Theranostics: NeuroEndocrine Applications, and Emerging Areas (Prostate, Myeloma)

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Use of molecular targeting vectors (e.g. peptides) labeled with diagnostic and therapeutic radionuclide.
Targeted Molecular Imaging and Therapy

Maintain High Affinity

Chemistry

Chelator Binding In Vivo

Stable Radiometal

Therapy

DOTA

225Ac

223Ra

212Pb

90Y

68Ga

Imaging

Therapy

Chemistry

Linker

Ligand

Target

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Neuroendocrine Tumors: Somatostatin Receptors

• 5 Subtypes; sstr2 primary target in NETs

• Transmembrane glycoproteins

• Internalization after binding SST

• Located on neuroendocrine tumor cells as well as activated leukocytes
Low Grade (G1): 
Less than 2 mitosis/10 hpf & Ki-67<3%

Intermediate Grade (G2): 
2-20 mitosis/10 hpf & Ki-67: 3-20%

High Grade (G3): 
>20 mitosis/10 hpf & Ki-67>20%
## Significant Improvement with Ga-68 DOTA Peptides over Conventional Octreoscan

<table>
<thead>
<tr>
<th></th>
<th>In-111 DTPA Octreotide (Octreoscan) SPECT</th>
<th>Ga-68 DOTA Octreotide PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution</td>
<td>10–15 mm</td>
<td>4–6 mm</td>
</tr>
<tr>
<td>Binding Affinity (IC50)</td>
<td>22 ± 3.6</td>
<td>2.5 ± 0.5</td>
</tr>
<tr>
<td>Radiation Dose per standard dosage</td>
<td>2.6 rem</td>
<td>0.4 rem</td>
</tr>
<tr>
<td>Radioisotope Production</td>
<td>Cyclotron</td>
<td>Generator</td>
</tr>
<tr>
<td>Convenience</td>
<td>2 day procedure; 3 visits</td>
<td>90min procedure, single visit</td>
</tr>
</tbody>
</table>
57 year old with ileal carcinoid, status post surgery, radiation therapy for metastases in the breast and left femur, rising serotonin.
Patient with ileal NET, s/p resection of primary and retroperitoneal nodes, considered for liver transplant
Status post resection of ileal NET 1 year ago, with increasing chromogranin A and pancreastatin.

Ileal NET s/p surgery with elevated CgA.
Ga-68 DOTATOC vs. In-111 Octreotide

- 84 pts, 13 for unknown primary, 36 staging, 35 posttx f/u
- Clinically relevant additional information to CI in 21%
- Unknown primary or residual tumor at primary site in 5 pts
- Unknown bone mets in 9 patients

Peptide Receptor Radiotherapy for NETs
BASELINE

$^{68}$Ga DOTATOC PET-CT
Treatment Protocol Y-90-DOTATOC

- Imaging to confirm presence of somatostatin receptors on tumors

- Typically 3 cycles of Y-90 DOTATOC, 120 mCi per cycle, every 6-9 week intervals

- Intravenous infusion given over 20 minutes with appropriate radiation shielding

- Co-infusion over 4 hours of 2 Liters of amino acid solution to reduce Y-90 DOTATOC uptake in kidneys

- Outpatient
Y-90 DOTATOC is administered typically with a fixed dose approach, using 2.78-4.44 GBq per cycle over 2-4 cycles.

Personalized dosimetry can guide the amount of administered activity to maximize tumor dose while not exceeding toxic levels to the kidneys, which is the critical organ PRRT.

Y-90 predominantly emits beta particles, which can be imaged with Bremsstrahlung radiation albeit with relatively low resolution. Y-90 also has a minor decay branch that results in emission of positrons that allow imaging with new generation time-of-flight PET/CT scanners.
Multiple approaches to enhance the therapeutic efficacy of PRRT for NETS

- High LET radionuclide
- Target modulation (Receptor upregulation)
- Peptide structure (High Binding Affinity)
**α Particle properties**

- **Mass**: $m_\alpha = 10^{-27}$ kg
- **Energy**: 4-9 MeV

<table>
<thead>
<tr>
<th>Nuclide</th>
<th>Energy (MeV)</th>
<th>Range (Cells)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^90$Y</td>
<td>2</td>
<td>200</td>
</tr>
<tr>
<td>$^{131}$I</td>
<td>1</td>
<td>40</td>
</tr>
<tr>
<td>$^{211}$At</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>$^{210}$Po</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

- **Properties**
  1. Massive
  2. High Energy
  3. Short Range
  4. DNA Breaks (DS)
  5. Lethal

Boudousq et al., PLoS ONE 8(7) 2013

**β Particle properties**

- **Mass**: $m_\beta = 10^{-31}$ kg
- **Energy**: ≤2 MeV

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**Tumor growth and survival curves after $^{212}$Pb-DOTATOC treatment.** BON-1 bearing mice were divided into 3 groups (Control, 120 µCi single dose, and 3 fractionated doses of 50 µCi, 50 µCi, and 20 µCi). $^{212}$Pb-DOTATOC was injected accordingly via tail vein. (n=9 for control, n=10 for the other groups)
Gallium-68 PSMA PET/CT for Prostate Cancer
70-y-old patient with PSMA-avid lymph node metastases on 68Ga-PSMA PET/CT before therapy (A) and on 177Lu-PSMA scintigraphy after first PSMA RLT (B), with remarkable reduction in uptake after second PSMA RLT (C). Richard P. Baum et al. J Nucl Med 2016;57:1006-1013
[68Ga]Pentixafor PET/CT and [18F]FDG PET/CT A–D Maximum intensity projections (MIP) of [68Ga]Pentixafor (A) and [18F]FDG PET/CT (B) of a 68-year-old male with histologically proven multiple myeloma indicating the better lesion-to-background contrast for [...]
Lu-177 Pentixather for Treatment of Multiple Myeloma

Imaging –

- Ga-88 Dototate FDA approved. 1/17 transitional pass-through payment from CMS
- Ga-88 Dototoc Uiowa preparing NDA (not exclusive) which will allow billing. Requires a radiochemist but will likely be cheaper than a commercial kit
- May bill for cost recovery for drug preparation in clinical trials.
  - Our direct costs. Independent CPA estimate of costs, submitted to FDA for approval
  - ~80% of insurance is covering (pre-Auth)

Treatment

- No FDA approval or coverage yet
- Filling for cost recovery for Y-90 Leu177 Dototate may be approved this spring (one private group in TX)
FDA believes that in most cases the cost of an investigational drug in a clinical trial intended to support a marketing application is an ordinary cost of doing business.

The purpose of permitting charging for an investigational drug in a clinical trial is to permit a sponsor to recover the costs of making certain drugs when clinical trials could not be conducted without charging because the cost of the drug.

A sponsor authorized to charge for its drug in a clinical trial can only recover its direct costs.
Theranostics: Strengths

• Active basic science research in identification of new targets for theranostics of neoplasms

• Expertise in Imaging

• Expertise in Dosimetry of Unsealed Radiation Sources

• Expertise with the Regulatory Environment of Radiopharmaceuticals
Funding environment for clinical trials to develop new agents

Developing a referral base, changing the practice from reading room to clinic

The number of radiologists involved with theranostics

Training the physician-scientists needed to develop the next generation of theranostic agents