RRMC – Santa Fe, NM

$^{203}\text{Pb}/^{212}\text{Pb}$ Theranostics for Cancer

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Disclosures

Michael K Schultz PhD is Chief Science Officer, Viewpoint Molecular Targeting, Inc.

No drugs presented are FDA approved.

Michael K Schultz has been selected as Best Dad Ever, 2018.

Selection Committee
$^{203}$Pb/$^{212}$Pb Theranostics for Cancer

- Theranostics
- Rationale for $\alpha$-particle therapy (vs $\beta$)
- Radionuclides for $\alpha$-particle therapy
- $^{203}$Pb/$^{212}$Pb based theranostics
- Preclinical imaging/therapy
- Production Chemistry
- Summary – promise and challenges
Theranostic Concepts

Combination of two words:

- **Therapeutic + Diagnostic**

- Sometimes referred to as Theragnostics and “Diapeutics.”

- Use of molecules that are labeled with radioactive atoms to identify cancer; and use the same molecule (or very closely related) to treat the cancer.

Enthusiasm about $\alpha$
Targeting Cancer Cells

- **Theranostic Agent**
  - Selective Binding to Cancer Cells
  - No Binding to Normal Cells
Designing Theranostics

1. Target

Binding

2. Ligand

3. Radiation Cage

Biochemistry | Chemistry | Radiochemistry
Designing Theranostics

Target

Binding

Ligand

Diagnostic atom

Gamma Rays

PET scans
SPECT scans

Biochemistry | Chemistry | Radiochemistry
Designing Theranostics

Target

Binding

Ligand

Therapeutic atom

Alpha-Beta particles

Biochemistry | Chemistry | Radiochemistry
Theranostics – Patient Care

- Patient presents with symptoms or other tests that indicate a particular cancer.
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- Patient presents with symptoms or other tests that indicate a particular cancer.
- Patient is injected with the diagnostic form.
- A medical scan is performed after a time for accumulation in the tumors.
- A dose plan is made by doctors.
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- A dose plan is made by doctors.
- Patient is treated with the therapeutic form.
- Response can be monitored with diagnostic form.
Value of Theranostics

- Diagnostic can be used to select patients for therapeutic clinical trials.
- Diagnostic can be used to develop a plan for the therapeutic dose.
- Particularly useful early in the clinical phase of development

Cancer Patients

Diagnostic Imaging

Negative for Target  Positive for Target

Conventional Therapy  Targeted Therapy
Why pursue alpha particle vs beta particle therapy?

68Ga-PSMA-11 PET/CT scans of patient A. Pretherapeutic tumor spread (A), restaging 2 mo after third cycle of 225Ac-PSMA-617 (B), and restaging 2 mo after one additional consolidation therapy (C). Clemens Kratochwil et al. J Nucl Med 2016;57:1941-1944

12/2014
PSA = 2,923 ng/mL

7/2015
PSA = 0.26 ng/mL

9/2015
PSA < 0.1 ng/mL
Why pursue alpha particle therapy?

Progression after beta particle therapy.

Virtual complete response to alpha therapy.


**α vs β particle properties**

<table>
<thead>
<tr>
<th>Particle</th>
<th>Mass</th>
<th>Energy</th>
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</thead>
<tbody>
<tr>
<td>β-</td>
<td>$10^{-31}$ kg</td>
<td>&lt;2 MeV</td>
</tr>
<tr>
<td>α</td>
<td>$10^{-27}$ kg</td>
<td>4-9 MeV</td>
</tr>
</tbody>
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- **Falzone et al., TheraNostics, 2018**
  - Modeled RBE of $^{212}$Pb vs $^{177}$Lu
  - $^{212}$Pb may be more effective in short range

- **Lee et al., Radiation Research, 2018**
  - Depth-dose distributions $^{212}$Pb vs $^{225}$Ac
  - Internalization improves RBE
Promising $\alpha$-Emitter “Series”

- Actinium-225 (Ac-225, $^{225}$Ac) 10 d
- Lead-212 (Pb-212, $^{212}$Pb) 11 h
- Thorium-227 (Th-227, $^{227}$Th) 18 d
- Radium-223 (Ra-223, $^{223}$Ra) 11 d
- Astatine-211 (At-211, $^{211}$At) 7 h

