue Earth Diagnostics: Consulting, Research support
- Alphasource: Consulting (spouse)
- Navidea: Research support (spouse)
- AbbVie: Research support (spouse)

**FDA disclosure:** Investigational tracers that are not FDA approved will be discussed. Off-label uses of FDA-approved tracers will be discussed.
Examples of clinical nuclear medicine

**Cancer imaging**
- Conventional bone scan
- Fluoride
- FDG
- DOTATATE
- Fluciclovine

**Heart imaging**
- $^{13}$NH$_3$-ammonia perfusion

**Radionuclide therapy**
- Sr-89
- I-131
- Sm-153
- Lu-177

**Neuroimaging**
- Hyperperfusion during epileptic seizure
- Dopamine transporter imaging
- Amyloid and tau PET in Alzheimer’s disease
- Brain tumor imaging with amino acid PET

**Kratochwil C, et al., 2014.**
Radiopharmaceuticals

- A radiopharmaceutical is a drug labeled with a radionuclide targeting biological process
  - the overall chemical structure determines biological properties
  - the radionuclide determines imaging and/or therapeutic properties
Radiopharmaceuticals

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  - the radionuclide determines imaging and/or therapeutic properties

D-glucose → 2-deoxy-2-[¹⁸F]fluoro-D-glucose (FDG)
PET (positron emission tomography) cameras detect the location and concentration of radioactive drugs in patients. PET/MRI system

$[^{18}\text{F}]\text{FDG}$ to detect increased sugar use by cancer

Metastatic ovarian cancer on FDG-PET/MRI

http://www3.gehealthcare.com/en/products/categories/magnetic_resonance_imaging/3-0t/signa_pet-mr
Radionuclides

- Unstable (radioactive) nuclei that decay over time decay
  - Also called isotopes, radioisotopes, radiolabels
  - Small subset are medically useful

- Broad categories of radionuclides in nuclear medicine
  - Single photon emitters (planar imaging, SPECT)
  - Positron emitters (PET)
  - Beta minus emitters
  - Auger emitters
  - Alpha emitters

Diagnostic radionuclides (photons)

Therapeutic radionuclides (particles)
Photons for tissue penetration and diagnostic imaging

Particulate radiation (electrons, alpha particles) for local energy/therapy deposition
Beta and alpha particles damage DNA in radionuclide therapy

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**Beta radiation**

- Sr-89
- Y-90
- I-131
- Sm-153
- Lu-177

**Alpha radiation**

- At-211
- Ra-223
- Ac-225

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Examples of radionuclides relevant to nuclear medicine

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-life</th>
<th>Primary emission(s)</th>
<th>Primary use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon-11</td>
<td>20.4 minutes</td>
<td>positron</td>
<td>PET</td>
</tr>
<tr>
<td>Nitrogen-13</td>
<td>10 minutes</td>
<td>positron</td>
<td>PET</td>
</tr>
<tr>
<td>Oxygen-15</td>
<td>122 seconds</td>
<td>positron</td>
<td>PET</td>
</tr>
<tr>
<td>Fluorine-18</td>
<td>110 minutes</td>
<td>positron</td>
<td>PET</td>
</tr>
<tr>
<td>Copper-64</td>
<td>12.7 hours</td>
<td>positron, electron</td>
<td>PET, (Therapy)</td>
</tr>
<tr>
<td>Gallium-68</td>
<td>68 minutes</td>
<td>positron</td>
<td>PET</td>
</tr>
<tr>
<td>Yttrium-90</td>
<td>64.6 hours</td>
<td>electron</td>
<td>Therapy, (PET)</td>
</tr>
<tr>
<td>Technetium-99m</td>
<td>6.0 hours</td>
<td>photon</td>
<td>Planar, SPECT</td>
</tr>
<tr>
<td>Indium-111</td>
<td>2.8 days</td>
<td>photon</td>
<td>Planar, SPECT</td>
</tr>
<tr>
<td>Iodine-123</td>
<td>13.2 hours</td>
<td>photon</td>
<td>Planar, SPECT</td>
</tr>
<tr>
<td>Iodine-124</td>
<td>4.2 days</td>
<td>positron</td>
<td>PET</td>
</tr>
<tr>
<td>Iodine-131</td>
<td>8.0 days</td>
<td>electron, gamma</td>
<td>Therapy, Planar, SPECT</td>
</tr>
<tr>
<td>Lutetium-177</td>
<td>6.7 days</td>
<td>electron, gamma</td>
<td>Therapy, SPECT</td>
</tr>
<tr>
<td>Radium-223</td>
<td>11.4 days</td>
<td>alpha</td>
<td>Therapy</td>
</tr>
<tr>
<td>Actinium-225</td>
<td>10 days</td>
<td>alpha</td>
<td>Therapy</td>
</tr>
</tbody>
</table>
What are theranostics?

“theranostics”

The word you've entered isn't in the dictionary. Click on a spelling suggestion below or try again using the search bar above.
What are theranostics?
What are theranostics?

- **Therapeutic + Diagnostic = Theranostic**
  - diagnostic test to stratify patients by likelihood to respond to a specific treatment
  - diagnostic test to monitor early response to treatment and predict efficacy

- Concept has been around for a long time
  - Radioiodine for the diagnosis and treatment of thyroid cancer (1940’s)
  - Measuring estrogen and progesterone receptors and HER2 expression in breast cancer to guide hormonal and targeted therapy

- In nuclear medicine, the same or very similar agent can serve as both a diagnostic and therapeutic agent
  - Typical paradigm is to perform diagnostic imaging to determine if a patient would benefit from the therapeutic form of the agent
  - Whole body imaging assess the entire tumor burden
Theranostics and radionuclide therapy for cancer

1. Based on radiopharmaceuticals that localize to cancer cells to selectively deliver a therapeutic radionuclide.

2. Often, a radiopharmaceutical can be labeled for imaging and for therapy: **theranostic approach**

3. Radionuclide therapies often have favorable adverse effect profile and can succeed after other therapies fail.

4. Imaging often guides therapy by demonstrating the entire tumor burden expresses the therapeutic target

1. DOTATATE

   - $[{^{68}\text{Ga}}]\text{DOTATATE}$ for imaging (NETSPOT)
   - $[{^{177}\text{Lu}}]\text{DOTATATE}$ for imaging (Lutathera)

Theranostics and radionuclide therapy for cancer

1. Based on radiopharmaceuticals that localize to cancer cells to selectively deliver a therapeutic radionuclide.

2. Often, a radiopharmaceutical can be labeled for imaging and for therapy: theranostic approach

3. Radionuclide therapies often have favorable adverse effect profile and can succeed after other therapies fail.

4. Imaging often guides therapy by demonstrating the entire tumor burden expresses the therapeutic target

![DOTATATE](image)

Examples of molecular imaging tied to radionuclide therapies

- Somatostatin receptors in neuroendocrine tumors
  - $[^{68}\text{Ga}]\text{DOTATATE}$
- Bone turnover in skeletal metastases
  - $[^{18}\text{F}]\text{fluoride}$
- Iodide transport in differentiated thyroid cancer
  - $[^{123/124}\text{I}]\text{iodide}$
- Norepinephrine transporter in neuroendocrine tumors
  - $[^{123}\text{I}]\text{MIBG}$
- Iodide transport in differentiated thyroid cancer
  - $[^{123/124}\text{I}]\text{iodide}$
- Prostate specific membrane antigen in prostate cancer
  - $[^{18}\text{F}]\text{DCFPyl}$
- Prostate specific membrane antigen in prostate cancer
  - $[^{18}\text{F}]\text{DCFPyl}$

- $[^{223}\text{Ra}]\text{Cl}_2$, $[^{153}\text{Sm}]\text{EDTMP}$, $[^{89}\text{Sr}]\text{Cl}$
- $[^{131}\text{I}]\text{MIBG}$
- $[^{177}\text{Lu}/[^{90}\text{Y}/[^{213}\text{Bi}]]\text{DOTATATE}$
- $[^{177}\text{Lu}/[^{225}\text{Ac}]]\text{DOTATATE}$
Neuroendocrine tumors (NETs)

- NETs represent a wide range of neoplasm arising from neuroendocrine cells
- Surgery is typically the only curative option
- Treatment depends on the anatomic location, type of NET, and stage
- Hormonally active tumors may cause significant morbidity and decrease quality of life
- Radiopharmaceuticals play key roles for imaging and treating NETs
Molecular imaging agents for NETs

**Somatostatin receptor ligands**

- $[^{18}F]FDG$
- $[^{68}Ga]DOTATATE$

**Norepinephrine transporter substrates**

- $[^{123/131}I]MIBG$

**Radiolabeled amino acids**

- 5-hydroxy-L-$[^{11}C]$tryptophan
- $[^{18}F]$FDOPA
Somatostatin Receptors and Peptide Ligands

Human somatostatin
14 amino acids

Octreotide
8 amino acids

Regulation of cell growth and hormone release

Table 1 | Characteristics of neuroendocrine tumours

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Well-differentiated neuroendocrine tumour or carcinoma</th>
<th>Poorly differentiated neuroendocrine carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour grade*</td>
<td>1 (low)</td>
<td>2 (intermediate)</td>
</tr>
<tr>
<td>Ki67 index (%) and/or mitotic count (per 10 HPF)</td>
<td>Ki67 &lt;3% and &lt;2 mitoses</td>
<td>Ki67 3–20% or 2–20 mitoses</td>
</tr>
<tr>
<td>Clinical course and findings on CT or MRI</td>
<td>Indolent course</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Incidence FDG-PET-positive lesions‡</td>
<td>Lower</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Somatostatin receptor expression‡</td>
<td>Higher</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Relatively good</td>
<td>Intermediate</td>
</tr>
</tbody>
</table>

Sensitivity for NETs

- $[^{68}\text{Ga}]\text{DOTATATE}$
- $[^{18}\text{F}]\text{FDG}$

35 year old woman with atypical neuroendocrine tumor

[18F]FDG

[68Ga]DOTATATE
34-year-old-woman with hepatic NET metastasis with no known primary tumor.
Prostate cancer continuum

Initial diagnosis, staging, and biopsy guidance
Detection and restaging of recurrence
Selection of appropriate therapy
Monitoring response to therapy

Higher serum PSA and faster PSA doubling time are associated with higher yield of PET imaging for biochemical recurrence
Molecular imaging agents for prostate cancer

**Skeletal scintigraphy**

- $^{99m}$Tc MDP
- $^{18}$F-fluoride
- Sodium $[^{18}$F$]$fluoride
- Sodium $[^{99m}$Tc$]$MDP

- Mineralized bone turnover

**Metabolism**

- Sodium $[^{11}$C$]$acetate
- Fatty acid metabolism and oxidative phosphorylation
- $[^{11}$C$]$Choline and $[^{18}$F$]$-labeled derivatives
- Membrane synthesis

**PSMA ligands**

- Antibodies including $[^{111}$In$]$capromab pendetide
- Small molecule PSMA ligands

**Receptor ligands**

- $[^{18}$F$]$FDHT
- Androgen receptors

**Bombesin derivatives**

- $[^{18}$F$]$FDHT
- Gastrin-related peptide receptor (GRPR)

**[18F]FDG**

- Glycolysis

**[18F]Fluciclovine**

- Amino acid transport
Prostate-specific Membrane Antigen (PSMA)

