Up and Coming Research Radiopharmaceuticals
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Objective

I. Theranostics
II. Classic Theranostic Agent
III. Role of PET
IV. Research Diagnostic Agents
V. Research Therapeutic Agents
VI. Role of a Nuclear Pharmacist

Assessment Question

1. An example of a classic theranostic agent:
   a. Cu-64
   b. Zr-89
   c. I-131
   d. All of the above because I am not sure.
Assessment Question
2. F-18 FLT is used for to detect/measure:
   a. Hypoxia
   b. Proliferation
   c. Glucose metabolism
   d. All of the above because FLT is pretty cool.

Assessment Question
3. Cu-64 Bombesin is used for imaging in which type of cancer?
   a. Prostate cancer
   b. Osteosarcoma
   c. Lung cancer
   d. None of the above because it does not exist!

Assessment Question
4. What are the characteristics of Ga-68? 
   (circle the answer that is most correct)
   a. Decays by positron emission
   b. Half Life -> 68 minutes
   c. Available via 68Ge-68Ga generator
   d. All of the above because I said so.
Assessment Question

5. You define your role as a nuclear pharmacist.
   a. True
   b. False

I. Theranostics: Definition

Thera(py) + (diag)nostics

II. Theranostics: Historical

Radioiodine, first theranostic agent
- First therapeutic use described in 23-79 C.E.
- First use for therapy was reported in 1941.
- 1940-1950s, uptake studies were also done.
- 1949, imaging on a rectilinear camera.
- First gamma camera, in 1952.
- First theranostic radiopharmaceutical: I-131
III. Role of PET

PET imaging + targeted radionuclide therapy = Theranostic Approach

Characteristics of PET RPs

Traditional RPs vs PET RPs

Annihilation Photon Generation via Positron Decay (Emission)

18F-FDG

- 2-[18F]fluoro-2-deoxyglucose or 18F-Fluoro-deoxy-glucose, most widely used
- Similar in structure to glucose
- FDA approved indications:
  - Epileptic foci in the brain
  - Myocardial glucose metabolism
  - Tumor glucose metabolism
  - Alzheimer’s Disease and Fronto-temporal dementia
18F-FDG PET and PET/CT Practice Guidelines in Oncology

A summary of the recommendations and practice guidelines of professional groups

April 2013

The recommendations and practice guidelines of professional organizations regarding the use of 18F-fluorodeoxyglucose (FDG) PET and PET/CT in oncology are summarized on the following pages for the nine indications approved by the Centers for Medicare and Medicaid Services (CMS). The summary is intended to serve as an educational tool for referring physicians, as well as nuclear medicine physicians and technologists. The summary does not include all published guidelines. Practice guidelines are revised and updated periodically, and new guidelines are written. Readers are advised to check the websites of professional organizations as well as published literature for current information.

- Head/Neck
- Thyroid
- Breast
- Lung
- Esophageal
- Colorectal
- Cervical
- Melanoma
- Lymphoma

**Shortcoming:**
- Not a specific tracer
- Targets glucose metabolism
- Inflammation vs tumor
- High uptake areas: brain, bowel & excretion

*New RPs are needed!*

**PET Radionuclides**

<table>
<thead>
<tr>
<th>Nuclide</th>
<th>Half-Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-18</td>
<td>110 min.</td>
</tr>
<tr>
<td>C-11</td>
<td>20 min.</td>
</tr>
<tr>
<td>N-13</td>
<td>10 min.</td>
</tr>
<tr>
<td>O-15</td>
<td>2 min.</td>
</tr>
<tr>
<td>Cu-64</td>
<td>12.7 hrs.</td>
</tr>
<tr>
<td>Sr-89</td>
<td>3.3 days</td>
</tr>
<tr>
<td>Y-86</td>
<td>14.7 hrs.</td>
</tr>
<tr>
<td>Ga-68</td>
<td>68 min.</td>
</tr>
<tr>
<td>Rb-82</td>
<td>1.3 min.</td>
</tr>
</tbody>
</table>

*Courtesy Los Alamos National Laboratory: http://periodic.lanl.gov/default.htm*
Two of the positron emitting nuclides are available from generator systems:

- Rubidium-82
- Gallium-68
Novel Imaging Agents

- Physical Half-lives ~ vector biological half life

->F-18 and Ga-68
Vs.
->Cu-64, Y-86 and Zr-89

IV. Research Diagnostic Agents: Cancer Imaging

Fluorine-18

$^{18}$F
F-18 Fluorothymidine
Proliferation

[18F]Fluorothymidine

- An analog of thymidine
- Detect/Monitor tumor proliferation
- Marker for DNA synthesis
- Phosphorylated by thymidine kinase