$m_1 v_1 = m_2 v_2$
**Ac vs Pb**

**Actinium-225**
- $T_{1/2} = 10$ d ($5 \alpha$'s)
- Central prod./distr.
- Capacity? Impurity?
- Fast daughter ingrowth
- mAbs (biological $T_{1/2}$)
- “Stable” Bi endproduct
- No matching imaging isotope

**Lead-212**
- $T_{1/2} = 11$ h ($2 \alpha$’s)
- $^{224}$Ra Generator ($T_{1/2} = 3.7$ d)
- Slower daughter ingrowth
- Peptides, small molecules
- $^{212}$Bi generator possible
- Stable Pb endproduct
- $^{203}$Pb elementally matched
**203Pb/212Pb Theranostic Pair**

- **203Pb** – diagnostic

  - $^{203}\text{Pb} \rightarrow ^{203}\text{Tl}$ (EC; stable)
  - 279 keV gamma (SPECT; $I = 81\%$)
  - $T_{1/2} = 52\;\text{h}$ (patient selection and dosimetry)

- **212Pb** – therapeautic

  - $^{212}\text{Pb} \rightarrow ^{212}\text{Bi}$ ($\beta$; $I = 100\%$)
  - Two $\alpha$’s in “series” ($^{212}\text{Bi}$ and $^{212}\text{Po}$)
  - $T_{1/2} = 11\;\text{h}$ (peptides, small molecules, faB's, RNA aptamers)

Li et al., 2017 *Appl. Rad. Isot.*
212/203Pb Chelators

DOTA  
TCMC  
PSC

Commercially Available

Iowa
Specifications

1. Full Automated
2. Single use cassettes
3. Sterile
4. Pyrogen free
5. Radiochemical Purity
6. Radionuclidic Purity
7. Rapid
8. Reproducible
9. $^{203}\text{Pb}$ and $^{212}\text{Pb}$

MLPT System

Li et al., 2017 ARI
203Pb Cyclotron Production/Purification

- 203Pb – Production/Impurities

  25 MeV

  205Tl (p, 3n) 203Pb

  203Tl (p, 3n) 201Pb (T1/2 = 9.33 hours; 90 h hold)

  205Tl (p, 2n) 204mPb (T1/2 = 1.12 hours)

  203Pb (T1/2 = 51.92 hours) → 203Tl Stable

  201Pb (T1/2 = 9.33 hours) → 201Tl (T1/2 = 72.91 hours)

  204mPb (T1/2 = 1.12 hours) → 204Pb Stable
  (small, optimizing)

Lantheus Medical Imaging

Li et al., 2017 Appl. Rad. Isot.
$^{203/212}\text{Pb}$ Purification

**Rapid Elution**

- Elution
  - 100mg resin
  - Acetae Buffer
  - Breakthrough
    - 50mg resin
    - 2M HCl

**Removal of impurities**

- $^{203}\text{Tl}$ (p, 3n) $^{201}\text{Pb}$ ($T_{1/2} = 9.33$ hours; 90 h hold)
- $^{205}\text{Tl}$ (p, 2n) $^{204m}\text{Pb}$ ($T_{1/2} = 1.12$ hours)
- $^{203}\text{Pb}$ ($T_{1/2} = 51.92$ hours)
- $^{201}\text{Pb}$ ($T_{1/2} = 9.33$ hours)
- $^{204m}\text{Pb}$ ($T_{1/2} = 1.12$ hours)
- $^{204}\text{Pb}$ Stable

**Manageable Pb breakthrough**

Li et al., ARI 2017
212Pb Production/Decay

Generator

228Th
2 y

224Ra
4 d

α

220Rn
1 min.

α

216Po
0.1 s

β

212Bi
60 min.

α

212Po
0.3 μs

β

212Pb
11 h

β

208Pb
stable

208Tl
3 min.

α

Process Basics
1. Ra-224 Generator Shipped.
2. Pb-212 Eluted from Generator.
3. Pb-212 Chelated to Ligand.
4. Pb-212 labeled ligand injected.

