A Promising Step for Prostate Cancer Treatment

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Development of PSMA Imaging Agents for Prostate Cancer Patient Management

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Disclosures

• Grant Support
  • DoD Prostate Cancer Research Program under grant W81XWH-14-1-0603
  • NIH SBIR R44 CA192451 grant subcontract from Cancer Targeted Technology (CTT)

• Cancer Targeted Technology Clinical Trial support

• Prostascint ($^{111}$In-Capromab Pendetide) is an FDA approved tracer

• All other PSMA radiopharmaceuticals in this presentation are in preclinical development or in clinical evaluation under FDA IND or CTA (clinical trial authorization – Europe)
CPE Information

• Target Audience: Pharmacists
• ACPE#: 0202-0000-19-041-L04-P
• Activity Type: Knowledge-based
Learning Objectives

• Describe the development of prostate specific membrane antigen (PSMA) imaging agents.

• Recognize the key molecular structures that are characteristic of PSMA imaging agents.

• Define the distribution of PSMA imaging agents in prostate and other cancer patients.

• Discuss how PSMA imaging informs patient management.

• Define the key differences between $^{68}$Ga and $^{18}$F PSMA agents.
Assessment Questions

1. Where is Prostate Specific Membrane Antigen found in the human body?
   A. In the blood
   B. In prostate cancer, renal cell carcinoma, hepatocellular carcinoma, lacrimal and parotid glands, and prostate tissue
   C. In prostate tissue and prostate cancer
   D. Not in normal tissues – only cancerous tissues
2. What attributes favor $^{18}$F-PSMA versus $^{68}$Ga-PSMA

A. Higher positron energy and wider availability of $^{68}$Ga-PSMA from generators
B. Longer $^{18}$F half-life and lower dose of $^{18}$F-PSMA injected
C. Longer $^{18}$F half-life and better image quality
D. Lower injection dose of $^{18}$F-PSMA versus $^{68}$Ga-PSMA
3. Which response is not a limitation of PSMA PCa imaging
   A. Urinary excretion of the agents may hinder detection of lesions near the prostate
   B. Androgen deprivation therapy may improve the sensitivity of PSMA imaging
   C. Uptake in the salivary and lacrimal glands may reduce the dose of tracer that may be injected
   D. $^{68}$Ga half-life may be challenging for imaging at 3 h post injection, the optimal imaging time point
Overview

• Prostate Cancer Progression
• PSMA Background
• PSMA Imaging Agent Development
• Comparison of $^{18}$F and $^{68}$Ga PSMA imaging agents
• Change in patient management
Prostate Cancer Progression

Men with suspected prostate cancer

Diagnose Stage

Localized or Locally advanced

Metastatic PCa

Castration Resistant PCa (CRPC)

Treatment Emergent?

Biphenotypic Expression?

Neuroendocrine PCa (NEPC)

AR$^{\text{Neg}}$; PSA$^{\text{neg}}$; Chromogranin A$^{\text{pos}}$

Persistent Androgen Dependent PCa (PADPC)

Active Surveillance
Prostatectomy
Radiation Therapy
Chemotherapy
Cryotherapy
Brachytherapy

Abiraterone (androgen synthesis enzyme inhibitor)

Enzalutamide (AR antagonist)

Androgen Pathway Independent PCa (APIPC)

ADT
Management of Prostate Cancer Patients

Cooperberg et al., JAMA 314:80-82, 2015
Prostate Specific Membrane Antigen

- PSMA is a glutamate carboxypeptidase (GPCII), N-acetyl-a-linked acidic dipeptidase I (Naaladase I) or a folate hydrolase
- Substrates:
  - Peptide/ small molecule α- or γ- linked glutamates
  - Poly-γ-glutamated folates
  - N-Acetyl-L-aspartyl-L-glutamate
- Naaladase hydrolyze N-Acetyl-L-aspartyl-L-glutamate to NAA and glutamate in synapses in brain.
- Plays a role in pain, brain trauma, stroke, spinal cord injury, schizophrenia, diabetic neuropathy, ALS, and drug addiction
- Kozikowski et al., evaluated structure activity relationships of naaladase inhibitors these were the starting point for current small molecule tracers.