- Type II transmembrane protein
- Glutamate carboxypeptidase
- Associated with aggressive disease
- Present in solid tumor neovessels
- Marker of androgen signaling

Curr Med Chem 2012

Slide courtesy of Marty Pomper MD, PhD (Johns Hopkins) and Steve Cho MD (University of Wisconsin-Madison)
Selected PET tracers targeting PSMA

- $[^{18}F]$DCFPyl
- $[^{68}\text{Ga}]$PSMA-11
- $[^{89}\text{Zr}]$DFO-J591
- $[^{68}\text{Ga}]$PSMA-11
- $[^{177}\text{Lu}]$PSMA-617

Glu-NH-CO-NH-Lys-(Ahx)-$[^{68}\text{Ga}(\text{HBED-CC})]$
Lu-177 PSMA for radionuclide therapy

Clinical trials demonstrating efficacy of radionuclide therapies

**ALSYMPCA Trial**
Ra-223 improves survival in castrate-resistant prostate cancer.

**NETTER-1 Trial**
Lu-177 DOTATATE improves progression-free survival in GEP neuroendocrine tumors.

**VISION Trial underway**
Lu-177 PSMA-617 for metastatic castrate resistant prostate cancer

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**ALSYPMA Trial**

**NETTER-1 Trial**

**VISION Trial underway**
Challenges and opportunities

- Reliable and economically viable supply chain of radionuclides for theranostics for preclinical research, clinical trials, and routine use
- Funding to support preclinical and early translational theranostic development
- Regulatory approval pathways for theranostics that address both the imaging and therapeutic aspects of the agent
- Adequate reimbursement for FDA-approved diagnostic and therapeutic agents
- Clinical adoption of approved theranostic agents
- Potential competition with other cancer therapies
- Incorporation earlier in cancer treatment and combination with other disease-specific treatments
Questions?
Background:

• The SNMMI has partnered with NCI on two previous meetings on targeted radionuclide therapy (2013 and 2014).

• In 2015 SNMMI recognized the growing importance of radionuclide therapy and formed the Therapy Center of Excellence to advance the development and utilization of radionuclide therapy.

• The development and implementation of theranostics is one of the Society’s highest priorities, and we anticipate that conferences such as this will contribute to the advancement and success of these important treatments.
Therapy Center of Excellence

Conference co-chairs:
- President: Dan Pryma, MD (University of Pennsylvania)
- Vice-President: Dan Lee, MD (Emory University)

The TCoE is:
- Dedicated to all aspects of the development and utilization of Targeted Radionuclide Therapy (TRT);
- A multidisciplinary group comprised of industry, pharma, physicians, scientists, government and regulatory agencies, as well as other stakeholders; and
- A venue to share ideas, develop educational offerings, and advance the utilization of radionuclide therapy.
Clinical Trials Network

Conference co-chair:
• John Sunderland, PhD (University of Iowa)

The **CTN Vision** is that the CTN will take a leadership role in advancing the use of molecular imaging and targeted radionuclide therapy, optimizing clinical trials to facilitate their translation and dissemination into clinical practice.

The CTN is uniquely positioned to work with the FDA, NCI, industry, and the academic nuclear medicine community to assist in developing well-defined pathways toward the regulatory approval of new radiopharmaceuticals.
Thank you:

• NIH and NCI (Jacek Capala) for hosting
• NCI and FDA employees for their support and participation
• Progenics for sponsoring this conference
• Thank you all for participating
Theranostics Consensus Conference
Goal Statement

Daniel A. Pryma, M.D.
Associate Professor of Radiology & Radiation Oncology
Chief, Division of Nuclear Medicine & Clinical Molecular Imaging
University of Pennsylvania Perelman School of Medicine
Overarching goal

• Ensure that patients have access to effective therapeutic radiopharmaceuticals and companion diagnostics.
Granular goals

- Define effective drugs
  - Understand:
    - Burdens of proof
    - Development cycles
    - Financial implications
    - Alternative technologies
Methodology

• Willing suspension of enthusiasm
• Think of all that can go wrong
• Discuss strategies to overcome challenges
• Reinvigorate enthusiasm
Layout

• Four sessions
  • Series of brief presentations
  • Q&A panel
• We encourage lively discussion!
Current state of technology

From iodine to PSMA
and a glimpse into the future
Potential of radiopharmaceutical therapy

• Treat cancer regardless of:
  • Lesion location
  • Lesion number
  • Lesion visibility

• Approachable companion diagnostics to enhance outcomes
Precision medicine

• For an individual patient:
  • Choosing optimal treatment
  • Figuring optimal dose
Nuclear medicine: Precision medicine

- Standard practice in nuclear medicine for over 70 years
- Theranostics enable precision medicine
Advantages of theranostics

- Confirm targeting
  - Fewer futile therapies
- Measure kinetics
  - Personalized dosing
- Learn about biology
  - The vast inhomogeneity of “cancer”
Disadvantages of theranostics

• Imperfect sensitivity of diagnostic component
  • Incorrectly exclude some from therapy
  • Inadequate replacement for alternative diagnostics
• Cost
  • Time
  • Money (short-sighted criticism?)
• Complexity
Therapeutic radiopharmaceuticals: dosing strategies

- Flat doses
- Weight based dosing
- Whole body/blood dosimetry
- Lesional/organ dosimetry
Choosing a dosing strategy

- Flat or weight based dosing is simple and easy.
- It works (possibly suboptimally).
- It’s a shame to not utilize the theranostic capacity.
- Need to prove it is better.
Difficulties with systemic dosimetry

• Not trivial to accurately compute relevant doses
  • High uncertainty
• Requires multiple scans
• Poor understanding of biological effects of physical doses
Lesional Dosimetry

229 rad/mCi
203 rad/mCi
125 rad/mCi

Courtesy of John Humm, PhD
Radiopharmaceutical therapies

Approved

- Sodium Iodine-131
  - Thyroid cancer
  - Hyperthyroidism
- Ra-223 dichloride for CRPC
- Sm-153 EDTMP, Sr-89 for osseous metastases
- I-131 tositumomab, Y-90 ibritumomab tiuxetan for lymphoma
- Intracavitary therapy with P-32 colloid
- Hepatic arterial radioembolization with Y-90 microspheres
- I-131 MIBG
- PRRT
- Lu-177 DOTATATE

Investigational

- PRRT
- Y-90 DOTATOC
- Lu-177 antagonists
- PSMA
  - I-131, Lu-177, Bi-213, Ac-225
- Ra-223 dichloride outside CRPC
- Radiolabeled antibodies
  - I-131 or Ac-225 antibody for leukemia
- At-211 MABG
- Many, many others
Radioiodine therapy:
Grave’s disease

Pyramidal Lobe

24 hour uptake: 65%
(normal 10-35%)

RT ANT LT

STERNAL MARKER

RT ANT LT

RAO

LAO
Radioiodine therapy:
Autonomous nodule
Radioiodine therapy: Toxic multinodular goiter
Radioiodine therapy: thyroid cancer

Initial Therapy

3 years after initial

5 years after initial
Thyroglobulin response

Time course of 5 years from initial therapy
Pre-therapy thyroglobulin 3300 ng/ml
Bone pain palliation

- Sr-89 chloride and Sm-153 EDTMP approved for bone pain palliation
  - Confirmed osteoblastic disease on bone scan
- Sr-89: $T_{1/2} 50.6$ d
- Sm-153: $T_{1/2} 1.9$ d
- Advantages of Sm-153 EDTMP
  - Shorter half-life
  - Imageable $\gamma$ emissions
Ra-223 chloride

- Radium-223 is an $\alpha$-emitter ($T_{1/2}$ 11.4 days)
- Calcium ion analog
  - Bone seeker
- Favorable results from early phase trials
- Phase III ALSYMPCA trial closed in 1/11
- Approved May 2013
Outcome of alpha-emitting bone seeking radiopharmaceutical

A Overall Survival

Hazard ratio, 0.70 (95% CI, 0.58–0.83) P<0.001

Radium-223 (median overall survival, 14.9 mo)
Placebo (median overall survival, 11.3 mo)

<table>
<thead>
<tr>
<th>Months since Randomization</th>
<th>Survival (%)</th>
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<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>95</td>
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<td>90</td>
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<td>9</td>
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<td>36</td>
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<td>39</td>
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**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Radium-223</th>
<th>Placebo</th>
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<tbody>
<tr>
<td></td>
<td>614 578 504 369 274 178 105 60 41 18 7 1 0 0</td>
<td>307 288 228 157 103 67 39 24 14 7 4 2 1 0</td>
</tr>
</tbody>
</table>

Lymphoma radioimmunotherapy

PRRT: peptide receptor radiotherapy

- Imaging of SSTR common (and approved) in US
- Therapy directed at SSTR common outside the US
  - Finally approved in US in January 2018
- Companion diagnostic
  - SPECT
  - PET
A Progression-free Survival

B Overall Survival (Interim Analysis)

No. at Risk

\( ^{177}\text{Lu-DOTATATE} \) group:
116 97 76 59 42 28 19 12 3 2 0

Control group:
113 80 47 28 17 10 4 3 1 0 0

\( ^{177}\text{Lu-DOTATATE} \) group:
116 108 96 79 64 47 31 21 8 3 0

Control group:
113 103 83 64 41 32 17 5 1 0 0

\( P<0.001 \)

\( P=0.004 \)
C Prespecified Subgroup Analysis of Progression-free Survival

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard Ratio (95% CI)</th>
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<tbody>
<tr>
<td>Extrahepatic metastases</td>
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<tr>
<td>Yes</td>
<td>0.20 (0.12–0.35)</td>
</tr>
<tr>
<td>No</td>
<td>0.15 (0.04–0.50)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td></td>
</tr>
<tr>
<td>&gt;ULN</td>
<td>0.21 (0.09–0.49)</td>
</tr>
<tr>
<td>≤ULN</td>
<td>0.19 (0.11–0.35)</td>
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<tr>
<td>Somatostatin receptor expression</td>
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<tr>
<td>Grade &lt;4</td>
<td>0.23 (0.12–0.41)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0.18 (0.08–0.39)</td>
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<tr>
<td>5-HIAA</td>
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<tr>
<td>&gt;2x ULN</td>
<td>0.15 (0.08–0.29)</td>
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<tr>
<td>≤2x ULN</td>
<td>0.19 (0.06–0.55)</td>
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<tr>
<td>Chromogranin A</td>
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<tr>
<td>&gt;2x ULN</td>
<td>0.19 (0.09–0.27)</td>
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<tr>
<td>≤2x ULN</td>
<td>0.11 (0.01–0.87)</td>
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<tr>
<td>Tumor grade</td>
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<td>ENETS Grade 2</td>
<td>0.15 (0.07–0.34)</td>
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<tr>
<td>ENETS Grade 1</td>
<td>0.24 (0.13–0.44)</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Male</td>
<td>0.24 (0.12–0.45)</td>
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<tr>
<td>Female</td>
<td>0.17 (0.08–0.35)</td>
</tr>
<tr>
<td>Age</td>
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</tr>
<tr>
<td>&gt;65 yr</td>
<td>0.24 (0.12–0.48)</td>
</tr>
<tr>
<td>≤65 yr</td>
<td>0.20 (0.10–0.38)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.21 (0.13–0.33)</td>
</tr>
</tbody>
</table>
metaiodobenzylguanidine - MIBG (aka Iobenguane)

