Isotope Program
U.S. Department of Energy

# Ac-225 DOE Isotope Program User Group Meeting

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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
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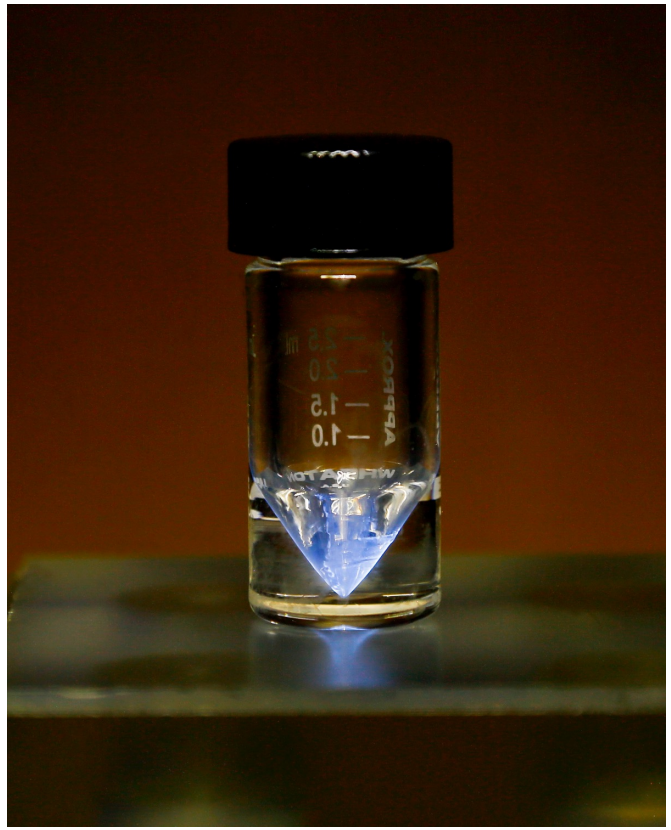
# Agenda

- 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 $^{225}Ac$
- Open Forum Q&A



ORNL $^{225}Ac$ Finished Product

# Alpha Emitter Market

- The alpha emitter market is expected to witness a healthy CAGR of 21% 2022-2028 to 37% from 2022-2027.[1]
- Driving the market is increased awareness about the potential benefits of targeted alpha therapy and the growing number of patients with cardiac and cancer ailments.
- Currently North America dominates the market, with the Asia Pacific region growing at the highest CAGR.

1. Market Watch news July 21, 2022, Morder Intelligence Alpha Emitter Market Report

# 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-PSMA-617 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

# Ac-225 Clinical Trials

- (8) Acute myeloid leukemia, $^{225}$Ac-lintuzumab, and in combination therapy, $^{225}$Ac-HuM195
- Colorectal Cancer, $^{225}$Ac-DOTA-M5A anti-CEA antibody
- (10)Prostate Cancer, $^{225}$Ac-PSMA I&T, $^{225}$Ac-J591, $^{225}$Ac-J591+ $^{177}$Lu-PSMA I&T, $^{225}$Ac-J591+ pembrolizumab + ARPI, $^{225}$Ac-antibody targeting human Kallikrein-2(hK2) for advanced Prostate cancer
- Multiple Myeloma, $^{111}$In and $^{225}$Ac-DOTA-daratumumab
- (2)Solid tumors - $^{111}$In and $^{225}$Ac-FPI-1434, $^{111}$In-FPI-1967 and $^{225}$Ac-FPI-1966 and vofatamab
- GEP-NET – $^{225}$Ac-somatostatin analog
- Metastatic Uveal melanoma - $^{225}$Ac-MTI-201

*Number in brackets indicates number of clinical trials.*

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# $^{225}$Ac Supply & Demand

**Current worldwide supply of $^{225}$Ac from $^{229}$Th/$^{225}$Ac generators ranges between 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**

