Isotope Program
U.S. Department of Energy

Ac-225 DOE Isotope Program User Group Meeting

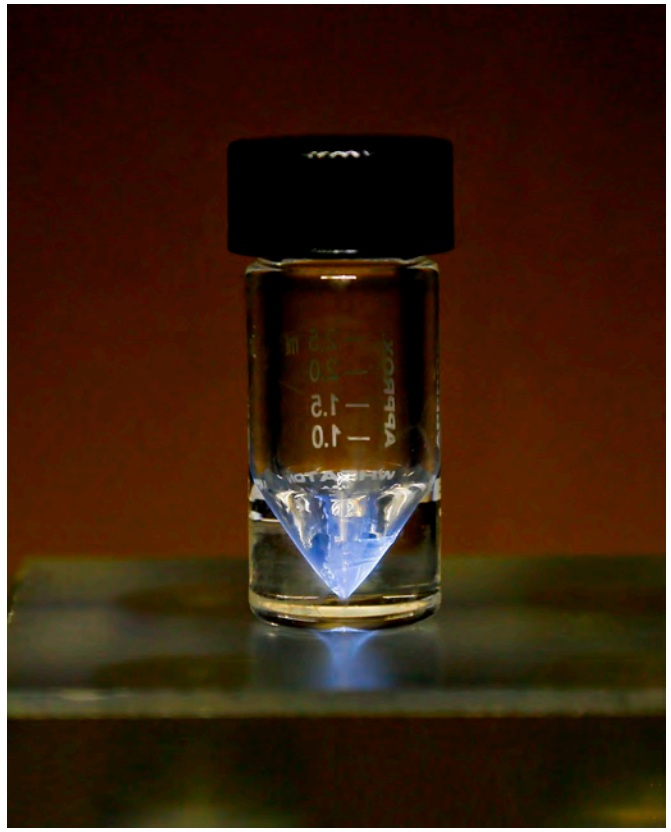
Eva Birnbaum, Los Alamos National Laboratory

Dan Stracener, Oak Ridge National Laboratory, Project Manager, U.S. DOE Tri-Lab

Brookhaven National Laboratory
OAK RIDGE National Laboratory
Los Alamos NATIONAL LABORATORY
NIDC NATIONAL ISOTOPE DEVELOPMENT CENTER
MANAGED BY THE U.S. DEPARTMENT OF ENERGY ISOTOPE PROGRAM
U.S. DEPARTMENT OF ENERGY

Agenda

- A brief perspective on supply/demand 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
- Improvements and alternate production routes being pursued
- Roundtable presentations on experiences with accelerator-produced ^{225}Ac
- Moderated Q&A session



ORNL ^{225}Ac Finished Product

Recent Clinical Experience with ^{225}Ac and ^{213}Bi-Labeled Compounds

Cancer Type	Radioconjugate	Patients
Leukemia	^{213}Bi-anti-CD33-mAb	49
	^{225}Ac-anti-CD33-mAb	76
Lymphoma	^{213}Bi-anti-CD20-mAb	12
Melanoma	^{213}Bi-anti-MCSP-mAb	54
Bladder cancer	^{213}Bi-anti-EGFR-mAb	12
Glioma	^{213}Bi-Substance P	68
	^{225}Ac-Substance P	20
Neuroendocrine tumors	^{213}Bi-DOTATOC	25
	^{225}Ac-DOTATOC	39
Prostate cancer	^{225}Ac-PSMA617	>400

^{225}Ac-DOTA-PSMA617 has demonstrated the power of Targeted Alpha Therapy (TAT) and is paving the way for a variety of other applications in oncology as well as infectious disease.

A. Morgenstern, C. Apostolidis, F. Bruchertseifer. *Seminars in Nucl Med*. **2020** *50(2)*: 119–123

^{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**

And

International Atomic Energy Agency. Technical Meeting Report "Supply of Actinium-225" IAEA Headquarters Vienna, Austria, October **2018**