Kozikowski et al., J. Med..Chem. 44:298-301, 2001
Prostate Specific Membrane Antigen

- 100 kDa transmembrane protein
- Not released in circulation
- Internalized upon inhibitor binding
- Highly expressed (>90%) in prostate cancer cells/tissue at all stages esp.
  - High-grade tumors
  - Androgen independent
  - Metastatic tumors
- Also expressed in non-prostatic solid tumor neovasculature
- Low level expression in healthy prostate, kidney, liver, small intestine and brain

Davis et al. PNAS, 102:5981-5986, 2005
First PSMA Imaging Agent – $^{111}$In-labeled Antibody for SPECT

- ProstaScint® ($^{111}$In-Capromab Pendetide)
  - FDA approved October 1996
- Murine Antibody
- Targets the intracellular domain of the PSMA
- Antibody uptake into cells limited. May only be taken up in dying cells where permeability is compromised
- Imaged up to 72 hours after injection
- Poor sensitivity and specificity
- Limited Use
First PSMA Imaging Agent – $^{111}$In-labeled Antibody for SPECT
Extracellular Domain Targeting Antibodies

\[ \text{ProstaScint} \]

\[ \text{111In-J591 (Bander)} \]

Molecular Classes of PSMA Inhibitors

- PSMA ligands of these classes tested in pre-clinical studies showed tumor uptake peaking at 0.5-1 h post-injection
- This best matches labeling with F-18 ($T_{1/2} = 110$ min) and Ga-68 ($T_{1/2} = 68$ min)
- When modifying binding ligand with a chelator, a spacer is required to enhance affinity
- Having multiple negative charges in the linker region minimizes non-target tissue uptake while not affecting tumor uptake
- For the urea-based agents, introduction of a hydrophobic naphthyl group significantly increased tumor uptake and reduced kidney uptake
- Phosphoramidate based inhibitors are irreversible

Lutje et al. Theranostics, 2015; 5:1388-1401
Potent PSMA Inhibitor

2-(phosphonomethyl)pentanedioic acid
(2-PMPA)
$IC_{50} \ 0.2 \text{ nM}$

Strong chelation between
a) phosphonate group to zinc ion in the active site
b) glutamate of the inhibitor with the C-terminal glutamate in the recognition site

Progress in PSMA Diagnostics
Iodine Labeled Urea-based Imaging Agents

$^{11}$C / $^{18}$F Urea-Based Imaging Agents

$[^{18}F]$DCFBC

$[^{18}F]$DCFPyL

$^{18}$F- PSMA-1007

18F-Phosphoramidate-based Agent

Behr, S. et al., *JNM* 2019 in press
CTT1057 – First-in-Human Study

PSA 65.9 ng/mL

• CTT1057 binds to PSMA with high affinity
• Rapidly internalized
• Uptake in primary prostate tissue correlates with PSMA immunohistochemical staining on tissue slices from prostatectomy tissue.
• Similar distribution to the urea-based agents
• Focal uptake seen in lesion that did not identified on standard of care imaging.

Behr, S. et al., *JNM* 2019 in press
Patient #10 PSA = 27.5 ng/mL

CTT1057
PSMA

PSMA – Sagittal image of the spine

CT – Sagittal image of the spine

Bone Scan

Behr, S. et al., *JNM* 2019 in press
**99mTc Urea-based Imaging Agents**

**99mTc-MIP-1404**

**99mTc-MIP-1405**

Bone Scan

**99mTc-MIP-1404**

Phase 3 clinical trials sponsor Progenics, Inc.

Hillier et al., JNM 54:1369-76, 2013
Vallabhajosula et al., JNM 55:1791-98, 2014
PSMA I&T, PSMA I&S

M = $^{68}$Ga, $^{111}$In, $^{177}$Lu

PSMA I&F

Schottelius, M. et al., *JNM* 60:71-78, 2019
$^{68}$Ga Urea-based Imaging Agents

PSMA-11 aka HBED-CC

PSMA-617
Ga PSMA-11 and 177Lu-PSMA617 Imaging

Imaging Response to AR Inhibition

Pre ADT  Post ADT

13 Lesions  22 Lesions

Hope, et al., JNM 58:81-84
Imaging Response to AR inhibition

- Upregulation of PSMA post ADT increases imaging sensitivity
- Increased uptake of PSMA may be the basis for $^{177}$Lu-PSMA therapy
- PSMA response may be used to evaluate new AR-based therapies

Hope, et al., *JNM* 58:81-84
Comparison of PET Imaging Isotopes

<table>
<thead>
<tr>
<th></th>
<th>$^{68}$Ga</th>
<th>$^{18}$F</th>
<th>$^{89}$Zr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-Life</td>
<td>68.3 m</td>
<td>109.8 m</td>
<td>78.4 h</td>
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<tr>
<td>Positron Energy</td>
<td>1.898 MeV</td>
<td>0.635 MeV</td>
<td>0.9 MeV</td>
</tr>
<tr>
<td>Availability</td>
<td>Generator (cyclotron) Limited</td>
<td>Widely Available</td>
<td>Regional Cyclotron</td>
</tr>
<tr>
<td>Injection Quantity</td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Image Quality</td>
<td>less background than Ga</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Comparative Dosimetry $^{68}$Ga / $^{18}$F PSMA

| Table: Dosimetry (OLINDA 1.1, ICRP60) comparison of PET imaging agents targeting PSMA |