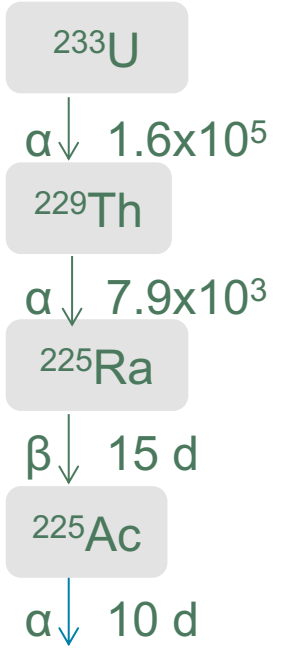
And

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**

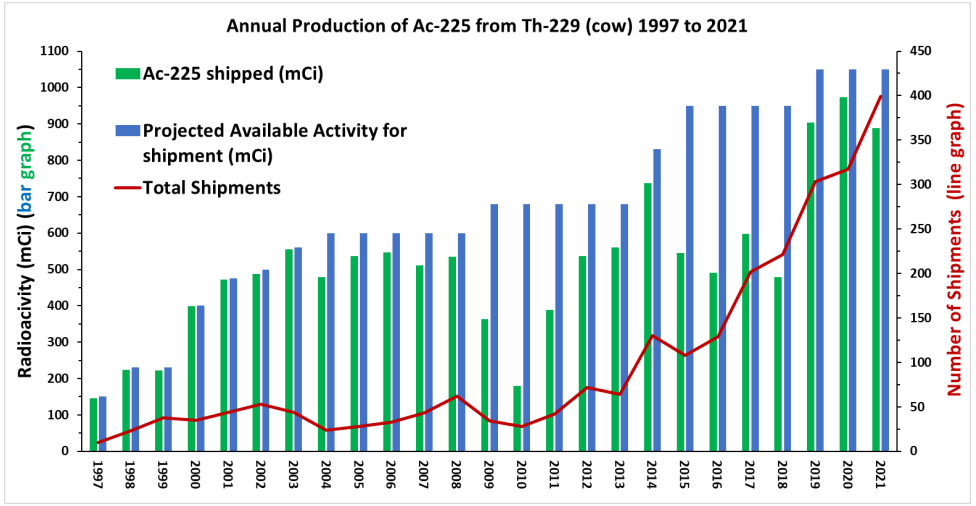
# Actinium-225 Production at ORNL

- 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

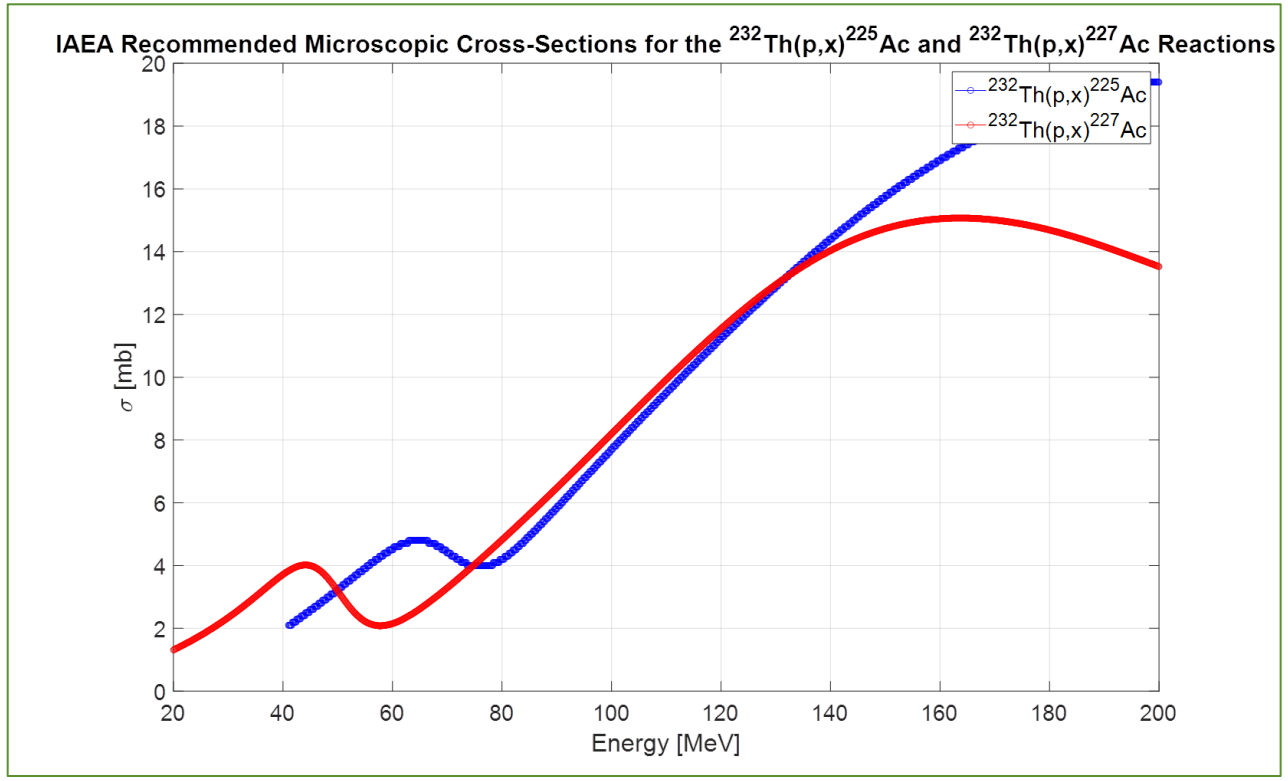



**Rationale for pursuing additional routes for production of $^{225}Ac$**

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