• Described by Wieland et al in 1979
• Substrate for norepinephrine transporter
• High specific activity formulation approved for pheochromocytoma/paraganglioma in July 2018
Patient outcomes

![Graph showing patient outcomes](image)
Evolutionary changes

• From single treatments to multiple cycles
• Next step: rational combinations
The recent past and near future

• Billions of dollars in radiopharmaceutical acquisitions and licensing
• Many ongoing trials
  • Dominated by PSMA
68Ga-PSMA-11 PET/CT at baseline and after 2 cycles of 177Lu-PSMA-617 in 78-y-old patient with mCRPC. Wolfgang P. Fendler et al. J Nucl Med 2017;58:1196-1200
Thank you!
Theranostics, precision medicine tools for oncology

Libero Marzella
Division of Medical Imaging Products
Office of Drug Evaluation IV
CDER/FDA
Theranostics overview

• definition
• contexts of use: focus on oncology
• radiopharmaceuticals as theranostic product pairs
• pathways for development of the diagnostic imaging component of theranostics
Theranostics

definitions, objectives
various precision medicine tools for individualized patient treatment

targeted therapies that combine diagnosis, treatment planning, drug delivery, response assessment

aim is to improve patient outcomes
Theranostics, biomarkers as precision medicine tools

Biomarkers, the *omics* revolution

- **scope**: *omics* spans the expression of genetic information from genes to transcripts, proteins, and metabolites
- **promise**: enhance understanding of mechanisms of disease and heterogeneity of disease expression; facilitate development of targeted therapies
- qualification of biomarkers as drug development tools

Theranostics, biomarkers as precision medicine tools

• in 2017, 50% of early-stage and 30% of late stage molecular entities in development included the use of biomarker tests [4].

• one third of recent drug approvals have had DNA-based biomarkers included in their original FDA submissions [5]

As cited by: Yearb Med Inform 2018:211-22
http://dx.doi.org/10.1055/s-0038-1667085
Theranostics, *in vitro* diagnostics as precision medicine tools

*in vitro* diagnostics: wide range of products

- tissue biopsy, liquid biopsy (exosomes), serum assays
  - regulated as devices by PMA, *de novo*, or 510(k)
  - developed and labeled for use singly or together with therapeutic
  - companion diagnostics are a specific diagnostic device for use with a specific therapeutic product as well as in the labeling of any generic equivalents and biosimilar equivalents of the therapeutic product
- see links below for guidance on co-development and listing of co-developed products

https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm
Theranostics, diagnostic imaging drugs as precision medicine tools

- *in vivo* imaging diagnostics
  - optical imaging using near infrared fluorescent drugs for intraoperative use e.g. indocyanine green
  - SPECT, PET imaging using radiopharmaceuticals e.g. somatostatin receptor imaging using In 111 pentetreotide, Ga 68 octatreotate
  - other imaging modalities using pharmacophores consisting of targeting and signaling moieties
  - diagnostic drug studied under IND; marketing applications as NDA or BLA
Theranostic “pairs” CD20 onco-targets

• I 131 tositumomab, dosimetric and therapeutic dosing (withdrawn from marketing)
• Y 90 ibritumomab tiuxetan therapeutic; In111 radiolabeled product used for dosimetry in clinical trials
Theranostic radiopharmaceutical “pairs”

• Ga 68 dotatate (dx), Lu 177 dotatate (rx) somatostatin receptor onco-targets; sequential FDA approval

• I 131 iobenguane norepinephrine transporter onco-target; FDA approval first as diagnostic then as therapeutic; I 131 example of radionuclide with usable dual emissions (γ,β)

• literature reports of studies of other theranostic pairs targeting various tumors
Theranostics, diagnostic imaging drug development approaches

- **co-development**: of diagnostic and therapeutic for marketing as “theranostic pair” for enrichment/selection of study patients, prognostic value, early assessment of treatment response, individualized, by-cycle therapeutic dosing

- use of qualified biomarkers or approved diagnostics in *early development* of therapeutic for exploratory assessments or as surrogates of efficacy

- **post-approval development** of diagnostic drugs for new indications for use with approved therapeutics to e.g. enhance safety or efficacy
  - e.g. post-approval development of therapeutic as new drug (repurposed as pharmacophore combined with a signaling moiety) to assess expression of pharmacologic target
Co-development plan: analytical characterization of diagnostic

- pharmacologic target occupancy
- preclinical proof of concept
- precision and accuracy
  - reproducibility
    - test-retest
    - reference standard: histopathology, phantom
  - clinical performance
    - biodistribution, dosimetry
    - signal to noise quantitation across tumor grade
    - diagnostic sensitivity and specificity
Theranostics, summary

• precision medicine tools for oncology
• various regulatory pathways for development
• theranostic radiopharmaceutical “pairs” under active development
  – potential uses of imaging diagnostic for selection of study patients, early assessment of treatment response, individualized, by-cycle therapeutic dosing
  – consider co-development of theranostic pairs to increase efficiency of studies
THERANOSTIC STUDIES
WHAT TO CONSIDER FOR TWO INVESTIGATIONAL AGENTS IN A SINGLE STUDY

• Diagnostic imaging agent to assess receptor expression for selection of patients suitable for treatment
• Early discussion with international Health Authorities on the development plan
• Coordination among different divisions with Health Authorities
• Minimum data to start a study with the two investigational agents
  - Safety, tolerability, PK, dose determination at least in one tumor type
• Theranostic approach in Phase I/II
IMAGING AGENT

• Same isotope as the therapeutic vs a different isotope
• What are the acceptable performance characteristics (partially, fully) to use in an investigational theranostic study
  • Analytical characterization
  • Optimal Imaging time
  • SoC Anatomical imaging
  • Histopathology
  • Clinical follow-up
  • A Combination of the above
  • Comparison to previous ascertainment of the truth
• How about if there is no SoT for the Imaging Agent
  • Clinical measures related to the therapeutic
• Stand-alone indications and labels or linked
Theranostics Consensus Conference 2018
The Challenges:
Strategies to Study Two Investigational Agents in a Single Trial

Annick D. Van den Abbeele, MD
Chair, Department of Imaging
Founding Director, Center for Biomedical Imaging in Oncology
Co-Director, Tumor Imaging Metrics Core
Disclosures

• Research funding support to the Dana-Farber Cancer Institute from Novartis, Pfizer, Bayer, GSK, BMS

• Unpaid Board member:, Centre for Probe Development and Commercialization (CPDC), Toronto, Canada

• Unpaid consultant: Fusion Pharmaceuticals
Lengthy, high risk (high attrition rate), and costly endeavor, large # of patients, a major barrier to rapid translation of scientific knowledge into clinical advances

Drug development

• Need new strategies that:
  – aid the early selection of promising candidates to move to pivotal trials, or termination of candidates unlikely to be successful
  – can provide evidence of biological activity in the initial stages of drug development
  – confirm on-target drug effects
  – identify patients who are more likely to benefit
  – allow repetitive, non-invasive quantitative longitudinal evaluation

de Vries EGE et al JCO 33(24), 2015:pp2585-2587
Biomarker-based selection strategy

- Meta-analysis of phase 1 clinical trials (346 published phase 1 trials, 351 arms, 13,203 pts)
- Personalized strategy was an independent predictor of improved response rates (RR) and PFS (median RR 31.1% vs 5.1%, p<.0001 and prolonged PFS 5.7 vs 2.95 months, p=.0002 when genomic biomarkers were used)
- Studies that used targeted agents without a biomarker had negligible response rates
- High efficacy levels can be achieved in phase 1 trials with the use of biomarker selection

Drug development

- Large gap between biopsy-based tumor characterization and what is actually happening in the various tumor lesions in a single patient and between patients
- Genomics, immunohistochemistry, PK/PD data, standard tumor assessment criteria by themselves are not enough to meet the goals of Precision Medicine

de Vries EGE et al JCO 33(24), 2015:pp2585-2587
Extensive intratumor heterogeneity, with 26 of 30 tumor samples from four tumors harboring divergent allelic-imbalance profiles and with ploidy heterogeneity in two of four tumors.
• “Genomic analyses from single tumor-biopsy specimens may underestimate the mutational burden of heterogeneous tumors”

• “A single tumor-biopsy specimen reveals a minority of genetic aberrations that are present in an entire tumor”

• “Such spatially separated somatic mutations altering pathway activity suggests that multi-regional analyses may be required to predict the therapeutic outcome”
Anatomical, Functional, and Molecular Imaging
Harnessing Cancer Molecular Imaging for Patient, Pharma and Regulatory Benefit
Imaging of Hallmarks of Cancer “Biomarkers”

<table>
<thead>
<tr>
<th>Targets</th>
<th>Tracers</th>
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</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>$^{90}$Zr-cetuximab</td>
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<tr>
<td>mutEGFR</td>
<td>$^{18}$F-PEG68-IPQA</td>
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<tr>
<td>HER2</td>
<td>$^{18}$F-ZHER2:2691</td>
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<tr>
<td>ER</td>
<td>$^{18}$F-FES</td>
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<tr>
<td>ENT1/TK1</td>
<td>$^{18}$F-FLT</td>
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<td>Chk-α</td>
<td>$^{18}$F-choline, $^{11}$C-choline</td>
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<td>AAT</td>
<td>$^{18}$F-FACBC</td>
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<tr>
<td>dCK</td>
<td>$^{18}$F-FAC</td>
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<td>Telomerase CD133 (stem cells)</td>
<td>$^{99m}$Tc-hTERT-ASON $^{64}$Cu-NOTA-AC133</td>
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<tr>
<td>GLUT-1/HKII Leucocytes</td>
<td>$^{18}$F-FDG</td>
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<td>$^{18}$F-WBC-FDG</td>
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<td>CXCR4 c-MET</td>
<td>$^{64}$Cu-AMD3465, $^{68}$Ga-CPCR4.2</td>
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<td>$^{18}$F-AH113804</td>
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<tr>
<td>αβ_1/αβ_2 VEGF-1 perfusion</td>
<td>$^{18}$F-flucilatide, $^{18}$F-galactoRGD</td>
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<td>$^{90}$Zr-bevacizumab $^{16}$O$_2$O$_2$</td>
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<td>hypoxia</td>
<td>$^{18}$F-MISO, $^{18}$F-HX4, $^{18}$F-FETNIM</td>
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<td>CAIX</td>
<td>$^{18}$F-FETA, $^{18}$F-FAZA, $^{64}$Cu-ATSM</td>
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<td>PARP-1</td>
<td>$^{18}$F-VM4-037, $^{90}$Zr-CG250</td>
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<td>heterogeneity</td>
<td>$^{18}$F-AG014361, texture/radiomics</td>
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<td>a.m.i.</td>
<td>$^{18}$F-ML-10</td>
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<td>Δ-caspase-3 phosphatidyl-ser</td>
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<td>ACS</td>
<td>$^{18}$F-C-acetate $^{18}$F-NFTG</td>
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<td>FAO</td>
<td>$^{18}$F-DMO, $^{64}$Cu-NOTA-pHLIP</td>
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<td>AR</td>
<td>$^{18}$F-IS-1</td>
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<td>sigma-2 R</td>
<td>$^{18}$F-octreotide, $^{68}$Ga-DOTA-TATE</td>
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<tr>
<td>SSTR-2</td>
<td>$^{90}$Zr-transferin</td>
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</table>

Molecular Imaging Explores the Hallmarks of Cancer Biology
“Virtual Biopsy”


Theranostics
Molecular Imaging Explores the Hallmarks of Cancer Biology

“Virtual Biopsy”

Metabolism Reprogramming: A Hallmark of Cancer

The First Fuel Supply: Elevated Glycolysis

The Second Fuel Supply: Mitochondrial Metabolism

All major oncoproteins and tumor suppressors have intimate connections with metabolic pathways through regulation of metabolic enzymes.

