Ac-225 User Group: Production Effort to Provide Accelerator-Produced $^{225}\text{Ac}$ for Radiotherapy

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Agenda

• A brief perspective on supply/demand and alternate production methods for $^{225}\text{Ac}$

• High-energy accelerator production of $^{225}\text{Ac}$ (with $^{227}\text{Ac}$ co-product)

• Additional routes of production being pursued

• Status of Drug Master File development, FDA interactions and licensing issues
Actinium-225 Production at ORNL

- ORNL has been the main supplier of $^{225}$Ac (via decay of existing $^{229}$Th stock) since 1997
- 10 Ci of $^{225}$Ac has been shipped in 1500 packages
- 6-12 campaigns are performed per year, and campaign 156 is currently underway

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

- The present supply of $^{225}$Ac derived from $^{229}$Th is insufficient for current medical and research demands of ~6 Ci/year.
Current worldwide supply of $^{225}$Ac from $^{229}$Th/$^{225}$Ac generators is estimated at 1200-1700 mCi/yr*

Patient doses, as informed by clinical trials, are estimated at:

- $^{225}$Ac: 2-5 µCi per patient kg
  (160-640 µCi/patient)

- $^{213}$Bi: 1 mCi per patient kg
  (Optimum generator loading estimated at 100-150 mCi $^{225}$Ac)

Projection of $^{225}$Ac demand assuming multiple, approved $^{225}$Ac and $^{213}$Bi drugs and robust clinical R&D programs could be in the hundreds of Ci/year**


### Addressing the Supply Chain: Various $^{225}\text{Ac}/^{229}\text{Th}$ Production Routes

<table>
<thead>
<tr>
<th>Facility</th>
<th>Nuclear Reaction</th>
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<tbody>
<tr>
<td>Reactor (thermal neutrons)</td>
<td>$^{226}\text{Ra}(3n,g)^{229}\text{Ra} \rightarrow ^{229}\text{Ac} \rightarrow ^{229}\text{Th}$ (plus $^{228}\text{Ra}$ target)</td>
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<tr>
<td>Accelerator (electrons)</td>
<td>$^{226}\text{Ra}(\text{g,n})^{225}\text{Ra} \rightarrow ^{225}\text{Ac}$</td>
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<tr>
<td>Accelerator (low energy particles)</td>
<td>$^{226}\text{Ra}(\text{p,2n})^{225}\text{Ac}$</td>
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<tr>
<td></td>
<td>$^{226}\text{Ra}(\alpha,\text{n})^{229}\text{Th}$</td>
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<tr>
<td></td>
<td>$^{226}\text{Ra}(\text{p,pn})^{225}\text{Ra}$</td>
</tr>
<tr>
<td></td>
<td>$^{232}\text{Th}(\text{p,x})^{229}\text{Th}$</td>
</tr>
<tr>
<td>Accelerator (high energy particles)</td>
<td>$^{232}\text{Th}(\text{p,x})^{225}\text{Ac}$</td>
</tr>
<tr>
<td></td>
<td>$^{232}\text{Th}(\text{p,x})^{225}\text{Ra} \rightarrow ^{225}\text{Ac}$</td>
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<td>$^{226}\text{Ra}(\text{n,2n})^{225}\text{Ra}$</td>
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<tr>
<td>Hot Cell Facility ($^{233}\text{U}$ processing)</td>
<td>$^{229}\text{Th}$ decay to $^{225}\text{Ac}$</td>
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</tbody>
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Accelerator Production via $^{232}\text{Th}(p,x)^{225}\text{Ac}$:

Initial R&D Promised Significant Impact

<table>
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<tr>
<th>Facility</th>
<th>Anticipated Single Target Ac-225 Yields (10 day irradiation)</th>
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<tbody>
<tr>
<td>LANL (100 MeV, 250-450 µA)</td>
<td>1.3-2.3* Ci</td>
</tr>
<tr>
<td>BNL (200 MeV, 165 µA)</td>
<td>2.2 Ci</td>
</tr>
</tbody>
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*Theoretical maximum value assumed for production with 450 µA on target resulting from recent facility investments.