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




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

**Future Planned Facility and Targetry investments at IPF and BLIP will further increase our single target projected yields to:**

- LANL 450 μA 2.3 Ci
- BNL 300 μA 4.0 Ci


*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*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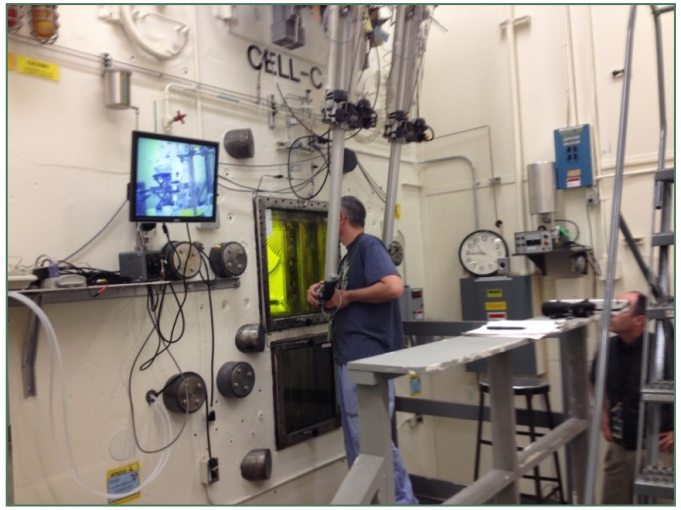
# Basis of the Tri-Lab Effort:

