Preclinical evaluation of $^{212}$Pb-based radiopharmaceutical therapy of prostate cancer

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Prostate-Specific Membrane Antigen (PSMA)

- Type II transmembrane protein
- Associated with aggressive prostate cancer (85-95% late stage patients)
- Present in solid tumor neovasculatures
- Marker of androgen signaling

High-affinity radiometal-based agents

Banerjee et al.  
PSMA-based radiotherapeutics: Radiometals

- To reduce toxicity in normal tissues
- Selection of radiometal to match the disease stage
- Risk/benefit of $\beta$- vs. $\alpha$-particle radiometals
- 40–60% patient respond to $^{177}$Lu-PSMA-617
The decay chain of $^{212}\text{Pb}$

- In vivo $\alpha$-particle nanogenerator of $^{212}\text{Bi}$
- Potential imaging ($\gamma$-ray) capabilities
- Half-life 10.6 hours
$^{86}\text{Y}/^{68}\text{Ga}$-labeled PET radiotracers


Advanced Accelerator Applications (AAA-Novartis)

$^{86}\text{Y}/^{177}\text{Lu}/^{68}\text{Ga-SRVI71}$

Courtesy: Dr. Richard Baum

$^{68}\text{Ga-SRVI71}$
Structure-activity relationship study: \(^{177}\text{Lu}\)-labeled compounds

Banerjee et al.  
Preclinical evaluation by $^{203}$Pb-labeled analogs

<table>
<thead>
<tr>
<th>Compound</th>
<th>$K_i$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>0.2-0.5</td>
</tr>
<tr>
<td>L2</td>
<td>8.5-10.3</td>
</tr>
<tr>
<td>L3</td>
<td>5.8-9.5</td>
</tr>
<tr>
<td>L4</td>
<td>6.3-7.8</td>
</tr>
<tr>
<td>L5</td>
<td>0.2-0.4</td>
</tr>
<tr>
<td>Pb-L2</td>
<td>10.1-15.3</td>
</tr>
<tr>
<td>Pb-L3</td>
<td>11.1-17.1</td>
</tr>
<tr>
<td>Pb-L5</td>
<td>0.5-0.9</td>
</tr>
<tr>
<td>DCIBzL</td>
<td>0.01-0.06</td>
</tr>
</tbody>
</table>

Fast renal clearance for $^{203}$Pb-L2, $^{203}$Pb-L3, $^{203}$Pb-L4 with TCMC chelating agent

(Banerjee et al. J Nucl Med 2020)
Time-dependent tissue uptake ($^{203}\text{Pb}$-labeled analogs)

[Graphs and images showing time-dependent tissue uptake in blood, kidney, and PSMA+ tumor for 1, 2, 4, and 24 hours.]
Radiopharmaceutical therapy: $^{212}$Pb-L2

High treatment efficacy in PSMA+ flank tumor model and PSMA+ micrometastatic model (100 uCi, single administration)

Tumor model: PSMA+/PSMA- PC3 flank

Study design

- Cell Injection
- Activity

Days post-treatment

Percent survival ($V_t/V_0 < 10$)

0 10 20 30 40 50 60 70 80 90

0

20

40

60

80

100

PIP Control (13 d)
PIP (1.5 MBq) (25 d)
PIP (3.7 MBq) (39 d)
flu Control (14.5 d)
flu (1.5 MBq) (7.5 d)
flu (3.7 MBq) (16 d)

control
$^{177}$Lu-PSMA-617 (37 MBq)
$^{212}$Pb-L2 (3.7 MBq)
Long-term radiotoxicity data

Dose-limiting organ: kidney
Maximum tolerated activity: ~ 40 μCi (1.5 MBq)
No hematologic toxicity
**Study design**

**Treatment group (kBq)**
- 0 (n=8), 9.3 (n=5), 18.5 (n=5), 37 (n=8), 74 (n=8)
- 9.3 x 2 (n=5), 18.5 x 2 (n=8)

**Activity injection**
- 0 (V_t/V_o ≤ 10)
- 7 (V_t/V_o ≤ 10)
- 56

**Acute toxicity study**
- 0, 37, 74
- 18.5 x 2 (n=3)

**Treatment group (kBq)** for acute toxicity (n=3)
- 0 kBq (PSMA+)
- 0 kBq (PSMA-)
- 18.5 kBq x 2 (PSMA-)
- 9.3 kBq (PSMA+)
- 9.3 kBq x 2 (PSMA+)
- 18.5 kBq (PSMA+)
- 18.5 kBq x 2 (PSMA+)
- 37 kBq (PSMA+)
- 37 kBq x 2 (PSMA+)

**Probability of V_t/V_o**
- DAYS AFTER START OF TREATMENT (d)

**Relative tumor volume (V_t/V_o)**

**PSMA+ (0 kBq)**
- Safe and effective activity
- 18.5 kBq x 2 (7 days apart)
$^{225}$Ac-L1 vs. $^{177}$Lu-L1

- **Percent survival**
  - Days after start of treatment [d]
  - Control (0 kBq)
  - $^{177}$Lu-L1 (37 MBq)
  - $^{225}$Ac-L1 (37 kBq)
  - $^{225}$Ac-L1 (74 kBq)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Median survival (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 kBq</td>
<td>47</td>
</tr>
<tr>
<td>37 MBq</td>
<td>48</td>
</tr>
<tr>
<td>37 kBq</td>
<td>56</td>
</tr>
<tr>
<td>74 kBq</td>
<td>79</td>
</tr>
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</table>

**Tumor model:**
PSMA+ micrometastatic

**Higher efficacy of $^{225}$Ac-L1 compared to $^{177}$Lu-L1**

**Alpha-camera imaging**

- $^{225}$Ac-L1: Fast renal cortical clearance
Summary

Significant therapeutic efficacy in PSMA+ PC3 PIP flank tumor model

Efficacy of α-particle emitting agents ($^{212}$Pb/$^{225}$Ac) in micrometastatic model

Optimized radiotheranostic agent, $^{68}$Ga/$^{177}$Lu-PSMA-R2 (NCT03490838)

Towards translation of $^{212}$Pb as a clinical therapeutic; getting the lead in! (Brechbiel et al. 2011, Dalton Trans)

Development and dosimetry of $^{203}$Pb/$^{212}$Pb-labelled PSMA ligands: bringing “the lead” into PSMA-targeted alpha therapy? (Santos et al. 2019, Eur J Nucl Med Mol Imaging)
Acknowledgement

Our Team

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DOE Isotope Program

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