Production of Alpha-emitting Radionuclides for Cancer Therapy

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Outline

• Background
• Availability of $^{225}\text{Ac}/^{213}\text{Bi}$ and $^{224}\text{Ra}/^{212}\text{Pb}$ generator systems through natural decay of $^{229}\text{Th}$ and $^{228}\text{Th}$
• New Initiatives to Enhance Production of Ac-225
  a. Direct production of $^{225}\text{Ac}$ in a high energy proton accelerator
  b. Reactor Production of $^{229}\text{Th}$ at ORNL High Flux Isotope Reactor (Nuclear Data)
  c. Production of $^{229}\text{Th}$ via low energy protons (Nuclear Data)

• Xofigo, 1st approved “targeted” alpha therapy (TAT) for treatment of advanced prostate cancer

• $^{227}\text{Ac}$ production: larger scale pilot demonstration
Isotope production, enrichment and distribution began at Oak Ridge just after WWII.
ORNL’s unique combination of radioisotope research and production assets

• High Flux Isotope Reactor (HFIR)
  – LWR, flux trap; 85 MW full power; peak thermal neutron flux of $2.1 \times 10^{15} \text{n.cm}^{-2}.\text{s}^{-1}$

• Hot Cell and Processing Facilities
  – Five active nuclear facilities including REDC and one radiological facility

• On path to reestablishing enrichment capabilities
Alpha-Emitting and Other Novel Therapeutic Medical Radioisotopes Available from ORNL

Alpha emitters:
- Actinium-225/Bismuth-213
- Radium-224/Lead-212
- Actinium-227/Thorium-227/Radium-223

High-energy Beta emitter:
- Tungsten-188/Rhenium-188

Low-energy Beta emitter:
- Strontium-89

Sample of Ac-225 in glovebox at REDC. Ac-225 has medical applications in the treatment of leukemia and many other cancers.
Therapeutic Nuclear Medicine

• Targeted therapy
  – α, β, γ emitters delivered to diseased tissue

• Strategies
  – Molecular targeting: Monoclonal antibodies, peptides, etc; \(^{90}\)Y, \(^{177}\)Lu, \(^{213}\)Bi
  – Natural targeting: Thyroid (\(^{131}\)I), Bone(\(^{89}\)SrCl\(_2\), \(^{223}\)RaCl\(_2\), \(^{153}\)Sm & \(^{188}\)Re Phosphate complexes, \(^{117m}\)Sn-DTPA), Liver (\(^{90}\)Y & \(^{166}\)Ho particles)
  – Brachytherapy: Prostate cancer (\(^{103}\)Pd, \(^{125}\)I, \(^{131}\)Cs), others

“Xofigo, 1st α-emitting radioisotope (\(^{223}\)RaCl\(_2\)), for treatment of bone cancer, received approval from FDA and European Commission in 2013”

“Zevalin”, 1st β-emitting radioisotope (\(^{90}\)Y-Ibritumomab tiuxetan) for treatment B cell non-Hodgkin's lymphoma

Prostate Cancer Seed
Alpha-Emitters for Therapeutic Applications

• Important attributes
  – High linear energy transfer
  – Half-life compatible with therapy
  – Versatile Chemistry
  – Availability

• Alpha-emitters of interest
  – $^{212}$Bi (60 m) and $^{213}$Bi (46 m)
  – $^{212}$Pb (10 h)/$^{212}$Bi
  – $^{225}$Ac (10 d)/$^{213}$Bi
  – $^{211}$At (7 h, accelerator produced)
  – $^{223}$Ra (11 d)
  – $^{227}$Th (19 d)/$^{223}$Ra

Radioimmunotherapy

ORNL $^{225}$Ac/$^{213}$Bi Generator
Availability of $^{225}\text{Ac}/^{213}\text{Bi}$ and $^{224}\text{Ra}/^{212}\text{Pb}$ generator systems through natural decay of $^{229}\text{Th}$ and $^{228}\text{Th}$

- Radiochemical extraction from $^{229}\text{Th}$ and $^{228}\text{Th}$ sources

$^{233}\text{U}/^{229}\text{Th}$

- $^{209}\text{Bi}$ (stable)
- $^{209}\text{Pb}$ (3.3 h)
- $^{208}\text{Pb}$ (stable)
- $^{217}\text{Rn}$ (0.5 ms)
- $^{213}\text{Po}$ (3.7 μs)
- $^{212}\text{Po}$ (0.3 μs)
- $^{212}\text{Bi}$ (60.6 m)
- $^{212}\text{Pb}$ (10.6 h)
- $^{208}\text{Tl}$ (3.1 m)
- Radioactive halflives: 0.3 μs, 64%, 3.1 m, 36%...