Potential: 2 α + 3 β

Li et al., 2017 Appl. Rad. Isot.
$^{212}\text{Pb}$ Production/Purification

- **Generators** (ORNL; Orano Med)

**Impurities**

- **Metals** ($\text{Fe}$, Ni, Cu, Tl, Ba, Pb)
  - Purification Pb-resin (Eichrom Technologies)

- **Radionuclides**
  - Th-228/232, Ra-224, U-232, actinides $\alpha$-spec. (<MDA)
  - Ra-224 breakthrough (<MDA)

Li et al., 2017 Appl. Rad. Isot.
Image-guided therapy for cancer

• Metastatic melanoma

Cancer of the skin
Melanoma is fastest growing cancer incidence in the US
Most diagnosed cancer in young adults under 30 years
Very poor prognosis for metastatic disease
Target: Melanocortin subtype 1 receptor (MC1R)

• Neuroendocrine tumors

Enigmatic cancer of the endocrine system
Poor prognosis
Current therapies are largely palliative
Target: somatostatin subtype 2 receptor (SST2R)
$^{203}\text{Pb}$ SPECT/CT (SST2R+ models)

$[^{203}\text{Pb}]\text{DOTATOC SPECT}$

**A**

- BON-1
- IMR-32

**B**

- IMR-32 Blocking

**NET/Carcinoid**

**Neuroblastoma**

Lee et al., In Prep

SUPPORTED BY THE IOWA NEUROENDOCRINE TUMOR SPORE
$^{203}$Pb SPECT (MC1R+ model)

No Blocking

Blocking

Li et al., Molecular Pharmaceutics, 2019
VMT-\(\alpha\)-NET Preclinical Development

\[\text{[}^{203}\text{Pb}]\text{DOTATOC} \quad \text{[}^{203}\text{Pb}]\text{PSC-TOC} \quad \text{[}^{203}\text{Pb}]\text{PSC-PEG2-TOC (VMT-\(\alpha\)-NET)}\]

A. 3 h

** vs DOTATOC

*** vs DOTATOC

p<0.008

B. 24 h

** vs DOTATOC

p<0.02

*** vs DOTATOC

p<0.006

C. Tumor-to-kidney ratio in %ID/g

*** vs DOTATOC

p<0.003

VMT-\(\alpha\)-NET improved tumor:kidney 8-fold vs DOTATOC
[\textsuperscript{212}Pb]VMT-\(\alpha\)-NET therapy. 5.0\times10^6 AR42J rat pancreatic acinar cells were implanted on the left shoulder of athymic nu/nu female mice. After 1 week, when the average tumor size became around 150 mm\(^3\), 274 MBq (7.4 mCi) \textsuperscript{212}Pb were reacted with 30 nmol VMT-\(\alpha\)-NET (9.1 MBq/nmol) in the presence of ascorbic acid (1 mg/ml) for 20 min at 85 °C. After reaction, the radio-peptide were purified by C-18 and resuspended with saline ascorbic acid (1 mg/ml). 0.37 MBq (10 \(\mu\)Ci) and 1.85 (50 \(\mu\)Ci) of \textsuperscript{212}Pb- VMT-\(\alpha\)-NET were injected via tail vein. DL-lysine (400mg/kg) was co-injected to block the kidney uptake of the radiotherapeutic.
VMT-α-NET survival benefit and tolerability

**Survival after $^{212}$Pb therapy**

- Untreated
- 10 $\mu$Ci
- 50 $\mu$Ci

**Body weight**

- Untreated
- 10 $\mu$Ci
- 50 $\mu$Ci

Days after therapy

Average body weight (g)
Promising Summary

- $^{203}\text{Pb} / ^{212}\text{Pb}$ a promising *theranostic* pair
  - $T_{1/2}$'s – peptides, small molecules, aptamers, fAb’s
- $\alpha$-particle therapy has potential advantages (vs $\beta$)
  - High LET
- Production/impurities (purifications) suitable to advance to clinical radiopharmaceuticals
  - Automated production (Li *et al.*, *Appl Rad Isot.*, 2017)
- Improved chelator for $\text{Pb}^{2+}$ is promising – modeling could explain improved labeling observed.
- Initial $^{203}\text{Pb}$ NIST standardization completed
Thank you! Questions?

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US NIH R01EB017279
US NIH I-CORPS NIH HHSN261201500069C
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