Nature Reviews Cancer vol 11 May 2011
The Third Fuel Supply: Aminoacid Metabolism
PI3K mutation Breast cancer
CKIT mutation GIST
KRAS mutation Lung adenocarcinoma
Testicular Hodgkin Lymphoma
AML

Baseline
Primary resistance
Complete Metabolic Response
Progressive Metabolic Disease
Sarcoidosis (iAE)
Complete Metabolic Response
Complete Metabolic Response

After 1 cycle
Metabolic response precedes anatomic response
Overall Survival by Best Response Achieved

- **STABLE DISEASE**: Median not reached
- **PROGRESSION On Imatinib**: Median 36 wks

Clinical benefit is obtained regardless of tumor shrinkage

Courtesy of George Demetri, MD
Imaging as a Pharmacodynamic Biomarker

- Helps test the underlying hypothesis
- Provides successful “proof of concept” study with reproducible and sustained evidence of target engagement, modulation and downstream effect as well as intra- and inter-patient controls
- Informs rational selection of dose and schedule
- Aids decision-making including key go/no go decisions

Sunitinib trial: $^{18}$F-FDG-PET

Drug reached the market 6 months ahead of schedule, with estimated savings of $200M (+ sales)

[Pfizer, personal communication]
Kidney Cancer Drugs Market Expected to Reach USD 4.5 Billion Globally by 2020, growing at a CAGR of 6.6% from 2014 to 2020 : Transparency Market Research

Transparency Market Research has announced the addition of the "Kidney Cancer Drugs Market (Major Drugs: Afinitor (Everolimus), Avastin (Bevacizumab), Inlyta (Axitinib), Nexavar (Sorafenib), Proleukin (Aldesleukin), Sutent (Sunitinib), Torisel (Tems流行的) Votrient (Pazopanib)) - Global Industry Analysis, Pipeline Analysis, Size, Share, Growth, Trends and Forecast 2014 - 2020" report to their offering.

More specific mechanisms of tumor biology, tumor heterogeneity, phenotype, and genotype can be measured earlier with molecular imaging, rather than waiting for the tumor size to either shrink or grow or for symptoms to appear. These may be clinically actionable.
Tumor Heterogeneity
Guiding Biopsy to the Relevant Site

Differential response to therapy may indicate a new mutation
Executing the Combination

• How do we implement the combination?
• When do we implement it?
• In whom do we implement it?

Multicenter trial testing a novel CDK 4/6 Inhibitor in Mantle Cell Lymphoma

Molecular Imaging Explores the Hallmarks of Cancer Biology

“Virtual Biopsy”

Adapted from Wester HJ. et al., Clin. Cancer Res, 2007
Molecular Imaging Explores the Hallmarks of Cancer Biology

“Virtual Biopsy”

1st Multicenter Trial of a CDK 4/6 Inhibitor in Mantle Cell Lymphoma

Baseline FLT-PET Day -6
Baseline FDG-PET Day -5
Cycle 1 FLT-PET Day 20
Cycle 1 FDG-PET Day 21

SCREENING 3 WEEK DAILY DOSE 125 mg 1 WEEK REST

Baseline FDG & FLT Tumor SUVmax > 5
Baseline Biopsy Day -4
Cycle 1 Biopsy Day 21

Baseline FLT-PET Day -6
Baseline FDG-PET Day -5
Cycle 1 FLT-PET Day 20
Cycle 1 FDG-PET Day 21
1st Multicenter FLT-PET Trial: CDK 4/6 Inhibitor in Mantle Cell Lymphoma

Pre FLT-PET  Post FLT-PET

Pre Ki67  Post Ki67

Pre pRb  Post pRb

Proliferative Response of Patients with FLT-PET

% Change Summed SUVmax

PR  SD  PD

FLT-PET Response vs. TTP

Prob. of Progression Free Survival

Time To Progression (days)

FLT-PET Responders (n=6)

FLT-PET Non-Responders (n=10)
Is target hit predictive of response (or lack thereof)?
Multicenter FLT-PET Trial: CDK 4/6 Inhibitor in Mantle Cell Lymphoma

Progressive Disease
Theranostics
Molecular Imaging Explores the Hallmarks of Cancer Biology

“Virtual Biopsy”

49-year-old man with diagnosis of MEN1 syndrome and biopsy-proven metastatic neuroendocrine tumor

68Ga-DOTATATE (SSR2 target, NETSPOT®)

4/18/17

9/16/2016
0.87 cm

Pituitary
$^{177}$Lu-DOTATATE (Lutathera®)
Theranostics of Neuroendocrine tumors

Pancreatic NET:
Ki-67 = 20%

Ileum NET:
Ki-67 = 2%

#Theranostics @IBA_RadioPharma
Theranostics of Prostate Cancer

- VISION Trial (Endocytote, Inc), 750 pts worldwide with PSMA (+) scans randomized in a 2:1 ratio to receive either Lu-177-PSMA-617 plus best supportive care vs. best supportive/standard care alone (may include novel anti-AR drug)
- Excluding pts with discordant FDG and PSMA scans
- Alternative primary endpoints are radiographic PFS and OS
- A positive assessment on either is sufficient for full approval
Molecular Imaging Explores the Hallmarks of Cancer Biology

"Virtual Biopsy"

Adapted from Wester HJ. et. al., Clin. Cancer Res, 2007 (Theranostics)
Prostate Cancer Metabolism

$^{18}$F-FDG

$^{18}$F-Fluciclovine

$^{11}$C-Acetate

University of Kansas Medical Center

Jadvar H. Seminars in Nuclear Medicine 2016;46:502-6
Molecular Imaging Explores the Hallmarks of Cancer Biology
“Virtual Biopsy”


Novel IO Imaging Agents
- [{\textsuperscript{90}Y}]Zevalin
- [{\textsuperscript{18}F}]FDG
- [{\textsuperscript{11}C}]Choline
- [{\textsuperscript{18}F}]Choline
- [{\textsuperscript{89}Zr}]Trastuzumab
- [{\textsuperscript{90}Y}]DOTATATE
- [{\textsuperscript{18}F}]FDOPA
- [{\textsuperscript{11}C}]HTP
- [{\textsuperscript{89}Zr}]Cetuximab
- [{\textsuperscript{89}Zr}]HER3
- [{\textsuperscript{18}F}]MPG
- [{\textsuperscript{89}Zr}]PD-L1
- [{\textsuperscript{89}Zr}]PD-L2
- [{\textsuperscript{86}Ga}]DOTATOC
- [{\textsuperscript{89}Zr}]DOTATATE
- [{\textsuperscript{11}C}]MET
- [{\textsuperscript{18}F}]FACBC

FDA-approved / In clinical trials / * Radionuclide therapy (Theranostics)
$^{18}$F-DCFPyL-PSMA

99mTc-MDP Wholebody Bone Scan
May 9, 2017

$^{18}$F-DCF PyL PET MIP
May 25, 2017
Theranostics:

$^{68}$Ga-PSMA-PET/$^{177}$Lu-PSMA

Baseline

After 2 cycles

After 4 cycles
Molecular Imaging Explores the Hallmarks of Cancer Biology

“Virtual Biopsy”

69 y.o. patient with castrate-resistant metastatic prostate cancer considered for treatment with an androgen receptor antagonist (MDV3100, enzalutamide)

- Biomarker
- Patient stratification
- Patient population enrichment
- Prognostic significance
- Clinically Actionable Test
- “Precision” medicine/imaging

Hricak et al
69 y.o. patient with castrate-resistant metastatic prostate cancer considered for treatment with an androgen receptor antagonist (MDV3100, enzalutamide)

- Improved assessment of therapeutic efficacy
- Early assessment of therapeutic efficacy
- Predictive power
- Biologically effective dose vs. MTD
- Shorter trials with less patients
- Lower costs
- Bring drugs to the market faster
- Enable translational cancer research
Immuno-Oncology
Molecular Imaging Explores the Hallmarks of Cancer Biology

“Virtual Biopsy”

Adapted from Wester HJ. et. al., Clin. Cancer Res, 2007

**Novel IO Imaging Agents**

- $^{89}$ZrLAD2M2C
- $^{89}$ZrCD8
- $^{89}$ZrCTLA-4
- $^{89}$ZrPD-1
- $^{89}$ZrPD-L1

**Radionuclide therapy** *(Theranostics)*

**Radionuclide therapy** *(Theranostics)*

**In clinical trials**

**FDA-approved**

**Blood vessel**

**Integrins**

**VEGFR**

**MMPs**

**Annexin V**

**PS**

**[69Zr]Bevacizumab**

**[94Cu]-CB-TE2A-AROG**

**[18F]FDG-6-phosphate**

**[18F]FDG**

**[11C]Choline**

**[18F]Choline**


**[18F]FACBC**

**[68Ga]DOTATOC**

**[68Ga]DOTATATE**

**[177Lu]DOTATATE**

**[90Y]DOTATATE**

**[18F]FDOPA**

**[11C]HTP**

**[89Zr]Trastuzumab**

**[89Zr]Pertuzumab**

**[89Zr]Cetuximab**

**[89Zr]HER3**

**[18F]MPG**

**[18F]FLT**

**[89Zr]CA19-9**

**[89Zr]CATS 9.0**

**PSMA**

**PSMA**

**[225Ac]FPX-01**

**[124I]cG250**

**[124I]cG250**

**[18F]FES**

**[11C]AcOH**

**[18F]FAZA**

**[64Cu]ATSM**

**[18F]MISO**

**Perfusion**

**[18O]H2O**

**[18F]DCFPyL**

**[68Ga]PSMA**

**[89Zr]PSMA**

**[55Co]PSMA**

**[177Lu]PSMA**

**[124I]cG250**

**pO2**

**CAIX**

**Hormone regulation**

**APUD system**

**DNA**

**Protein Synthesis**

**Hormone regulation**

**Thymidine kinase 1**

**Choline kinase**

**Hexokinase**

**[18F]Glutamine**

**GLUT**

**CHT**

**LAT1/2**

**Sst/GRP**

**DAT/NET SERT**

**ENT/CNT**

**EGFR/Her2/Her3**

**CD20**

**CA19.9**

**Extracellular matrix**

**Mesothelin**

**PSMA**

**PSMA**

**[69Zr]Mesothelin**

**AC**

**CD28**

**TCR**

**T cell**

**Adapted from Wester HJ. et. al., Clin. Cancer Res, 2007**
CD8+ T-cells Before and during pembrolizumab (anti-PD1) treatment
$^{89}$Zr-IAB22M2C
Anti-CD8 Minibody