$^{232}\text{U}/^{228}\text{Th}$

- $^{228}\text{Th}$ (1.91 y)
- $^{224}\text{Ra}$ (3.66 d)
- $^{220}\text{Rn}$ (55.6 s)
- $^{226}\text{Ra}$ (14.9 d)
- $^{217}\text{Rn}$ (0.5 ms)
- $^{213}\text{Po}$ (3.7 μs)
- $^{213}\text{Bi}$ (45.6 m)
- $^{212}\text{Bi}$ (60.6 m)
- $^{212}\text{Pb}$ (10.6 h)
- $^{208}\text{Tl}$ (3.1 m)
- Radioactive halflives: 0.3 μs, 64%, 3.1 m, 36%...
Radioimmunotherapy (RIT) Concept

- **Radionuclide**
- **Chelator (or fullerene?)**
- **Linker**
- Typical attachment to amine group on Lysine
- **Method for Targeting Cancer Cell Epitopes:** Antibody or Fragment, Peptide
Polyaminocarboxylate (PAC) Chelators and Fullerenes
Radioimmunotherapy treated control

Day 0

Day 1

Day 3

Day 5

Kennel and Mirzadeh, 2000
**225**Ac - A Promising Isotope for α-Therapy

Treatment of Acute Myelogenous Leukemia (AML) with Bismuth-213

Posterior 60-Minute Summation

Rate/Minute

Dose 1

Dose 4

Patient No. 4

Courtesy of Actinium Pharmaceutical Inc. and Sloan Kettering Cancer Center, NY
Peptide receptor α-therapy of glioblastoma with Bi-213

Courtesy of Alfred Morgenstern at ITU

Before treatment

7 weeks post 3rd treatment

5 weeks post 1st treatment

9 weeks post 4th treatment

5 weeks post 2nd treatment

treatment continued to date : 5 cycles)

Overall survival: >23 months

Patient 6 – Glioblastoma grade IV (male, 59 y)
Nanoparticles Platform for in-vivo Delivery of Radionuclides
LaPO₄ Nanoparticles Platform for in-vivo Delivery of Actinium-225

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Half-life</th>
<th>α-Energy (MeV)</th>
<th>α-Recoil Energy (keV)</th>
<th>Recoil Range (nm)</th>
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<tbody>
<tr>
<td>$^{225}$Ac</td>
<td>10 d</td>
<td>5.829</td>
<td>107</td>
<td>20</td>
</tr>
<tr>
<td>$^{221}$Fr</td>
<td>4.9 m</td>
<td>6.341</td>
<td>116</td>
<td>22</td>
</tr>
<tr>
<td>$^{217}$At</td>
<td>32.3 ms</td>
<td>7.067</td>
<td>130</td>
<td>24</td>
</tr>
<tr>
<td>$^{213}$Bi</td>
<td>46 m</td>
<td>8.376</td>
<td>154</td>
<td>29</td>
</tr>
</tbody>
</table>

In-vitro Release of $^{225}$Ac, $^{221}$Fr and $^{213}$Bi from La($^{225}$Ac)PO₄ NPs
Core/Shell Design of LaGd\(^{\text{225}}\)Ac nanoparticles

\[ \text{La}^{3+} \text{(TPP}^5\text{)}_2 \rightarrow \text{La}^{3+} \text{(TPP}^5\text{)}_2 \rightarrow \text{GdPO}_4 \text{ Shells} \]

\[ \text{LaGd}^{(225}\text{Ac}) \text{PO}_4 \text{ Core} \]

LaGd\(^{225}\)Ac nanoparticles are synthesized by a core-shell approach. The core is composed of LaGdPO\(_4\) nanoparticles, and the shell is made of GdPO\(_4\). The reaction involves the formation of LaGd\(^{\text{225}}\)Ac complex in the core, followed by the formation of GdPO\(_4\) shell at 90 °C for 3 h.
SPECT/CT of $^{225}$AcLaPO$_4$ Targeted Nanoparticles

MAb 201B-NP

MAb 201B-NP & cold MAb

MAb 14-NP control
Background of Actinium-225 Production at ORNL

- ORNL has been the main supplier of $^{225}\text{Ac}$ (via decay of existing $^{229}\text{Th}$ stock) since 1997, with an annual budget of $1.8$ M.

- $700$-$900$ mCi of $^{225}\text{Ac}$ is harvested annually from $130$–$900$ mCi $^{229}\text{Th}$ stock at ORNL.

