Isotope Program
U.S. Department of Energy

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

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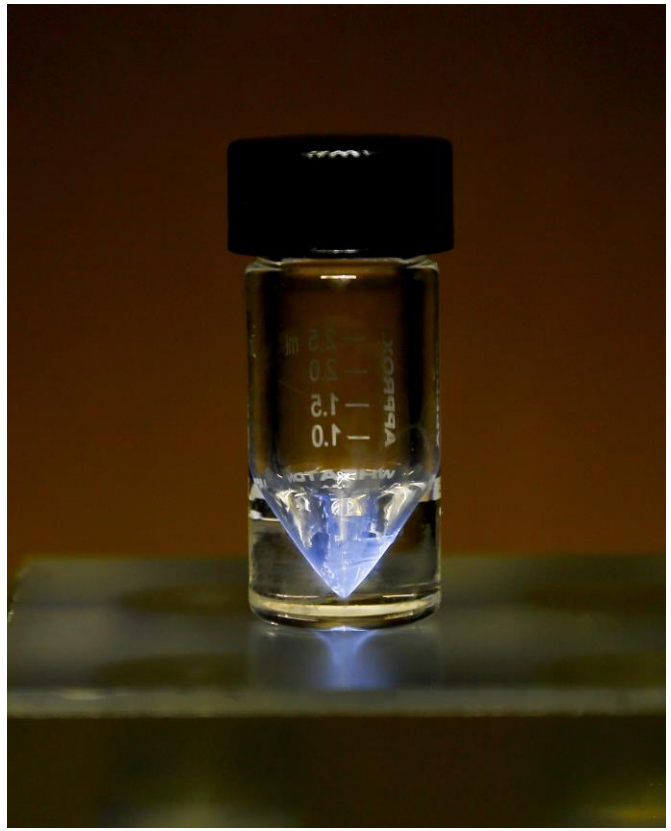
Agenda

- A brief perspective on supply/demand and alternate production methods for ^{225}Ac
- High-energy accelerator production of ^{225}Ac (with ^{227}Ac co-product)
- Status of Drug Master File development, FDA interactions and licensing issues
- Roundtable presentations on experiences with accelerator-produced ^{225}Ac
- Open Forum



ORNL ^{225}Ac Finished Product

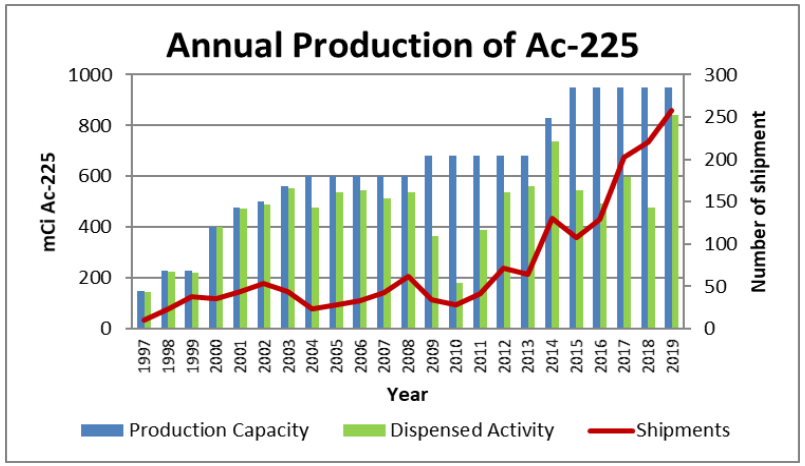
Actinium-225 Production at ORNL

- 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 148 is currently underway

^{233}U
↓ α 1.6x10^{5}
^{229}Th
↓ α 7.9x10^{3}
^{225}Ra
↓ β 15 d
^{225}Ac
↓ α 10 d

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.