Day 1  Day 2  Day 3  Day 7

Courtesy of ImaginAb
Molecular Imaging

- Can provide noninvasive, quantitative, longitudinal insights into whole-body tumor characterization and drug behavior
- Is relevant to guide rational drug and combination therapy development
- Multiple radiotracers can be used to interrogate the tumor in the same patient
- Consider molecular imaging tracers as companion diagnostic tests
Molecular Imaging

• If there is biological or pharmacological rationale for a molecular imaging tracer, it should be included in the prospective trial design.
• Put molecular imaging to the test by elevating it as a primary endpoint and validate it.
• Include molecular imaging in innovative trials such as: pragmatic trials, registry-based randomized trials, adaptive, personalized medicine, platform and basket trials, pilot and feasibility studies.
Future is bright

• Gathering all the stakeholders as you did here today
• Developing strategic efforts to prioritize targets and more effectively link imaging biomarkers as companion diagnostics to drugs in prospective multicenter trials
• Maximize quantitative accuracy
• Obtain level 1 evidence-based data demonstrating impact of molecular imaging on go/no go decisions, patient management and patient outcome
• Include validated molecular imaging tracers in practice guidelines and get reimbursed
Future

• Success will depend on *multidisciplinary* collaboration on a local, national and global level between pharmaceutical industry partners, imaging device manufacturers, radiopharmaceutical companies, academia, NIH/NCI and regulatory bodies

• Will require transparency and sharing of knowledge, standardization, validation and harmonization of molecular imaging and other technologies

• Need to collect data warehouses that can be combined with other relevant databases (“-omics”, clinical, IO, ex vivo sensing, pathology, liquid biopsies…) and mine them with AI
Strategies to Study Two Investigational Agents in a Single Trial

Cindy Welsh
Division of Medical Imaging Products
Office of Drug Evaluation IV CDER/FDA

NCI SNMMI theranostic conference November 8, 2018
Initial CDER Experience

• Imaging agent used during drug development and initial marketing phase for patient selection based upon biodistribution (2002)
  – 111-In Ibritumomab tiuxetan / 90Y therapeutic
  – 111-In product was not marketed separately
  – Biodistribution imaging requirement removed from labeling (2011) based upon post marketing registry data
Recent CDER Experience

• Developed as an independent diagnostic agent
  – 68Ga Dotatate: localization of SSTR + NETs
  – post-market off-label use for patient selection, clinical management, and response to treatment (Hope et al, 2017)

• Developed as an independent therapeutic agent
  – 177Lu Dotatate: treatment of SSTR + GEPNETs
  – No dosimetry requirement for marketing
Theranostic Regulatory Pathway Options

Parallel development of diagnostic and therapeutic investigational agents

- Analytical characterization of diagnostic, for example
  - In vitro characterization of receptor occupancy
  - Proof of concept in animal studies
    - Receptor binding, biodistribution
    - Estimated human dosimetry
Theranostic Regulatory Pathway Options

Parallel development of diagnostic and therapeutic investigational agents

- Analytical characterization of diagnostic
  - Individual patient dosimetry and biodistribution
  - Determine diagnostic dose, imaging window, image interpretation, safety

- Performance characterization of diagnostic
  - Sensitivity and specificity - Win Criteria: Same 2 out of 3 central, blinded, independent readers succeed
  - Agent should beat a clinically meaningful threshold or accepted/approved comparator (non-inferior also feasible)

- Note that evidence for the efficacy of the diagnostic agent might be derived from clinical outcomes of therapeutic studies
Theranostic Regulatory Pathway Options

Parallel development

– Clinical outcome data from therapeutic studies that could be leveraged for the diagnostic development

• Patient selection
• Response to therapy
• predictive (enrichment strategy for response or toxicity)
Parallel development

- Data from a diagnostic agent development may be used to inform the therapeutic development
  - Biodistribution and dosimetry
  - Estimates initial first in human dosing
  - Set dose limits to off target organs
In Conclusion

Diagnostic and therapeutic theranostic agents can be developed efficiently in parallel with cooperation between the sponsor, DMIP, and disease specific OHOP team with early and frequent collaboration.

Data from the development programs can be leveraged to choose endpoints, determine indication statements, and inform labeling.
Guidance Documents

FDA webpage

Guidances:
Clinical Trial Imaging Endpoint Process Standards Guidance for Industry
Guidance for Industry Developing Medical Imaging Drug and Biological Products Part 1: Conducting Safety Assessments
Guidance for Industry Developing Medical Imaging Drug and Biological Products Part 2: Clinical Indications
Guidance for Industry Developing Medical Imaging Drug and Biological Products Part 3: Design, Analysis, and Interpretation of Clinical Studies
Guidance for Industry, Investigators, and Reviewers Exploratory IND Studies

PET FDA page
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm085783.htm
multiple documents available on this page (scroll to bottom of page)

Guidances
Guidance Investigational New Drug Applications for Positron Emission Tomography (PET) Drugs
Thank you.
Personalized Dosimetry – balancing cost with outcome and science (academic perspective)
Outline

What is dosimetry?
How do you do it?
Why do you do it?
Is it worth the cost?

Radioactivity interacts with matter and deposits energy – damage.
Absorbed dose is

\[ D[\text{Gy}] = \frac{E[\text{J}]}{m[\text{kg}]} \]
Dosimetry Basics

2 methods

1. Activity-based with phantom derived S values
2. Dose rate-based using Monte Carlo and patient-specific anatomy (gold standard)

Both ‘require’ multiple time point 3D in vivo emission and transmission images (SPECT/CT or PET/CT)
NO AD-based Treatment planning for RPT

Standard is the chemotherapy paradigm of dose escalation

AA limit is set by patients with maximum retention

BUT great inter-patient variability – Xbeam is limited by NO toxicity

RPT is radiation just as Xbeam

![Graph](image)
Admin Activity (AA) vs Abs Dose

Example of patient variability

Previously demonstrated that 75 cGy to WB increases RM toxicity

\(^{131}\text{I}-\text{anti-CD20 Ab; NHL patients}

Wahl, RL Semin Oncol ‘03
Reasons not to do dosimetry

The capacity argument:
‘We don’t have the infrastructure…’
‘We don’t have the staff….’
‘We have lost our physicist….’
‘Dosimetry costs too much…’
‘Do we really need 3 scans…?’

Project Fear:
‘Dosimetry will scare the companies away…’
‘Dosimetry will kill therapy..’
‘Dosimetry will kill nuclear medicine..’
‘Not fair on patients…’
‘Accuracy is poor…’
‘Volume outlining is impossible…’

The fatalistic argument:
‘Dosimetry doesn’t work…’
‘The treatment is safe and effective as it is…’
‘We help those that can be helped…’
‘It’s isn’t worth investigating until after we know it works…’
‘The patient will die soon anyway…’

‘I like to complain and do nothing to make things better.’

Marcus Aurelius (161 – 180)
Kurt Cobain (1967 – 1994)

Credit: G. Flux Royal Marsden. EANM ‘18
Reasons not to do dosimetry

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**The fatalistic argument:**
- ‘Dosimetry doesn’t work…’
- ‘The treatment is safe and effective as it is…’
- ‘We help those that can be helped…’
- ‘It’s isn’t worth investigating until after we know it works…’
- ‘The patient will die soon anyway…’
Cost – compare

Rad Onc ($42k)
- 25 fractions of IMRT
- PTE Dosimetrist TP and TP software
- PTE Physics QA and QA software
- Linacs and PTE Therapists
- Physician

RPT (~$20-40k)
- $5-10k+ for drug
- $1-2k for SPECT/CT scan and PTE Techs
- PTE for physicist for TP
- MC capability, registration and curve fitting software
- Physician
Cost to Patient

Cost of re-treatment, cost of lower life expectancy

5-8 weeks of daily treatment for External beam vs. 1 week of pre-therapeutic scans

Cancer therapy needs multi-modality approach. 30% inefficiency – combination with other lesser accurate modalities – 50% inefficiency

Right drug for the right patient -> right amount, right combination of modalities for the right patient.
Trial designs

Data collection for dosimetric analysis during Phase I evaluation will likely save money and time in later stage trials. This is from the perspective of being able to better assess the factors that lead to toxicity or to a favorable treatment outcome.

Including a data collection effort in phase II or III trials that could lead to a sub-group analysis (similar to what is currently done w/ all of the trial result papers published in NEJM) that would examine whether there is evidence that dosimetry-driven treatment would have reduced toxicity and improved tumor control. Such sub-group analyses are considered hypothesis generating and are typically evaluated in subsequent trials.

Credit: G. Sgouros. Private communication
Reasons not to do dosimetry

The capacity argument:
‘We don’t have the infrastructure…’
‘We don’t have the staff….’
‘We have lost our physicist….’
‘Dosimetry costs too much…’
‘Do we really need 3 scans…?’

Project Fear:
‘Dosimetry will scare the companies away…’
‘Dosimetry will kill therapy..’
‘Dosimetry will kill nuclear medicine..’
‘Not fair on patients…’
‘Accuracy is poor…’
‘Volume outlining is impossible…’

Not necessarily. Every RPT is potentially different. Start with more and reduce if possible (validated) or circumstances permit.

The fatalistic argument:
‘Dosimetry doesn’t work…’
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‘The patient will die soon anyway…’

1. Historically true.
   3D imaging has greatly improved accuracy
   Uncertainty analyses give estimates of accuracy
   Registration software has also improved
Reasons not to do dosimetry

**The capacity argument:**
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‘Volume outlining is impossible…’

1. Historically true.
3D imaging has greatly improved accuracy
Uncertainty analyses give estimates of accuracy

2. Historically true.
Many studies in the past and still presently use sub-optimal dosimetry (poor input data, assumptions from other RPT, use diagnostic dosimetric assumptions)

**The fatalistic argument:**
‘Dosimetry doesn’t work…’
‘The treatment is safe and effective as it is…’
‘We help those that can be helped…’
‘It’s isn’t worth investigating until after we know it works…’
‘The patient will die soon anyway…’
Dosimetry is more than AD

Dosimetry doesn’t explain everything!
Other correlates exist!

Dosimetry is more than calculation of absorbed dose, but whatever correlates exist, including the absorbed dose will only improve personalization of TP.

Dosimetry constantly becoming more sophisticated: PK models, small scale dosimetry, e.g.
Radiobiology -> bioeffect modeling (BED, EUD)
Importance of organ volume in self irradiation

Correlation between kidney dose (Gy) and creatinine clearance loss/year (% baseline) N=18

Barone, et al. JNM ‘05
Correlation between BED and creatinine clearance loss/year

TP examples

PRRT
I-131
Anti CD20
Sm-153/XRT

Considerations: range of isotope, size and number of tumors, localized distribution, disseminated disease, orthogonal toxicities for combinations, different dose patterns or dose rates, RBE, dose non-uniformity
THANK YOU FOR YOUR ATTENTION!
Absorbed Dose: Energy (damage) absorbed per unit mass. Unit: Gy

\[
\tilde{A}_S \times \Delta \times \phi_{t \leftarrow s}
\]

\[
\frac{\text{sources are internal, constraint is normal organ toxicity}}{M_t}
\]
Absorbed fraction methodology uses MIRD S-values\textsuperscript{a} determined from idealized geometrical model (no tumors) and Monte Carlo

\[ \tilde{A}_S \times \Delta \times \phi_{t\leftarrow s} \]

\[ M_t \]

S-value

OLINDA/EXM\textsuperscript{b} is a widely used software which uses MIRD S-values, requires only TIA

\textsuperscript{a} MIRD Pamphlet #11
\textsuperscript{b} Stabin \textit{et al.} JNM '05
Time-Integrated Activity*

Activity images
1. planar, use anterior – posterior methodology $^a$
Involves background subtraction (artistic), technical problems of scatter and attenuation only poorly corrected - very high uncertainty, whole organ only.
2. SPECT or PET, 3 – dimensional images enable better reconstruction $^b$

Register images over time

(*formerly Cumulated activity)

$^a$ MIRD #16 Siegel et al. JNM '99
$^b$ He et al. Phys Med Biol '05
MIRD #21 Bolch et al. JNM '08
MC - Dose Rate Integration

3-D dose rate images

\[ D(x, y, z) = \int_{0}^{\infty} \dot{D}(x, y, z, t) dt \]

Advantages?