- $6$-$12$ campaigns are performed per year, and campaign 126 is currently underway.

Rationale for R&D related to production of $^{225}\text{Ac}$

- The present supply of $^{225}\text{Ac}$ is insufficient for current medical and research demands of $\sim6$ Ci/year.

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Annual Production of Ac-225

![Graph showing annual production of Ac-225](image-url)
Production $^{225}$Ac from Decay of $^{229}$Th

Theoretical Ac-$^{225}$ Yield from Ra-$^{225}$ Decay
(At t=0, Ra activity = 60 mCi)

Growth and Decay of $^{225}$Ra and $^{225}$Ac Separated from $^{229}$Th at 60 d
($N_0 = 1$ Ci $^{229}$Th)

Radioactivity, mCi

Ac-$^{225}$ separated and shipped at time-interval shown below

At t=0, Ra activity = 60 mCi

Production $^{225}$Ac from Decay of $^{229}$Th
New Initiatives to Enhance Production of Ac-225

- Direct production of $^{225}$Ac in a high energy proton accelerator
- Reactor Production of $^{229}$Th at ORNL High Flux Isotope Reactor (Nuclear Data)
- Production of $^{229}$Th via low energy protons (Nuclear Data)
Direct production of $^{225}$Ac in a proton accelerator

The new collaboration between ORNL, BNL and LANL aims at developing a plan for full-scale production and stable supply of $^{225}$Ac by irradiating $^{232}$Th targets in the BNL BLIP and LANL IPF, and target processing at ORNL.

ORN2L Contributions:

- Develop the processing chemistry

- Evaluate yields and impurities

- Construct and evaluate $^{225}$Ac/$^{213}$Bi Generator

- Provide Ac and generator to selected customers for in vivo evaluation

1st publication of tri-lab efforts: Griswold et al, Large Scale Accelerator Production of $^{225}$Ac: Effective Cross Sections for 78-192 MeV Protons Incident on $^{232}$Th Targets (in print, App. Rad. Isot., 2016)
Challenges Associated with Accelerator-Based Production of $^{225}$Ac -- Complex Chemistry

**Thorium Target Mass:**
1-10 g – initial mass, 50-100 g – anticipated for Ci-level targets

**Production of Radiolanthanides:**
Significant challenge to separate trivalent Ln-isotopes from $^{225}$Ac (specifically $^{140}$La and $^{141}$Ce)

**Production of large quantities of fission products:**
In the 100-200 MeV proton energy range, for every mCi of $^{225}$Ac, 12.5 mCi of fission products are produced

**Timing:** The $^{227}$Ac/$^{225}$Ac ratio (~0.2% at EOB) gets worse with time

**Toxicity:** Biological toxicity of minute amount of 0.2% $^{227}$Ac in $^{225}$Ac is not evaluated
Accelerator Production of $^{225}$Ac (cont.)
Chemical Process for Accelerator-Produced $^{225}\text{Ac}$

Proposed Ac-225 Processing Flow Sheet

LANL
BNL
ORNL
For a 10 day irradiation of a 5 g cm$^{-2}$ $^{232}$Th target at IPF or BLIP, yield of $^{225}$Ac is ~1.5 Ci at EOB with ~0.2% contamination from $^{227}$Ac

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Yield at EOB</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>IPF: 250 µA, 90 MeV</td>
</tr>
<tr>
<td></td>
<td>(Ci)</td>
</tr>
<tr>
<td>$^{225}$Ac</td>
<td>1.5</td>
</tr>
<tr>
<td>$^{226}$Ac</td>
<td>N/M</td>
</tr>
<tr>
<td>$^{227}$Ac</td>
<td>$2.7 \times 10^{-3}$</td>
</tr>
<tr>
<td>$^{227}$Th</td>
<td>6.3</td>
</tr>
<tr>
<td>$^{228}$Th</td>
<td>$2.2 \times 10^{-1}$</td>
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<tr>
<td>$^{99}$Mo</td>
<td>$1.8 \times 10^1$</td>
</tr>
<tr>
<td>$^{140}$Ba</td>
<td>3.1</td>
</tr>
<tr>
<td>$^{139}$Ce</td>
<td>$1.1 \times 10^{-2}$</td>
</tr>
<tr>
<td>$^{141}$Ce</td>
<td>1.4</td>
</tr>
<tr>
<td>$^{143}$Ce</td>
<td>1.4</td>
</tr>
<tr>
<td>$^{144}$Ce</td>
<td>$9.0 \times 10^{-2}$</td>
</tr>
</tbody>
</table>
HPLC Separation of $^{225}\text{Ac}$ from $^{140}\text{La}$ and other radiolanthanides, showing only major radioactive species.
Second HPLC Separation of $^{225}$Ac From $^{140}$La – Gradient and Chromatogram
Reactor production of Th-229