^{225}Ac Supply & Demand

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*

*International Atomic Energy Agency. Technical Meeting Report "Alpha Emitting Radionuclides and Radiopharmaceuticals for Therapy" IAEA Headquarters Vienna, Austria, June **2013**

US DOE Offices of Nuclear Energy and Nuclear Physics "2008 Workshop on The Nation's Needs for Isotopes: Present and Future" Rockville, MD August **2008

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

Facility	Nuclear Reaction
Reactor (thermal neutrons)	$^{226}Ra(3n,g)^{229}Ra \rightarrow ^{229}Ac \rightarrow ^{229}Th$ (plus ^{228}Ra target)
Accelerator (electrons)	$^{226}Ra(g,n)^{225}Ra \rightarrow ^{225}Ac$
Accelerator (low energy particles)	$^{226}Ra(p,2n)^{225}Ac$ $^{226}Ra(a,n)\ ^{229}Th$ $^{226}Ra(p,pn)\ ^{225}Ra$ $^{232}Th(p,x)\ ^{229}Th$
Accelerator (high energy particles)	**$^{232}Th(p,x)^{225}Ac$** $^{232}Th(p,x)^{225}Ra \rightarrow ^{225}Ac$
Accelerator (high energy neutrons)	$^{226}Ra(n,2n)\ ^{225}Ra$
Hot Cell Facility (^{233}U processing)	^{229}Th decay to ^{225}Ac

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Accelerator Production via $^{232}Th(p,x)^{225}Ac$:

Initial R&D Promised Significant Impact

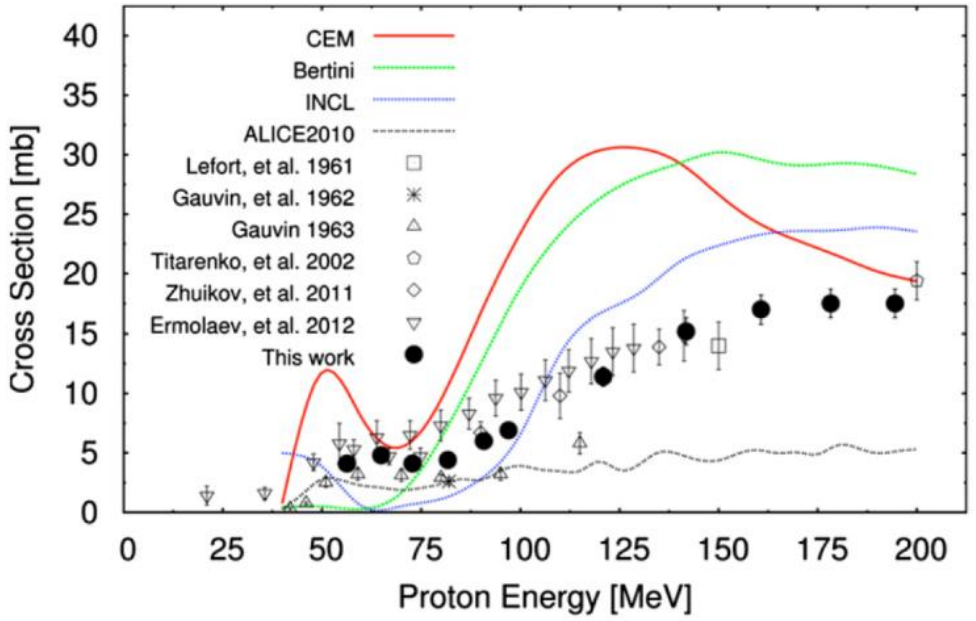

Fig. 1. Experimental and theoretical cumulative cross sections for the formation of ^{225}Ac by the proton bombardment of thorium.

Facility	Anticipated Single Target Ac-225 Yields (10 day irradiation)
LANL (100 MeV, 250-450 μA)	1.3-2.3* Ci
BNL (200 MeV, 165 μA)	2.2 Ci

** Theoretical maximum value assumed for production with 450 μA on target resulting from recent facility investments.*

*J.W. Weidner et al. Appl. Radiat. Isot. 70 (**2012**) 2602*
*J.W. Engle et. al. Phys. Rev. C. 88 (**2013**) 014604*
*J.W. Engle et. al. Radiochim. Acta 102 (**2014**) 569*
*J.R. Griswold et. al. Appl. Radiat. Isot. 118 (**2016**) 366*

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

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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