Imaging Agent: [F-18] FLT
Human Studies

Clinical Trials.gov

F-18 Fluoromisonidazole
Hypoxia
F-18 Fluoromisonidazole

FMISO
- 1H-1-(3-[18F]-fluoro-2-hydroxy-propyl)-2-nitro-imidazole or [18F]-fluoromisonidazole
- Azomycin-based hypoxic cell sensitizer
- As a radiolabeled agent, used to image and quantitate tumor hypoxia
- Dose ≤ 10 mCi

Nitroimidazole

How Nitroimidazole works:
- Bind to oxygen-deprived cells covalently
- FMISO is trapped, provides image of hypoxia via PET
- Reversible in the presence of oxygen
- Renal elimination

FMISO: Human Studies
Tumor Hypoxia Imaging


FMISO vs Cu-64 ATSM

Copper-64

$^{64}$Cu
Cu-64 Bombesin

Prostate Cancer

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Chemical structure of $^{64}$Cu-CB-TE2A-AR06


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<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>Clinical Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{64}$Cu-trastuzumab</td>
<td>Breast Cancer (HER2)</td>
</tr>
<tr>
<td>$^{64}$Cu-Nanoparticles</td>
<td>Atherosclerotic plaques</td>
</tr>
<tr>
<td>$^{64}$Cu-DOTA-cetuximab</td>
<td>Cervical Cancer</td>
</tr>
<tr>
<td>$^{64}$Cu-PTSM</td>
<td>Neurology/neuropsychiatry</td>
</tr>
<tr>
<td>$^{64}$Cu-TETA-OC</td>
<td>Neuroendocrine Tumors</td>
</tr>
</tbody>
</table>

Gallium-68

$^{68}$Ga

Continued rapid growth in $^{68}$Ga applications: update 2013 to June 2014.


Increase Interest in Ga-68

Gallium-68

- Decays by positron emission
- Half Life -> 68 minutes
- Stable 68Ga(3+) complexes
- Available via 68Ge-68Ga generator

68Ge-68Ga generator

- Consist of parent 68Ge
- Decays to 68Ga
- Yield ≥ 80%
Ga-68 DOTA Peptides

**Neuroendocrine Tumor**

**Ga-68 Human Studies**

**NETs imaging**

<table>
<thead>
<tr>
<th>AGENT</th>
<th>Target</th>
<th>Claim to Fame</th>
<th>NID Study Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{68}$Ga-DOTA-octreotide</td>
<td>SSTR2, SSTR3, some SSTR3</td>
<td>SSTR imaging sensitivity 56-100%</td>
<td>FDA approved, widely used.</td>
</tr>
<tr>
<td>$^{68}$Ga-DOTATATE</td>
<td>Primarily SSTR2</td>
<td>Staging and search for unknown primary</td>
<td>Vanderbilt University</td>
</tr>
<tr>
<td>$^{68}$Ga-DOTANOC</td>
<td>SSTR2, SSTR3, SSTR5</td>
<td>Localize primary tumors and metastases</td>
<td>Indiana University</td>
</tr>
<tr>
<td>$^{68}$Ga-DOTATOC</td>
<td>SSTR2, SSTR3, SSTR5</td>
<td>Useful in assessment for PRRT with $^{90}$Y-TOC/177Lu-TATE</td>
<td>University of Iowa</td>
</tr>
</tbody>
</table>
Zirconium-89

$^{89}\text{Zr}$

Zirconium-89

- Radiometal, Cyclotron produced
- Decays by positron emission, 395 keV
- Half Life $\geq 78.4$ hours
- “Immuno-PET”
**89Zr Research Tracers**

Table 1. Overview of the described preclinical and clinical studies using 89Zr-labeled antibodies.

<table>
<thead>
<tr>
<th>Target</th>
<th>Type of tracer</th>
<th>Targeting vector</th>
</tr>
</thead>
<tbody>
<tr>
<td>CUBV7</td>
<td>Protein</td>
<td>CD38-185</td>
</tr>
<tr>
<td>CUBV6</td>
<td>Novel Heat Shock</td>
<td>CD38-185</td>
</tr>
<tr>
<td>CD52</td>
<td>Monoclonal antibody</td>
<td>CD38-185</td>
</tr>
<tr>
<td>EGFR</td>
<td>Peptide</td>
<td>HER2</td>
</tr>
<tr>
<td>GPC2*</td>
<td>Stck</td>
<td>HER2</td>
</tr>
<tr>
<td>HER1</td>
<td>Cytokinetic</td>
<td>HER2</td>
</tr>
<tr>
<td>ICR-1</td>
<td>Herceptin</td>
<td>HER2</td>
</tr>
<tr>
<td>LMCA</td>
<td>Monoclonal antibody</td>
<td>HER2</td>
</tr>
<tr>
<td>PRIMA</td>
<td>Protein</td>
<td>HER2</td>
</tr>
<tr>
<td>PRED</td>
<td>Serum</td>
<td>HER2</td>
</tr>
<tr>
<td>VEGF*</td>
<td>Breast, head, and neck squamous cell carcinoma and ovarian</td>
<td>HER2</td>
</tr>
</tbody>
</table>