- No dependency on modelized anatomy.
- Voxelized results
- Tumor dosimetry
- Radiobiology
- Modeling for new aspects

\[ D_{xyz} \]

Sgouros et al. JNM '04
Personalized Dosimetry – balancing cost with outcome and science

Frank I. Lin, MD
Chief, Targeted Radionuclide Therapy Section
NIH/NCI/CCR/MIP
A focused discussion

Dosimetry is needed!

Personalized Dosimetry – balancing cost with outcome and science
Why do we do dosimetry?

Estimating radiation exposure/dose to:

Normal Organs

- Predicting toxicity
- Maximum tolerated dose
- Keep below organ tolerance dose

Tumor

- Calculating tumor dose
- Predicting response to therapy
Toxicity Evaluation

- Dosimetry gives you an estimated tissue dose but the actual desired information is presence of adverse events (e.g. organ damage)
- Difference: dosimetry gives you an opportunity to predict the AE before it happens
- With non-radioactive drugs -> give drug and collect AE information

Table 5 Adverse Reactions Reported in Pooled Data (≥25% of Patients who Received Lynparza)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>3 or more lines of prior Chemotherapy</th>
<th>3 or more lines of prior Chemotherapy</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 n=223 %</td>
<td>Grades 3-4 n=223 %</td>
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<tr>
<td>Blood and Lymphatic disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>34</td>
<td>18</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>64</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>43</td>
<td>4</td>
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<tr>
<td>Diarrhea</td>
<td>31</td>
<td>1</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>General disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue/asthenia</td>
<td>66</td>
<td>8</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis/URI</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue disorders</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia/musculoskeletal pain</td>
<td>22</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 6 Laboratory Abnormalities Reported ≥25% of Patients in Pooled Data

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>3 or more lines of prior Chemotherapy</th>
<th>3 or more lines of prior Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 n=223 (%)</td>
<td>Grades 3-4 n=223 (%)</td>
</tr>
<tr>
<td>Decrease in hemoglobin</td>
<td>90</td>
<td>15</td>
</tr>
<tr>
<td>Decrease in absolute neutrophil count</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>Decrease in platelets</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>Decrease in lymphocytes</td>
<td>56</td>
<td>17</td>
</tr>
<tr>
<td>Mean corpuscular volume elevation</td>
<td>57</td>
<td>-</td>
</tr>
<tr>
<td>Increase in creatinine</td>
<td>30</td>
<td>2</td>
</tr>
</tbody>
</table>

*Adverse Event data for olaparib from FDA label
Should we do (personalized) dosimetry for toxicity evaluation?

• Depends on the toxicity profile
• Dosimetry results need to be actionable
• Useful dosimetry is one that would let me predict the occurrence of an AE

Factors affecting usefulness

• Useful if discrete organ damage is an expected AE
• Useful if narrow therapeutic window
• Less useful if overall toxicity of agent is low

*Adverse Event data for $^{177}$Lu-DOTATATE
Tumor lesion dosimetry

• Dosimetry allows an estimate of dose delivered to tumor
• Using radiobiology data -> predict tumor response on a lesion-by-lesion basis

• Purpose:
  • Dosimetry for toxicity evaluation = see if dose reduction is necessary
  • Tumor lesion dosimetry = see if dose needs to be increased
Challenges

- Number of lesions can be overwhelming
- Automation and software can help – but still very labor-intensive
- Unlike XRT, no easy way to selectively increase dose to particular tumor
- When to dose increase?
  - Lesion with lowest dose? (lowest common denominator)
  - Whole body dosimetry (Bexxar)

Typical Metastatic Disease – $^{68}$Ga-DOTATATE Scan
Other considerations

• Target organ dosimetry can be used to push dose to MTD – how will you know the incidence of other AEs are?

• Can do dosimetry to stop futile doses
  • If no lesion receives ablative doses, treatment likely will not work
  • Extreme example = MIBG or DOTATATE scan with no or minimal uptake
  • But qualitative read is probably sufficient without doing extensive dosimetry

• Final dosimetry methodology should ideally be user-friendly, not too inconveniencing to patients, and streamlined
Conclusion – should we do personalized dosimetry?

• For toxicity evaluation: in certain situations it can be helpful
  • Agents with high incidence of discrete organ-damage SAE
  • Narrow therapeutic window
  • Dosimetry does not help with predicting many side effects of systemic agents
  • Probably an agent-specific, limited (targeted) dosimetry approach would be more useful
  • e.g. kidney dosimetry in agents known to cause high % of renal SAE

• For lesion dosimetry:
  • Many challenges
  • Dosimetry results must be actionable, with clear guidelines on how management is to be changed based on results
Personalised Dosimetry Balancing costs with outcome and science: the AAA experience

M.F. Mariani MD, PhD, DABT
Theranostics Consensus Conference - November 8th, 2018
Improving Patient Management through Unique Theragnostic Platform

Ga-68 labeled

Same Targeting Molecule

Lu-177 labeled

Ga-68 PET

- Diagnosis
- Selection for PRRT / RLT or other treatment
- Follow-up

Lu-177 PRRT / RLT

ELECTRONS TREAT TUMORS FROM WITHIN

PRRT = Peptide Receptor Radionuclide Therapy
RLT = RadioLigand Therapy
Introduction: the NETTER-1 study

First international, multicenter, randomized, controlled study
Evaluate efficacy and safety of $^{177}$Lu-DOTATATE + SSAs compared to Octreotide LAR 60mg
Subjects: inoperable, SSTR positive, midgut NET, progressive with Octreotide LAR 30mg

$^{177}$Lu-DOTATATE was safe and more effective than Octreotide 60 mg:

- **PFS** (Not Reached vs 8.5 months, p<0.0001)
- **ORR** (13% vs 4%, p=0.0008)
- **OS** (Not Reached vs. 27.4 months, interim analysis; p=0.0043)

A Marketing Authorization was granted for this product in Europe and in USA, in September 2017 and January 2018 respectively.
**Aim of the Dosimetry/PK sub-study**

**Aim:** Evaluate dosimetry and PK in patients enrolled in Phase III NETTER-1 dosimetry substudy

**Methods:** 20 patients (mean age 58 years, range 30-74) were treated according to NETTER-1 protocol.

Commercial amino acid solutions (Aminosyn II 10% or Vamin 18) were administered for renal protection. The administration of this solution (2 L) was started 30 minutes before the start of PRRT, and continued for a total of 4 hours.
Octeroscan® Positivity in NETTER-1 (Lutathera)

- Octreoscan® positivity (≥ normal liver uptake) was one of the inclusion criteria (Octeroscan = $^{111}$In-DTPA-Octreotide)
- OctreoScan® Tumour Uptake and Extent of Tumour Burden Scales

✓ Tumour Scoring

Tumor Uptake grade OctreoScan®:

1) < Liver (Excluded)  
2) = Liver  
3) > Liver  
4) Very intense (>>Kidneys, spleen)

✓ Extent of Tumour Burden

Tumour Burden score OctreoScan®:  
Limited  
Moderate  
Extensive
Methods (Dosimetry assessment)

- >5 whole body planar images acquired within the 7 days post-administration.
- ROIs drawn on whole body, liver, spleen, kidneys, urinary bladder and the tumors.
- Time-activity experimental data for each organ was fitted by a bi-exponential curve.
- Time integrated activity coefficient derived for all source organs were used to calculate the absorbed dose values in target organs via OLINDA/EXM.
- The correction for the individual masses of the source organs was applied for each patient.
NETTER-1 Results:

Blood clearance and urine excretion profiles

Blood clearance after a single 7.4 GBq administration of $^{177}$Lu-DOTATATE

Tri-exponential curve, with rapid clearance and broad tissue distribution

Cumulative injected activity eliminated vs time in the urine after a single 7.4 GBq administration

Mono exponential curve, with rapid elimination in the urines
Absorbed doses per unit of IA (Gy/GBq) in the normal organs. Median values (black dash); 25% and 75% percentiles (lower and upper limit of the boxes); minimum and the maximum value observed (vertical bars / whiskers).

Estimated absorbed doses (Gy/GBq) in normal organs in line with published literature.

- 0.65 Gy/GBq kidneys (19.24 Gy for 29.6 GBq total dose)
- 0.04 Gy/GBq red marrow (1.18 Gy for 29.6 GBq total dose)
- 0.07 Gy/GBq total body (2.07 Gy for 29.6 GBq total dose)
Predicted cumulative absorbed doses to normal organs for all patients, calculated for 4 planned administrations of 7.4 GBq (29.6 GBq total) $^{177}$Lu- DOTATATE.

| Absorbed dose in normal organs for 29.6 GBq (Gy) |
|---------------------------------|----------------|-----------|----------------|------------------|---------------------|
| Kidneys | Liver | Spleen | Red marrow | Urinary bladder wall | Total body |
| Mean    | 19.4  | 8.9    | 25.1       | 1.0              | 12.8             | 1.6             |
| SD      | 8.7   | 6.7    | 23.8       | 0.8              | 5.3               | 0.8             |

23 Gy (EBRT threshold for kidneys) were exceeded in 7 patients
2 Gy (EBRT threshold for red marrow) would have been exceeded in 1 patient who did not complete the 4 cycles

The treatment was well tolerated, with no clinically significant renal toxicity and mild-transient hematological toxicity.
Hematological toxicity was mild and reversible in most patients.

2 patients with transient G3 WBC/ANC toxicity.

No correlation with bone marrow absorbed doses was evident, except for platelet toxicity, which was mild (G1) and not clinically relevant.
Toxicity relative to kidney absorbed dose

Only Grade 1 kidney (serum creatinine, CTCAE 4.03) in 4 patients
- Creatinine increase was already present at baseline in 2 subjects
- No correlation between the mild (G1) observed toxicity and renal absorbed dose
**NETTER-1 Results: Tumor dosimetry**

Time-activity curves in tumor masses indicate that $^{177}$Lu-DOTATATE has prolonged intense uptake in tumor lesions.

Cumulative absorbed doses are high, and particularly elevated in the majority of lesions.

Causes for inter/intra-patient variability include SSR expression level, specific shape, vascularization.

Data confirm high persistence in tumor lesions.
The safety and efficacy data collected in the long clinical experience with $^{177}$Lu-DOTATATE confirm that the product, at the dose of 200 mCi given for 4 times at 8 weeks intervals, is well tolerated and does not need personalized dosimetry, both from a safety and efficacy perspective.