<table>
<thead>
<tr>
<th>Absorbed Dose (mGy/MBq)</th>
<th>18F-CTT1057</th>
<th>68Ga-PSMA-11</th>
<th>18F-DCFPyL</th>
<th>18F-PSMA-1007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ</td>
<td>This work</td>
<td>Afshar-Oromieh et al.</td>
<td>Szabo et al.</td>
<td>Giesel et al.</td>
</tr>
<tr>
<td>Adrenals</td>
<td>9.39E-03</td>
<td>1.42E-02</td>
<td>3.11E-02</td>
<td>1.94E-02</td>
</tr>
<tr>
<td>Brain</td>
<td>5.82E-03</td>
<td>9.00E-03</td>
<td>2.19E-02</td>
<td>7.20E-03</td>
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<tr>
<td>Breasts</td>
<td>5.15E-03</td>
<td>8.80E-03</td>
<td>4.57E-03</td>
<td>8.06E-03</td>
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<tr>
<td>Gallbladder Wall</td>
<td>1.43E-02</td>
<td>1.44E-02</td>
<td>1.44E-02</td>
<td>2.22E-02</td>
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<tr>
<td>LLI Wall</td>
<td>1.23E-02</td>
<td>1.23E-02</td>
<td>1.05E-02</td>
<td>4.83E-02</td>
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<tr>
<td>Small Intestine</td>
<td>9.36E-03</td>
<td>1.63E-02</td>
<td>9.13E-03</td>
<td>1.56E-02</td>
</tr>
<tr>
<td>Stomach Wall</td>
<td>7.54E-03</td>
<td>1.20E-02</td>
<td>1.16E-02</td>
<td>1.42E-02</td>
</tr>
<tr>
<td>ULI Wall</td>
<td>8.82E-03</td>
<td>5.40E-02</td>
<td>1.67E-02</td>
<td>4.08E-02</td>
</tr>
<tr>
<td>Heart Wall</td>
<td>1.79E-02</td>
<td>1.09E-02</td>
<td>1.29E-02</td>
<td>2.51E-02</td>
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<tr>
<td>Kidneys</td>
<td>6.74E-02</td>
<td>1.62E-01</td>
<td>9.45E-02</td>
<td>1.70E-01</td>
</tr>
<tr>
<td>Liver</td>
<td>1.59E-02</td>
<td>3.09E-02</td>
<td>3.80E-02</td>
<td>6.05E-02</td>
</tr>
<tr>
<td>Lungs</td>
<td>1.33E-02</td>
<td>1.02E-02</td>
<td>1.08E-02</td>
<td>1.11E-02</td>
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<tr>
<td>Muscle</td>
<td>7.22E-03</td>
<td>1.05E-02</td>
<td>6.32E-03</td>
<td>1.00E-02</td>
</tr>
<tr>
<td>Pancreas</td>
<td>9.12E-03</td>
<td>1.38E-02</td>
<td>2.44E-02</td>
<td>1.92E-02</td>
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<tr>
<td>Red Marrow</td>
<td>7.04E-03</td>
<td>9.20E-03</td>
<td>1.04E-02</td>
<td>1.33E-02</td>
</tr>
<tr>
<td>Osteogenic Cells</td>
<td>9.15E-03</td>
<td>1.42E-02</td>
<td>9.58E-03</td>
<td>1.55E-02</td>
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<tr>
<td>Skin</td>
<td>4.98E-03</td>
<td>8.85E-02</td>
<td>4.05E-03</td>
<td>7.30E-03</td>
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<tr>
<td>Spleen</td>
<td>1.60E-02</td>
<td>4.46E-02</td>
<td>1.85E-02</td>
<td>7.39E-02</td>
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<tr>
<td>Testes</td>
<td>1.03E-02</td>
<td>1.04E-02</td>
<td>1.01E-02</td>
<td>8.37E-03</td>
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<tr>
<td>Thymus</td>
<td>6.71E-03</td>
<td>9.90E-03</td>
<td>5.56E-03</td>
<td>9.90E-03</td>
</tr>
<tr>
<td>Thyroid</td>
<td>5.46E-03</td>
<td>9.70E-03</td>
<td>8.56E-03</td>
<td>8.50E-03</td>
</tr>
<tr>
<td>Urinary Bladder Wall</td>
<td>2.82E-01</td>
<td>1.30E-01</td>
<td>8.64E-02</td>
<td>1.87E-02</td>
</tr>
</tbody>
</table>