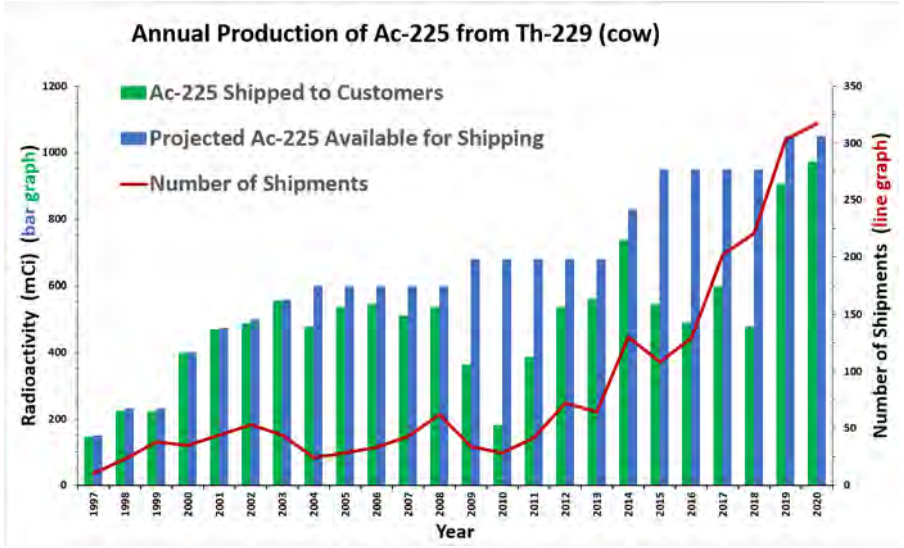
US DOE Offices of Nuclear Energy and Nuclear Physics "2008 Workshop on The Nation's Needs for Isotopes: Present and Future" Rockville, MD August **2008

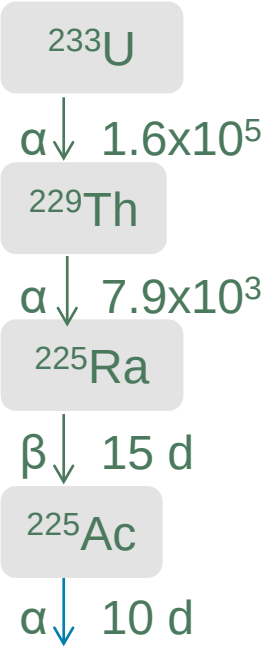
Actinium-225 Production at ORNL

- ORNL has been the main supplier of ^{225}Ac (via decay of existing ^{229}Th stock) since 1997
- >10 Ci of ^{225}Ac shipped in >2000 packages
- Approximately 1 Ci of ^{225}Ac is harvested annually from 130 mCi ^{229}Th stock at ORNL
- Thirteen 4-week campaigns are performed per year, with weekly customer shipments

Rationale for pursuing additional routes for production of ^{225}Ac

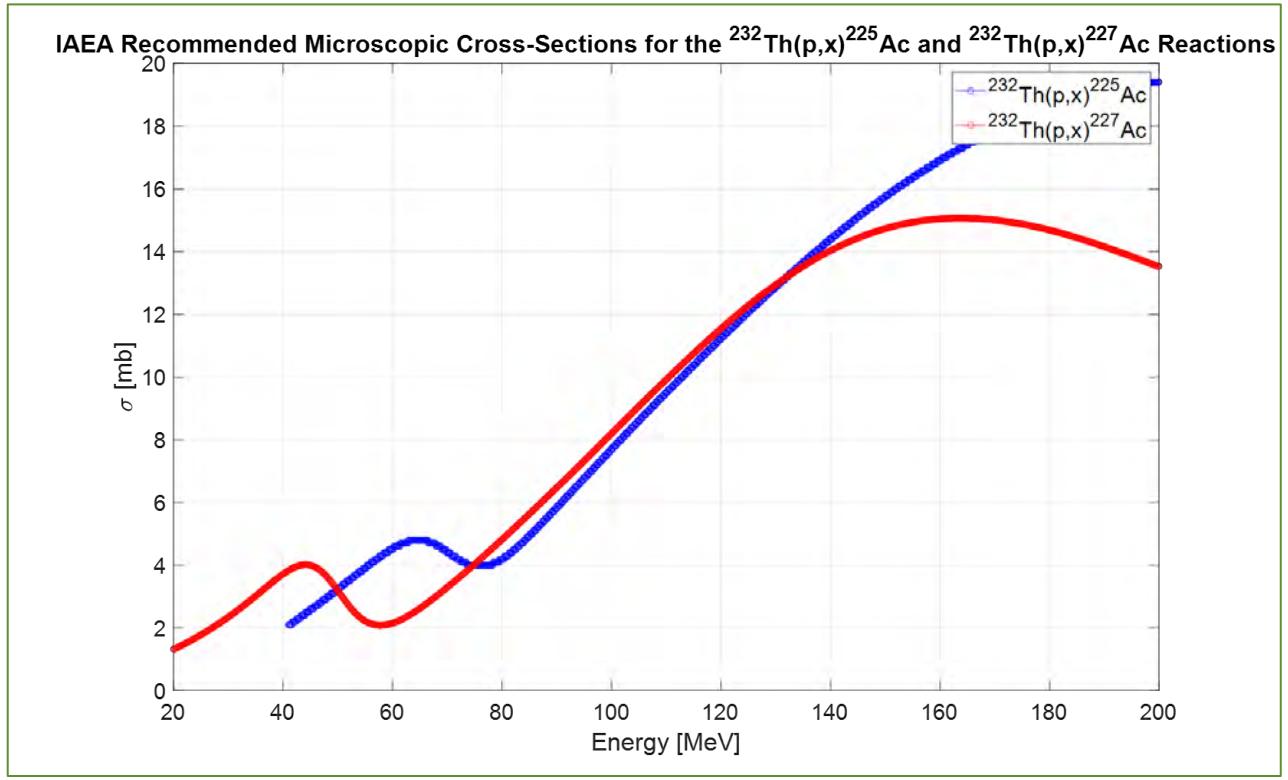
- The present supply is insufficient to meet the growing research and medical applications demands for ^{225}Ac