As for the more classical PK/PD approach, dosimetry is an important tool at initial stages of development, to support the identification of a well-tolerated and efficacious cumulative dose and therapeutic scheme to be used in Phase III studies.

The definition of optimal dose regimens are guided by efficacy and safety considerations. They are specific for a given clinical indication and patient population and aim at maximizing the benefit for oncological patients.

The selected dose will maximize the probability of efficacy in the overall patient population, while keeping control of the toxicity parameters.

On the contrary, a personalized dosimetry-based approach would have severe limitations:

- Complex patient management and Increased risks of errors
- High costs for Health Care systems and low patient compliance
- Access to treatment limited to fewer centers with specific capabilities
- Production and logistic challenges for personalized doses
Complex manufacturing and supply chain

Isotope Supply

AAA internal Production

Hospital (external)

Patient dose
Vial calibration
Standard dose of 7.4GBq/cycle
Aseptic conditions
Patient selection based on $^{68}$Ga diagnostic

$^{176}$Lu precursor
Produced in calutrons

$^{177}$Lu Isotope
Produced in nuclear reactors

DOTATATE
Solid phase peptide synthesis
Aseptic vial filling

Lutathera
Semi-manual or with application robot
Aseptic conditions
On demand production
Parametric release
3 days shelf life

Octreotide
DOTA-TATE
Sterile Stock

Target Isotope $^{177}$Lu

Lutathera® Labeling
Sterile vial

Patient Delivery
Back-up
The safety and efficacy data collected in the long clinical experience with \(^{177}\)Lu-DOTATATE confirm that the product, at the dose of 200 mCi given for 4 times at 8 weeks intervals, is well tolerated and does not need personalized dosimetry, both from a safety and efficacy perspective:

- The **high variability of dosimetry data** and **lack of correlation between kidney and bone marrow absorbed dose and toxicity** confirm that **clinical, hematological and biochemical assessments are the most reliable tools to monitor potential toxic effects**.

- Similarly, **tumor dosimetry data** show a rather **high variability** of tumor absorbed doses. Generally, **time-activity curves in tumor masses** confirm that \(^{177}\)Lu-DOTATATE has a good **uptake and prolonged retention in tumor lesions**. Personalized dosimetry would not be useful in determining patient-based dose adjustment, and could lead to select sub-optimal therapeutic dose.
Reviewing Radiation Dosimetry: Examples and Issues

Stanley H. Stern, PhD
FDA/CDER Office of New Drugs
Division of Medical Imaging Products

Theranostics Conference 2018
• 21 CFR 312.23(a)(10)(ii) **IND content, radioactive drugs**
  “... sufficient data from animal or human studies to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration to a human...”

  refers to SNMMI/MIRD methodology and ICRP recommendations

**Issues**

- FIH trials: Animal data tend to underestimate human organ doses within a very broad range of uncertainty (Sparks & Aydogan, 1999)

- Theranostic pairs: Fidelity of **Dx**-drug to **Tx**-drug in biodistribution, retention, and loss in normal-tissue and in tumor? **Dx**-drug for patient selection? For dosimetry?
• **Radium Ra 223 dichloride injection** (2013)
  
  *for castration-resistant prostate cancer, in patients with symptomatic bone metastases and no known visceral metastatic disease*

  **Issue**: $\alpha$ vs. $\beta$, $\gamma$ — $\alpha$ Relative Biological Effectiveness $\approx 5$?

• **Lutetium Lu 177 dotatate injection** (2018)

  *for somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in adults*

• **Iobenguane I 131 injection** (2018)

  *for unresectable, locally advanced, or metastatic pheochromocytoma or paraganglioma in iobenguane-scan-positive adults and children $\geq 12$ years old*

  **Issues**: Weight-based vs. “fixed” dosing? Individual dosimetry: once vs. cycle-to-cycle? What are radiation-toxicity thresholds, acute & long-term? Would patients survive long enough to manifest clinical toxicity?
THE NEED FOR RADIATION DOSIMETRY-BASED TREATMENT PLANNING IN TARGETED RADIONUCLIDE THERAPY

Jacek Capala

NCI
Acknowledgement

Slides marked are modified from a keynote presentation at EANM’18 by

Glenn Flux
Royal Marsden Hospital & Institute of Cancer Research
Sutton UK
Dose Sculpting

2-D Planning

3-D Conformal

IMRT
Irradiation of Metastases with One Setup
Treatments historically governed by activity administered:

- 100 mCi radioiodine for thyroid ablation
- 200 mCi radioiodine for thyroid therapy
- 200 mCi Y-90 microspheres for treatment of liver metastases
- 200 mCi I-131 mIBG for neuroendocrine tumours
- 200 mCi x 4 for Y-90 DOTATATE of neuroendocrine tumours
- 200 mCi x 4 for Lu-177 DOTATATE for neuroendocrine tumours
- 200 mCi x 4 for Lu-177 PSMA for bone metastases
- 50 kBq/kg x 6 for Ra-223 for bone metastases

Empirical (chemotherapy) paradigm – learning from observation and experience...
<table>
<thead>
<tr>
<th>Red marrow:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bianchi (2012) 0.04 – 0.4</td>
</tr>
<tr>
<td>Chittenden (2015) 177-994</td>
</tr>
<tr>
<td>Metastatic lesions:</td>
</tr>
<tr>
<td>Kolbert (2007) 0.03 – 2.6</td>
</tr>
<tr>
<td>Pacilio (2016) 0.9 – 8.9</td>
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<tr>
<td>Salivary glands:</td>
</tr>
<tr>
<td>Jentzen (2006) 0.2 - 1.2</td>
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<tr>
<td>Kidneys:</td>
</tr>
<tr>
<td>Chittenden (2015) 2-15</td>
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<tr>
<td>Thyroid remnants:</td>
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<tr>
<td>Minguez (2016) 0.2 - 160</td>
</tr>
<tr>
<td>Bone surfaces</td>
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<tr>
<td>Chittenden (2015) 2331 – 13118</td>
</tr>
<tr>
<td>Organ or lesion</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Red marrow</td>
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<td>Tumors</td>
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*Pretherapeutic.  †Posttherapeutic.
Clinical trials

Treatment according to Gy, even with an uncertainty on the absorbed dose, will deliver a narrower range of responses.

Example:
Target absorbed dose 60 Gy, with a 30% uncertainty.
An RCT would be comparing a large range of unknown doses with a narrow range of known doses
Randomising between knowledge vs ignorance...
FIGURE 5. Tumor dose–response relationship for patients with PNETs treated with PRRT using \textsuperscript{177}Lu-DOTATATE, including tumors larger than 2.2 cm (A) and only tumors larger than 4 cm (B).
154 patients who stopped therapy for reasons other than progression or clinical deterioration.

50 patients who received exactly four cycles of $^{177}$Lu-DOTAoctreotate.
TO DO OR NOT TO DO DOSIMETRY?

That is *not* the question:

- Patient safety
- Treatment justification (patient selection)
- Treatment optimisation
- Health economics

Just a matter of time and effort
Dose Sculpting

2-D Planning

3-D Conformal
Conclusion - Reasons for dosimetry

Part 1: Safety

- 200 mCi = 7,400,000,000 radioactive decays per second, each second
  - This may be justified but it is not safe!

- Radiation dosimetry for each individual treatment, particularly for new radiotherapeutics, must be mandatory until clinical trials show that is not relevant to outcome.

- All people have their radiation doses monitored or estimated except patients undergoing radionuclide therapy.

- We, physicians, medical physicists, and funding and regulatory agencies, are responsible for radiation safety of the patients.
Conclusion - Reasons for dosimetry

Part 2: Benefit

• Treatments will be more effective.
• Cost/benefit ratio will improve for the insurance, health authorities, and industry.
• Combination with other therapeutic modalities, particularly external RT, will be enabled.
• TRT will enter the mainstream of cancer management.
Conclusion - Reasons for dosimetry

Part 3: Fun

This is new territory. The great opportunity we have for exciting, ground breaking, multi-disciplinary, multi-national collaborations.

Imaging (quantitative) and dosimetry enable participation in new areas of research – precision medicine, radiomics, artificial intelligence, deep learning...

Lots more ‘healthy discussions’ to come. One scan or 8? A rough dosimetry estimate or 3 decimal places?

If we set the goals right, we will overcome all barriers!
Expensive Drugs, Expensive Trials, What Data is Needed for Reimbursement

Dane J. Dickson MD
Disclosures

- Financial Interest: Taproot Health
- Speaker Honoraria: Novartis
- Previous Research Grants: Roche/Genentech, Eli Lilly, Celgene, Illumina, Thermo Fisher
Testimonial

“Dane, you’re not a cookie-cutter academician. . . which isn’t bad.”

Razelle Kurzrock, MD
Director of Moores Cancer Center at UCSD

1 Medical Oncologist Rural Idaho covering more than 20,000 miles

2 Previous Director of Precision Medicine at CMS’s Palmetto MolDX.

3 Director of Precision Medicine Policy and Registries at the Knight Cancer Center at OHSU

4 Former CEO of CureOne and now CEO of Taproot Health.
Lutetium-177 (177Lu-Dotatate)

A Progression-free Survival

No. at Risk

177Lu-DOTATATE group 116 97 76 59 42 28 19 12 3 2 0
Control group 113 80 47 28 17 10 4 3 1 0 0

B Overall Survival (Interim Analysis)

No. at Risk

177Lu-DOTATATE group 116 108 96 79 64 47 31 21 8 3 0
Control group 113 103 83 64 41 32 17 5 1 0 0

P < 0.001

Medicare Approach to Drug Coverage
Medicare Approaching Drugs (On or Off Label)

DATA DOES NOT DRIVE COVERAGE - Listing Does

- FDA Approval
- Literature Review
- Compendia Listing
  - Lexi-Drugs
  - AHFS-DI
  - DrugDex
  - NCCN
  - Elsevier/Gold Standard Clinical Pharmacology
- Updating Codes
  - Disease Specific based on NCCN or other
Private Payor Approach to Drug Coverage
A Payors Frame of Mind

BASELINE, BENEFIT, WASTE AND NEW STANDARDS OF CARE

J Clin Oncol. 1999 May;17(5):1413-24
A Payors Frame of Mind

“FDA Approval and Compendia Listing are not Everything”
Private Payers Approaching On-Label Drugs

COVERAGE IS MUCH MORE COMPLICATED

- FDA Approval
- Compendia Listing
- Literature
- Formularies
- Pathways
- Co-Pays
- Prior Authorization
- Updating Codes
  Disease Specific based on NCCN or other
Private Payers Approaching Rare Disease

COVERAGE IS DEPENDENT ON ACCESS TO MEDICAL DIRECTOR
Right to Try Legislation
National Right to Try Legislation
GOOD OR BAD FOR DRUG DISCOVERY

Patients with:
- Life-threatening disease
- Exhausted approved treatments
- Who are willing to give consent and
- Where drug has been through at least phase 1 testing

May request:
Access to drug from pharmaceutical company directly

No Liability:
Against anyone who will not provide access to these drugs

May 30, 2018

Future Directions
Unifying of Payors, Providers, and Patients
Better Data for Better Understanding of Benefit
Leveraging Real World Registries to Generate Research Grade Outcome Data