1\textsuperscript{st} term of cross-section refers to thermal and 2\textsuperscript{nd} term to resonance integrals. The values in parenthesis are fission cross-sections at thermal and epi-thermal neutrons, respectively.
Reactor Production of Thorium-229

- Projected $^{229}\text{Th}$ yield for 6 cycle irradiations: 18-23 mCi per g of $^{226}\text{Ra}$, with $^{228}\text{Th}$ and $^{227}\text{Ac}$ contaminations of 3000 and 50 times larger.

- 20 mCi of $^{229}\text{Th}$ will generate ~140 mCi of $^{225}\text{Ac}$ per year

Production of $^{229}$Th via Proton-induced Reactions on $^{232}$Th

Thorium Proton Bombardment Reaction Block Diagram

Various Excitation Functions for Proton Bombardment of $^{232}$Th

$\gamma$-Ray Spectrum of Purified Pa Fraction
(Th230-2, PaPPT-T5, 6/15/2011)
Production of $^{229}$Th via Proton-induced Reactions on $^{232}$Th

Summary

- Excitation function for the $^{232}$Th[$p,4n$]$^{229}$Pa reaction has been measured with good precision; excitation function peaks at 28 MeV, 150 mb.

- Measurements of thick target production show cross section is dominated by the following two reactions:
  
  $^{232}$Th[$p,4n$]$^{229}$Pa(1.5 d, $EC$$^{229}$Th
  $^{232}$Th[$p,α$$^{225}$Ac(63 m, $β$)$^{229}$Th

- Irradiating 1 gram of $^{232}$Th (~0.5 mm) for 1 year at 100 µA of 35 MeV protons and exiting at 25 MeV would yield ~28 mg of $^{229}$Th (5.6 mCi).

Future Work

- Additional nuclear data for short-lived $^{229}$Ac is necessary to determine cross section of $^{232}$Th[$p,α$$^{229}$Ac reaction
- The thick target yield from $^{230}$Th target expected to be 3-5 times greater than from $^{232}$Th target
$^{227}\text{Ac}$ production: larger scale pilot demonstration

- $^{227}\text{Ac}$ is made via irradiation of $^{226}\text{Ra}$ targets at HFIR

- ORNL entered into a production R&D phase shortly after hosting the 2013 International TAT conference
  Preliminary feasibility R&D was followed by two years of

1st HFIR Rabbit containing 2 Ra pellets

1st 50-mg $^{226}\text{Ra}$ pellet
Xofigo, 1st approved “targeted” alpha therapy (TAT) for treatment of advanced prostate cancer

- Prostate cancer is the second leading cause of cancer death in American men, behind lung cancer
- $^{223}\text{Ra}$ targets new bone growth, like $\text{Ca}$
- $^{223}\text{Ra}$ is derived from an $^{227}\text{Ac}$ generator

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**$^{225}\text{Ra Biodistribution}$**

Kennel and Mirzadeh, 2005

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$\alpha$ (5.7 MeV)

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$\beta$
Ra-226 target design

- Up to 13 pellets can be stacked in a welded-aluminum rabbit for irradiation at HFIR
- Total RaCO$_3$/Al volume: $\sim$1.3 cm$^3$
- Total Ra-226 mass: 0.7 g (0.749 g of RaCO$_3$)
- aluminum mass: 2.748 g
- Ra-226 mass limit based on heat calculations and the target temperature during irradiation (dose rates will limit Ra-226 mass per target to about 600 mg)

Figure 5. Configuration of 13 RaO/Al pellets for irradiation at HFIR. Some of the components include; 1) finned aluminum rabbit, 2) rabbit end caps (aluminum), 3) fill material – aluminum foil or quartz wool, and 4) radium oxide pellets (13) – 0.250” diameter and 0.125” thick.
New HFIR-HT rabbit design

- Changes were made to the rabbit design to facilitate the in-cell welding process
- The bottom cap will be EB-welded outside of the hot cell
- The circumference of the top cap will be welded first — under a helium cover gas
- The plug will be welded after evacuating the chamber and backfilling with high-purity helium (twice)

Body is aluminum alloy 6061
End caps are 4047 aluminum (required for welding)
TEAM

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Suzanne Hogle
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Dan Stracener (Project Manager, accelerator produced Ac-225 and Ac-227)
John Krueger (Oversight)