Brookhaven National Laboratory | Oak Ridge National Laboratory | Los Alamos National Laboratory | NIDC National Isotope Development Center — Managed by the U.S. Department of Energy Isotope Program | Isotope Program, U.S. Department of Energy | U.S. Department of Energy

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



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.*

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

*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*

Brookhaven National Laboratory | Oak Ridge National Laboratory | Los Alamos National Laboratory | NIDC National Isotope Development Center — Managed by the U.S. Department of Energy Isotope Program | Isotope Program U.S. Department of Energy | U.S. Department of Energy

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 μA 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

Brookhaven National Laboratory | Oak Ridge National Laboratory | Los Alamos National Laboratory | NIDC National Isotope Development Center — Managed by the U.S. Department of Energy Isotope Program | Isotope Program U.S. Department of Energy | U.S. Department of Energy

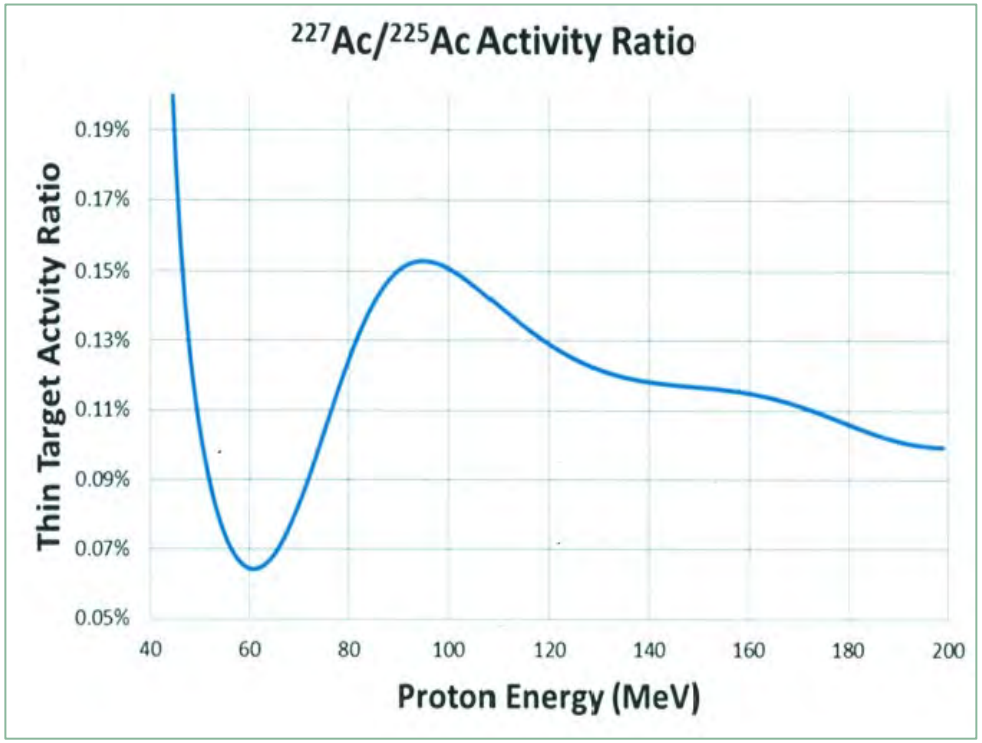
Accelerator Product and ^{227}Ac

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.

Brookhaven National Laboratory · Oak Ridge National Laboratory · Los Alamos National Laboratory · NIDC National Isotope Development Center, Managed by the U.S. Department of Energy Isotope Program · Isotope Program, U.S. Department of Energy · U.S. Department of Energy

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)

* Sgouros et al, *J. Med Imaging & Rad. Sciences*, **2019**, 50(4) https://doi.org/10.1016/j.jmir.2019.11.120
Jiang et al., *Curr. Radiopharmaceuticals*, **2018**, 11(3) https://doi.org/10.2174/1874471011666180423120707