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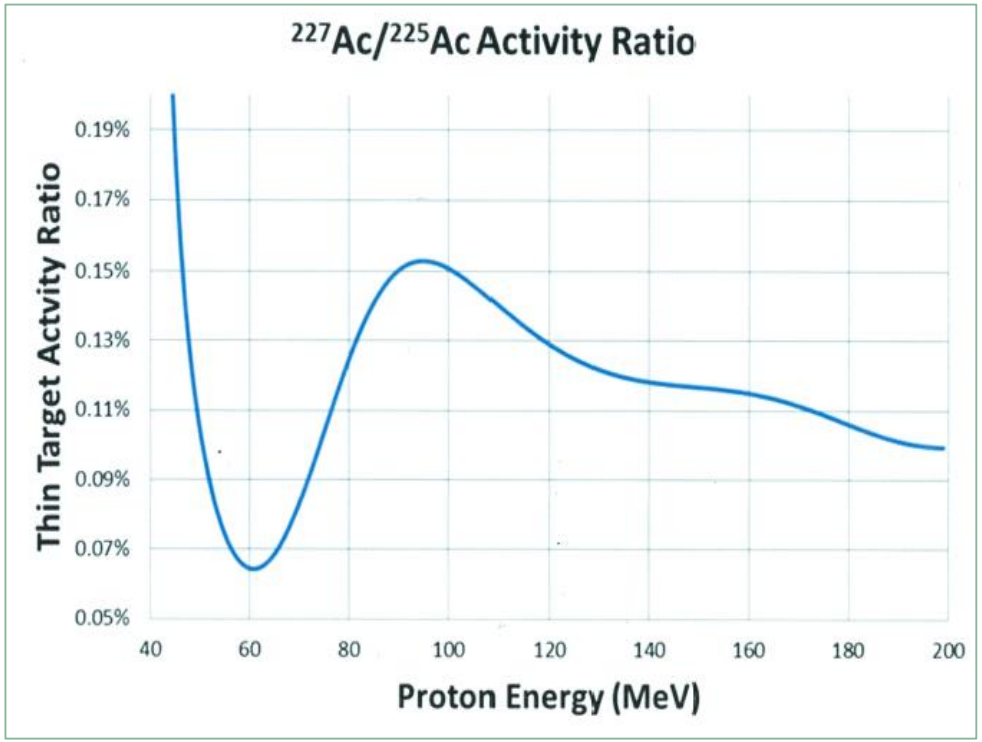
Accelerator Product and ^{227}Ac

Production of ^{225}Ac via high-energy accelerator results in the co-production of ^{227}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}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}Ac to ^{225}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.

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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)

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^{225}Ac User Group: DMF Developments, FDA Interactions and Licensing Details

Ariel Brown

National Isotope Development Center

June 23, 2019

DMF/FDA Updates

- Drug Master Files are being prepared for both Ac-225 products for reference within our customer's future regulatory submissions
- DMF filings are anticipated for:
  - CY2019 (accelerator product)
  - 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

Licensing

- Feedback from some customers has indicated that they are not able to add Ac-227 to their radioactive material licenses or that their limits for Ac-277 may be restrictive
  - In some cases, the funds/infrastructure is not available/in place for financial assurance or a decommissioning funding plan (DFP)
- 10 CFR Part 30, Appendix B lists values for isotopes with half-lives >120 days that trigger this requirement
- There is currently a federal petition for rulemaking to change these values as to not hinder the utilization or development of relevant isotopes
- We are engaging the NRC for further discussion on this topic, and would like to hear from any customers/sites that are being affected by this issue
- Similar issues/requirements apply to international facilities that are receiving the material
- We recommend that anyone interested in purchasing the accelerator-produced material should initiate an amendment to their license as soon as possible

Summary

- The Tri-Lab effort is routinely producing ^{225}Ac and *product is available* for end users and shipments to multiple users have been completed
- We have distributed over 275 mCi of accelerator produced ^{225}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}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

Thank You!

For more information: **https://isotopes.gov/**

Please visit the US DOE Isotope Program booth (# 467)

Attend the *Radiochemistry and Chelation Poster Session* tonight (6:30-8:00) at Exhibit Hall C: ***US DOE Tri-Lab Production Effort to Provide Accelerator-Produced ^{225}Ac for Radiotherapy: 2019 Update*** (Publication 1612)

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The Impact of ^{227}Ac Roundtable Discussion

Rebecca Abergel (Lawrence Berkeley National Laboratory)

Jeffrey Norenberg (University of New Mexico, School of Pharmacy)

Robert Hobbs (Johns Hopkins, Radiation Oncology and Molecular Radiation Sciences)

Dale Ludwig (Actinium Pharmaceuticals, Inc.)