**TARGETED** → Tissue Specific Delivery  
**RADIONUCLIDE** → Use of Radiation  
**THERAPY** → Treatment
Therapy: “TARGETED”

Therapy: “Radionuclide”

<table>
<thead>
<tr>
<th>Nuclide</th>
<th>Emission</th>
<th>Half-life</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac-225</td>
<td>alpha</td>
<td>30d</td>
<td>Accelerator</td>
</tr>
<tr>
<td>At-211</td>
<td>alpha</td>
<td>7.2h</td>
<td>Accelerator</td>
</tr>
<tr>
<td>Ra-223</td>
<td>alpha</td>
<td>11.4d</td>
<td>Generator</td>
</tr>
<tr>
<td>Bi-212</td>
<td>alpha</td>
<td>60.6min</td>
<td>Generator</td>
</tr>
<tr>
<td>Bi-213</td>
<td>alpha</td>
<td>45.7min</td>
<td>Generator</td>
</tr>
<tr>
<td>Lu-177</td>
<td>beta/gamma</td>
<td>6.7d</td>
<td>Reactor</td>
</tr>
<tr>
<td>I-131</td>
<td>beta/gamma</td>
<td>8d</td>
<td>Reactor</td>
</tr>
<tr>
<td>Y-90</td>
<td>beta</td>
<td>2.67d</td>
<td>Generator</td>
</tr>
</tbody>
</table>

Therapy: “TARGETED”

PRESS RELEASE

Advanced Accelerator Applications (AAA) announces Pivotal Phase 1 NETTER-1 Study of Lu技术 in Patients with Mid/High Neuro Endocrine Tumors.

Today, Advanced Accelerator Applications (AAA) announces the start of the pivotal Phase 1 NETTER-1 clinical study investigating the treatment of Neuro Endocrine Tumors (NETs). The NETTER-1 study is a Phase 1 clinical trial designed to evaluate the safety and efficacy of advanced accelerator technology for the treatment of NETs. The study will evaluate the use of Lu-177 radiotherapy in patients with advanced, progressive, and refractory NETs. The study is expected to enroll up to 50 patients worldwide, and results will be presented at the 2015 American Society of Clinical Oncology (ASCO) meeting.

18/12/2015
Therapy: Ac-225

A Phase I/II Study of Low-Dose Cytarabine and Lintuzumab Ac-225 in Older Patients with Previously Untreated Acute Myeloid Leukemia

**Full Title**
A Phase I/II Study of Low-Dose Cytarabine and Lintuzumab Ac-225 in Older Patients with Previously Untreated Acute Myeloid Leukemia

**Purpose**
This randomized, double-blind, placebo-controlled trial was designed to evaluate the safety and efficacy of low-dose cytarabine in combination with lintuzumab in older patients with previously untreated acute myeloid leukemia. The study aimed to determine the maximum tolerated dose (MTD) and assess the clinical benefit of this combination therapy.

**Two-part protocol**
1. Dose Escalation of 225Ac-Lintuzumab (MTD).
2. Efficacy to control AML.

Therapy: Ra-223

Randomized, double-blind protocol
1. Ra-223 dichloride VS
2. Placebo, saline

Theranostics: I-124/I-131

Selumetinib-Enhanced Radioiodine Uptake in Advanced Thyroid Cancer

VI. Role of the Nuclear Pharmacist

What can the Nuclear RPh do?

• Participate in protocol development
• Coordinate with RS, Compliance, IRB
• Acquire RPs (where, when and how much $)
• Outside Vendor Credentialing
• Resolve possible RAML issues
• Train on RP safe handling procedures
• Develop dispensing procedures
• Create patient information handouts
NM clinical protocols: coordination

1. Reviewers
2. RS
3. NMPRC
4. CRC
5. IRB
6. IND/RDRC

Examples of Documents:
What can the Nuclear RPh do?

Future Prospect of PET: nearly endless...

Role of a Nuclear Pharmacist: virtually boundless...

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