**Effective Dose (mSv/MBq)**

- $^{68}$Ga-PSMA-11: 2.01E-02
- 18F-DCFPyL: 2.36E-02
- 18F-PSMA-1007: 1.39E-02
- 18F-CTT1057: 2.20E-02
Comparison of Normal Organ SUVs

<table>
<thead>
<tr>
<th>Organs</th>
<th>Median SUVmean</th>
<th>Median SUVmean</th>
<th>Median SUVmean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacrimal</td>
<td>2.58</td>
<td>6.66</td>
<td>7.5</td>
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<tr>
<td>Parotid</td>
<td>3.35</td>
<td>13.62</td>
<td>16.1</td>
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<tr>
<td>Submandibular Gland</td>
<td>3.82</td>
<td>15.65</td>
<td>17.3</td>
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<tr>
<td>Blood pool</td>
<td>2.22</td>
<td>1.37</td>
<td>1.8</td>
</tr>
<tr>
<td>Liver</td>
<td>3.46</td>
<td>5.51</td>
<td>6.8</td>
</tr>
<tr>
<td>Kidney</td>
<td>8.39</td>
<td>33.5</td>
<td>49.6</td>
</tr>
<tr>
<td>Spleen</td>
<td>2.86</td>
<td>6.6</td>
<td>9.1</td>
</tr>
<tr>
<td>Duodenum</td>
<td>2.25</td>
<td>9.35</td>
<td>13.8</td>
</tr>
<tr>
<td>Bone marrow (Iliac crest)</td>
<td>0.8</td>
<td>0.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1.55</td>
<td>2.28</td>
<td>2.9</td>
</tr>
</tbody>
</table>

* - Data from 14 UCSF Ga68-PSMA-11 patients

Behr, S. et al., JNM 2019 in press
PSMA Imaging – Does it change patient management?

<table>
<thead>
<tr>
<th>Study</th>
<th>Total Patients</th>
<th>Positive 68Ga-PSMA PET/CT</th>
<th>Management Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afaq et al., JNM 2018</td>
<td>100</td>
<td>42%</td>
<td>39%</td>
</tr>
<tr>
<td>Sterzing et al., EJNMMI 2016</td>
<td>42</td>
<td>73.5%</td>
<td>60.5%</td>
</tr>
<tr>
<td>Shakespeare et al., Radiat Oncol 2015</td>
<td>54</td>
<td>57.6%</td>
<td>53.7%</td>
</tr>
<tr>
<td>Dewes et al., Radiat Oncol 2016</td>
<td>15</td>
<td></td>
<td>53.3%</td>
</tr>
<tr>
<td>Albisinni et al., BJU Int 2017</td>
<td>131</td>
<td>75%</td>
<td>75%</td>
</tr>
<tr>
<td>Morigi et al., JNM 2015</td>
<td>38</td>
<td>68%</td>
<td>63%</td>
</tr>
<tr>
<td>Roach et al., JNM 2018</td>
<td>431</td>
<td></td>
<td>51%</td>
</tr>
</tbody>
</table>

68Ga-PSMA detected new disease sites in many patients.
UCSF Multiparametric $^1$H Prostate MRI

- 597 prostate cancer patients scanned in 2013 – prior to and after therapy
- > 7,000 patients in UCSF prostate imaging database.
- The magnitude of $^1$H mpMRI changes related to Gleason grade
Integrated Approach to PCa Imaging in Patient Management

- Multiparametric $^1$H MRI
- Hyperpolarized (HP) $^{13}$C MRI
- Multi-HP probe Approach
- New HP Probes

- PET/MRI
- PET/CT
- New PET Probes

- Image guided Biopsies
Closing remarks/conclusion

• A number of PSMA-targeting imaging agents have been discovered and are under evaluation in pre-clinical models and clinical trials. PSMA tolerates significant bulk.

• These agents have demonstrated high uptake in primary and metastatic prostate tumors.

• Uptake is seen in some normal tissues such as lacrimal, parotid and submandibular glands, prostate tissue and clearance organs, kidney and bladder.

• PSMA is not specific to prostate cancer and has been imaged in renal cell carcinoma and hepatocellular carcinoma among others.

• PSMA-based imaging is high relevant in men with biochemical recurrence, especially with low PSA, where disease is not evident on conventional imaging.
1. Where is Prostate Specific Membrane Antigen found in the human body?
   A. In the blood
   B. In prostate cancer, renal cell carcinoma, hepatocellular carcinoma, lacrimal and parotid glands, and prostate tissue
   C. In prostate tissue and prostate cancer
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