DMF/FDA Updates

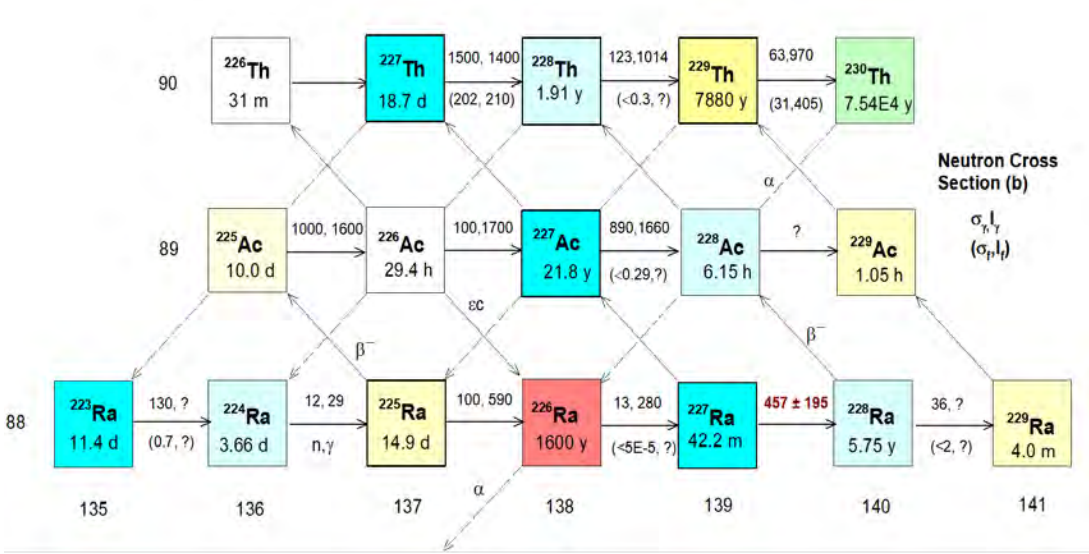
- A Type II Drug Master File (DMF) was submitted in December 2019 for accelerator produced Ac-225
- A Type II DMF was submitted in December 2020 for the ^{229}Th-derived ^{225}Ac product
- Interaction with the Food and Drug Administration is ongoing in reference to both products
- We are committed to making these products available to our customers/the medical community and are happy to address any further questions

Continuing Efforts to Increase Availability of ^{225}Ac

- Increasing frequency and size of accelerator ^{225}Ac batches
- Addressing technical and logistical challenges while ensuring product is consistent and reliable
- Additional facility investments in progress to enable more frequent and larger batch sizes
- Building in processing capability redundancy to enhance reliability

Alternative Routes of Production Under Investigation

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



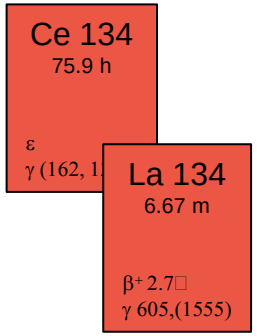
S. Hogle et al., *Reactor Production of Thorium-229*, Appl. Radiat. Isot. 114, 19 (2016)

Complementary Imaging Isotope Under Development

- ^{134}Ce is a potential f-element PET imager that is chemically similar to Ac and Th.
- The $^{134}Ce/^{134}La$ can be used to image ^{225}Ac when reduced ($^{134}Ce^{III}$) and ^{227}Th when oxidized ($^{134}Ce^{IV}$).

$$^{134}Ce \xrightarrow{\varepsilon} {}^{134}La \xrightarrow{\beta+} {}^{134}Ba_{(stable)}$$

^{134}Ce $t_{½}$ = 3.2 d
^{134}La $t_{½}$ = 6.7 min



Evaluation batches in progress!

Brookhaven National Laboratory | Oak Ridge National Laboratory | Los Alamos National Laboratory | NIDC National Isotope Development Center, Managed by the U.S. Department of Energy Isotope Program | Isotope Program, U.S. Department of Energy | U.S. Department of Energy

T.A. Bailey et al., *Nature Chemistry,* (2021) **13**, 284–289

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 440 mCi of accelerator produced ^{225}Ac to evaluators
- We are working with companies and research hospitals in preparation to support Phase I trials – we have observed increased adoption of the accelerator product
- ^{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 with DOE
- Continuing to scale up availability of this important isotope

Thank You!

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

Presentations & Agenda

1:10 – 1: 25 PM **Rebecca Abergel** (University of California, Berkeley)

1:25 – 1: 40 PM **Ekaterina Dadachova** (University of Saskatchewan)

1:40 – 1: 55 PM **Jim O'Leary and Thomas Armor** (Fusion Pharma)

1:55 – 2: 10 PM **Neil Bander** (Weill Cornell)

2:10 – 2: 25 PM **George Sgouros** (Johns Hopkins University)

2:25 – 3: 00 PM **Q&A & Discussion**