Diagnostic Modules
- LDTs – Existing Tech
- Panomics
- New Tech

Therapeutic Modules
- Off Label
- Compassionate Use/ Right to Try
- Combination Therapy
- Theranostics
Bridging the Gap: Funding and Resources at NCI for Theranostics

Paula M. Jacobs, Ph.D.
Division of Cancer Treatment and Diagnosis, NCI
Cancer Imaging Program
Outline

➢ Grants
  • General NIH funding
  • Specialized imaging funding
  • SBIR/STRR funding

➢ NCI Experimental Therapeutics Program (NExT)

➢ Orphan Drug Grants

For links, please request the presentation jacobsp@nih.gov

No conflicts of interest to report
General Funding

➢ Funding Opportunities and Notices- NIH & NCI
  • http://grants.nih.gov/grants/guide/
  • http://www.cancer.gov/researchandfunding/funding/announcements

➢ Common types of grant
  • Unsolicited – R01, R03, R21
  • Request for applications (RFA)
  • Program announcement (PA/PAR)
  • All now divided into “Clinical Trial not allowed”, “Clinical Trial Optional” and “Clinical Trial Required”

➢ See the CIP website for details: Current Funding Opportunities
Some Initiatives For Theranostics

➢ PAR-18-530: Academic-Industrial Partnerships for Translation of Technologies for Cancer Diagnosis and Treatment (R01)
➢ PAR-18-011: Early Phase Clinical Trials in Imaging and Image-Guided Interventions (R01)
➢ PAR-17-093: Academic-Industrial Partnerships to Translate and Validate in vivo Cancer Imaging Systems (R01)
➢ PAR-18-252: Image-guided Drug Delivery (R01))
➢ PAR-18-020: NCI Clinical and Translational Exploratory/Developmental Studies (R21)
➢ RFA-CA-17-023: Integration and Validation of Emerging Technologies to Accelerate Cancer Research (R33)
➢ PAR-16-116: Bioengineering Research Partnerships (U01)
➢ PA-16-040: Exploratory/Developmental Bioengineering Research Grants (EBRG) (R21)s
Grant Funding For Imaging (3)

➢ SBIR & STTR
  • The Small Business Innovation Research (SBIR) **PA-18-573 (Clinical trial required)** and **PA-18-574 (Clinical trial not allowed)** 2.9% set aside

➢ Small Business Technology Transfer (STTR) **PA-18-575 (Clinical trial not allowed)** & **PA-18-576 (Clinical trial required)**, 0.4% set aside
  • ~$700M annually at NIH; $115 at NCI
But grants don’t get you into the clinic.......
Bridging the “Valley of Death”

Structure-Activity-Relation
Toxicology studies
Chemical Process development
NCI Experimental Therapeutics Program (NExT)
NOT A GRANT PROGRAM

- Projects need a clear path to clinic/patient benefit
- Integrates a variety of prior decentralized and uncoordinated programs
- Provides access to NCI resources and >50 yrs. experience in drug development
- Simple application process
- External expert review, then internal expert review
- Applicant is a key member of the team: involved in project planning, implementation, and has full access to data
- Three Aspects: Discovery, Development, Clinical
Dramatically increase the flow of early-stage drug candidates into the DCTD therapeutics pipeline by leveraging knowledge from innovative research and discoveries made at leading academic institutions and biotechnology companies.

And

Provide the extramural community the opportunity to participate in a highly collaborative drug discovery partnership with the NCI.
Early access to enabling, leading-edge translational technologies and tools

- PK/PD Modeling
- Toxicology/Safety Pharmacology
- GMP Scale-Up – unique GMP protein facility
- Imaging supported by Cancer Imaging Program – biodistribution & dosimetry
- Development/validation of PD assays supported by the Pharmacodynamics Assay Development & Implementation Section (PADIS) and by the National Clinical Target Validation Laboratory (NCTVL).
- Clinical Assay Development Program (CADP) development and validation of clinical assays (including diagnostic).
➢ Currently sponsors over 100 INDs
➢ Approx. 11,000 registered investigators at over 3,300 institutions
➢ Over 750 active protocols
➢ 150-250 new protocols/year
➢ Approx. 30,000 patients accrued/year
➢ Over 80 collaborative agreements (CRADAs, CTAs, and CSAs) with pharmaceutical companies (Collaborators)
Next Resources Currently Support

- Investigational drugs and biologics
- Investigational imaging agents
- Academic, biotech and pharmaceutical company projects
- Phase 0, 1 and 2 clinical trials
- HTS, Hit-to-Lead and Lead optimization

**NOT basic research**
Distribution of applications by type and applicant

- **Biologic**: 30%
- **Imaging**: 3%
- **Small Molecule**: 65%
- **Nanoparticle**: 1%
- **Natural Product**: 1%
- **Radiotherapy**: 0%

**By Applicant**

- **Pharma**: 8%
- **Non-Profit**: 12%
- **Biotech**: 35%
- **Academic**: 42%
- **Government**: 3%
- **Others**: 3%
# Imaging & Imaging-guided Therapy Projects

<table>
<thead>
<tr>
<th>Name, First Name</th>
<th>Institution</th>
<th>Project Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verholen, Frank</td>
<td>Bayer</td>
<td>Radium-223 Combination Studies</td>
</tr>
<tr>
<td>Choyke, Peter</td>
<td>CCR NCI</td>
<td>A Phase II Study of F-18 DCFBC, a Prostate Specific Membrane Antigen-Target</td>
</tr>
<tr>
<td>Frangioni, John</td>
<td>BIDMC</td>
<td>A NIR Fluorophore for Clinical Translation of Image-Guided Oncologic Surgery</td>
</tr>
<tr>
<td>Griffiths, Gary</td>
<td>CCR NCI</td>
<td>Large Scale Preparation of IR700-Panitumumab for Clinical Use</td>
</tr>
<tr>
<td>Kirsch, David</td>
<td>Duke/Lumicell</td>
<td>Using Molecular Imaging to Detect Microscopic Residual Cancer During Surgery</td>
</tr>
<tr>
<td>Peng, Ben</td>
<td>XL Sci-Tech, Inc</td>
<td>Image guided radioembolization of liver tumors</td>
</tr>
<tr>
<td>Rittenhouse-Olson, Kate</td>
<td>For Robin</td>
<td>hJAA-F11 antibody for breast cancer detection and treatment</td>
</tr>
<tr>
<td>Rosenthal, Eben</td>
<td>UAB/Stanford</td>
<td>Intraoperative Optical Imaging to Guide Surgical Resection of Cancer</td>
</tr>
<tr>
<td>Schnitzer, Jan</td>
<td>PRISM</td>
<td>Developing hAnnA1-based immunoconjugates for cancer detection and treatment</td>
</tr>
</tbody>
</table>
Access to NExT (next.cancer.gov)

Who: Researchers in academia, government and industry, nationally and internationally.

Receipt Dates: February 15, June 15, October 15

http://next.cancer.gov/
Orphan Drugs – not NCI, but relevant
Orphan Drugs

➢ Drugs or biologics (not devices) intended to treat, diagnose, or prevent a rare disease or condition... or,

➢ A drug that will not be profitable within 7 years following FDA marketing approval (rare)

➢ Pathway for devices available, but not identical

➢ Can submit common application to EMA

➢ The disease or condition prevalence <200,000 in the US or for diagnostics expected to be administered to <200,00 a year

➢ Medically plausible (orphan) subsets of common diseases (e.g. metastatic melanoma)
Benefits of Orphan Designation

➢ Purely financial in nature:
  • Seven years of market exclusivity
  • Up to 50% of tax credits for clinical research expenses
  • Waiver of marketing application fees (e.g., $2.3 M to file)

➢ However…
  • Often the first step in FDA communication
  • OOPD may provide informal guidance
  • May also attract venture capital

➢ Can apply for FDA grants to support clinical research
Orphan Products Grants Program

- Drugs, biologics, medical devices, or medical foods qualify
- ~$14 million dollars appropriated per year
- $200- $400K/year for 2 to 4 years
  - Up to $200K for up to three years for phase 1 studies
  - Up to $400K for up to four years for phase 2 and higher
- Re-competition is allowed
- Available to domestic or foreign, public or private, for-profit or nonprofit entities
- Request for Application (RFA) available on web site http://www.fda.gov/orphan
Thanks for your attention

Imaging.cancer.gov  Jacobsp@mail.nih.gov

SBIR & STTR: Three-Phase Program

- Proof-of-Concept study
- $150,000 over 6 months (SBIR) or 1 year (STTR)

Direct to Phase II
- Skip Phase I

- Commercialization stage
- Use of non-SBIR/STTR funds

Phase I
- Research & Development
- Commercialization plan required
- $1 million over 2 years

Fast Track Application
Combined Phase I & II

Phase II

Phase III
COMMERCIALIZATION

- Hard caps on award sizes: $225,000 for Phase I; $1.5 million for Phase II
- Certain awards may exceed these caps if covered by topic-specific waivers
- Actual funding may vary by topic
SBIR Eligibility Requirements

- Applicant is a Small Business Concern (SBC), organized for-profit U.S. business
- 500 or fewer employees, including affiliates
- PI’s primary employment (>50%) must be with the SBC at time of award & for duration of project
- > 50% U.S.-owned by individuals and independently operated
  - OR
- > 50% owned and controlled by other business concern/s that is/are > 50% owned and controlled by one or more individuals
  - OR
- > 50% owned by multiple venture capital operating companies, hedge funds, private equity firms, or any combination of these
STTR Eligibility Requirements

- Applicant is a Small Business Concern (SBC), organized for-profit U.S. business
- Formal cooperative R&D effort
  - Minimum 40% by small business
  - Minimum 30% by US research institution
- US Research Institution: college or university; non-profit research organization; Federally-Funded R&D Center (FFRDC)
- Principal Investigator’s primary employment may be with either the SBC or the research institution
- SBC must have right to IP to carry out follow-on R&D and commercialization
Reasons to seek SBIR/STTR Funding

➢ Provides seed funding for innovative technology development
➢ Not a Loan; repayment is not required
➢ Doesn’t impact stock or shares in any way (i.e., non-dilutive)
➢ Intellectual property rights retained by the small business
➢ Provides recognition, verification, and visibility
➢ Helps provide leverage in attracting additional funding or support (e.g., venture capital, strategic partner)
Orphan Drugs – not NCI, but relevant
Is the Disease or Condition Rare?

➢ The disease or condition prevalence <200,000 in the US
➢ Acute diseases or conditions: yearly incidence may be used in some cases to estimate the patient population (<200,000 in the US)
➢ Diagnostics and preventatives: may only be subjected to <200,000 patients in the US annually
➢ Medically plausible (orphan) subsets of common diseases (e.g. metastatic melanoma)
   • No salami slicing
Medically Plausible (Orphan) Subsets

➢ There is some property of the drug such that the use of the drug would be limited to the subset of the disease or condition
➢ E.g., toxicity profile, mechanism of action
➢ The drug would not be used in the full complement of the disease
➢ Regulatory term to delineate persons expected to use the drug
➢ Not a clinical definition
Request for Orphan Designation

➢ Possibly the simplest FDA submission
➢ The request must be made prior to the submission of a BLA or NDA
➢ An IND is not required for submission
➢ May be submitted from sponsors from any country
➢ May be private citizens, academic institutions, for-profit, non-profit, small biotech, industry, etc.