Facility investments at IPF and BLIP have increased our projected production capacity

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Fig. 1. Experimental and theoretical cumulative cross sections for the formation of $^{225}\text{Ac}$ by the proton bombardment of thorium.
Basis of the Tri-Lab Effort:

**Leveraging Unique Isotope Program Facilities, Capabilities, and Expertise to Address $^{225}$Ac Supply**

**ORNL** - Approximately 25 years of experience in the isolation of $^{225}$Ac from fissile $^{233}$U via $^{229}$Th

**LANL Isotope Production Facility (IPF) at LANSCE**; 100 MeV incident energy up to 275 mA for routine production

**BNL Linac at the Brookhaven Linac Isotope Producer (BLIP)** 165 μA intensity to targets at incident energies ranging from 66-202 MeV
Production of $^{225}\text{Ac}$ via high-energy accelerator results in the co-production of $^{227}\text{Ac}$ ($t_{1/2} = 21.8$ y)

Ratio improves at higher proton energy, but degrades with longer irradiation time – we understand this ratio at an exquisite level of detail.

$^{227}\text{Ac}$ co-product creates a unique set of challenges – perceptions and facility licensing (NRC), patient waste disposition.

These challenges are not unique and have been addressed for other isotope products.

Instantaneous activity ratio of $^{227}\text{Ac}$ to $^{225}\text{Ac}$ for a thin Th target as a function of proton beam energy. Note that beam energy range captures current capabilities at BNL’s BLIP and LANL’s IPF facilities.
General Accelerator-Produced $^{225}$Ac Product Conclusions

- **Accelerator-produced $^{225}$Ac performs similar to $^{229}$Th-derived $^{225}$Ac**
  - direct labeling efficiencies are comparable
  - $^{213}$Bi generator performance is the same
  - the impact of $^{227}$Ac content on dosimetry has been demonstrated to be small

- **Challenges remain with respect to the logistical considerations associated with the $^{227}$Ac co-product**
  - facility licensing (decommissioning funding plans)
  - discussions ongoing with the NRC to potentially obtain an exemption as previously done for $^{68}$Ge
  - patient waste (likely not an issue for an approved drug)
Alternative Routes of Production Under Investigation

- ANL electron linac production route
  \( ^{226}\text{Ra}(\gamma,n)^{225}\text{Ra} \rightarrow ^{225}\text{Ac} \)
- BNL low energy cyclotron route
  \( ^{226}\text{Ra}(p,2n)^{225}\text{Ac} \)
- ORNL neutron production route
  \( ^{226}\text{Ra}(3n,\gamma)^{229}\text{Ra} \rightarrow ^{229}\text{Ac} \rightarrow ^{229}\text{Th} \)
DMF/FDA Updates

• Drug Master File was submitted in December 2019 for the accelerator Ac-225

• DMF filings are anticipated for:
  – CY2020 ($^{229}$Th-derived $^{225}$Ac product)

• Interaction with the Food and Drug Administration is ongoing in reference to both products

• We are committed to making these products available to our customers/the medical community and are happy to address any further questions
Summary

• The Tri-Lab effort is routinely producing $^{225}\text{Ac}$ and product is available for end users and shipments to multiple users have been completed

• We have distributed over 325 mCi of accelerator produced $^{225}\text{Ac}$ to evaluators

• We are working with companies and research hospitals in preparation to support Phase I trials - DMF will be submitted late this calendar year

• $^{227}\text{Ac}$ content is clinically insignificant from a dosimetry/toxicity perspective – but challenges with perception and regulatory compliance remain; we have a well-defined forward path to address these challenges with DOE
Thank You!

For more information: [https://isotopes.gov/](https://isotopes.gov/)