## 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 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

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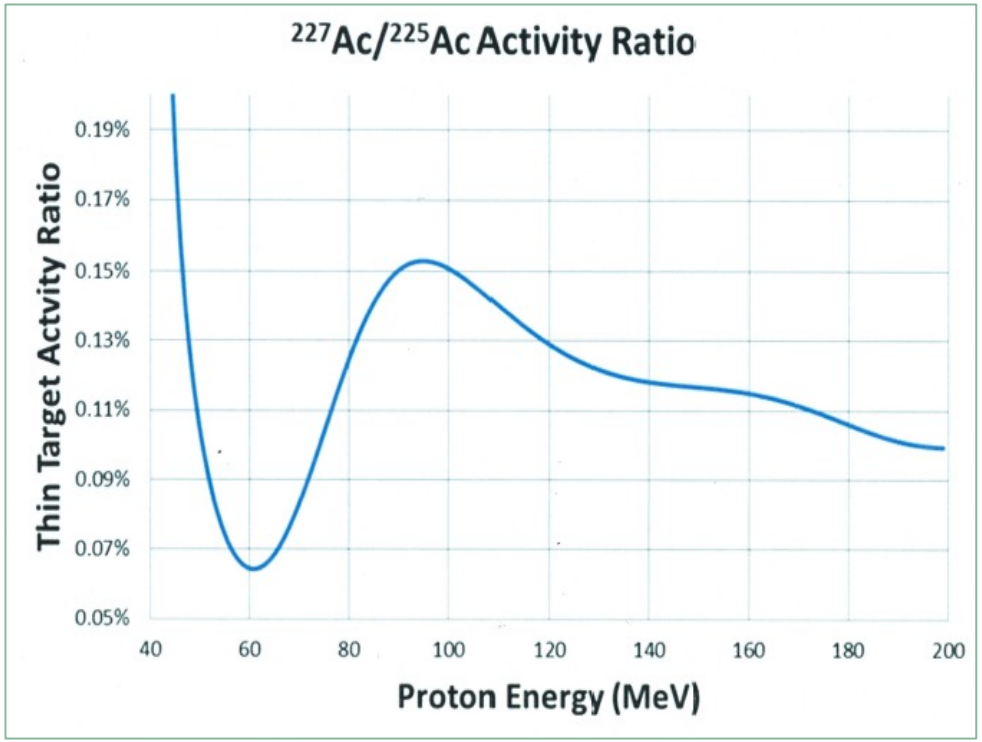
# Accelerator Product and $^{227}$Ac

**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 –this ratio and its time dependence are precisely known ≤ 2%

**$^{227}$Ac co-product creates a unique set of challenges – perceptions and facility licensing (NRC), 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

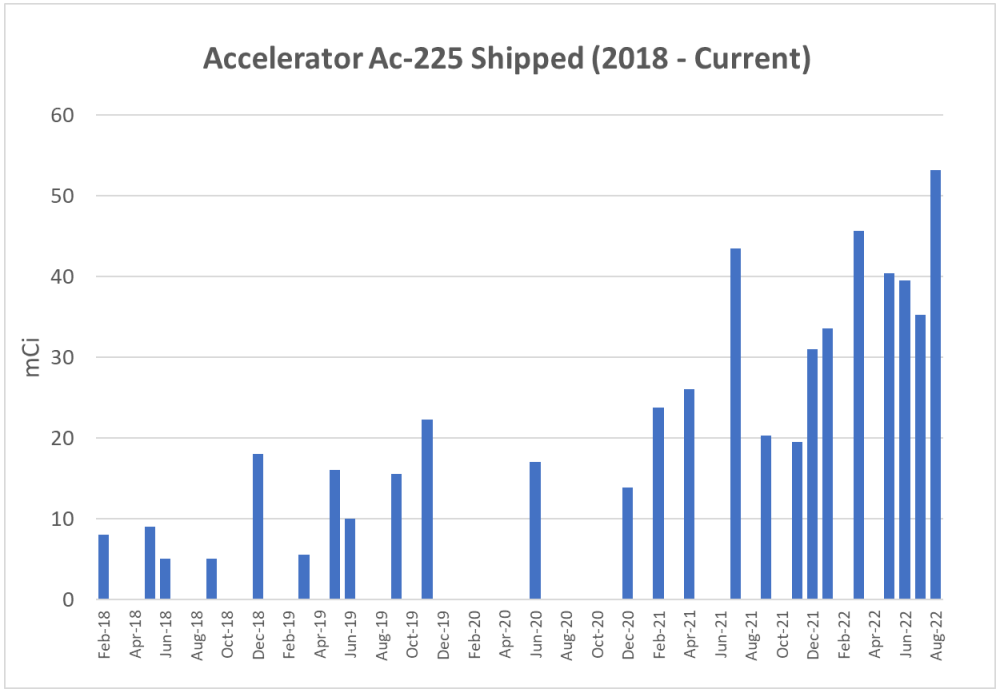
- **Accelerator-produced $^{225}$Ac performs similar to $^{229}$Th-derived $^{225}$Ac**
  - direct labeling efficiencies are comparable
  - $^{213}$Bi generator performance is the same
  - the impact of $^{227}$Ac content on dosimetry has been demonstrated to be small
- **Challenges remain with respect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

# 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

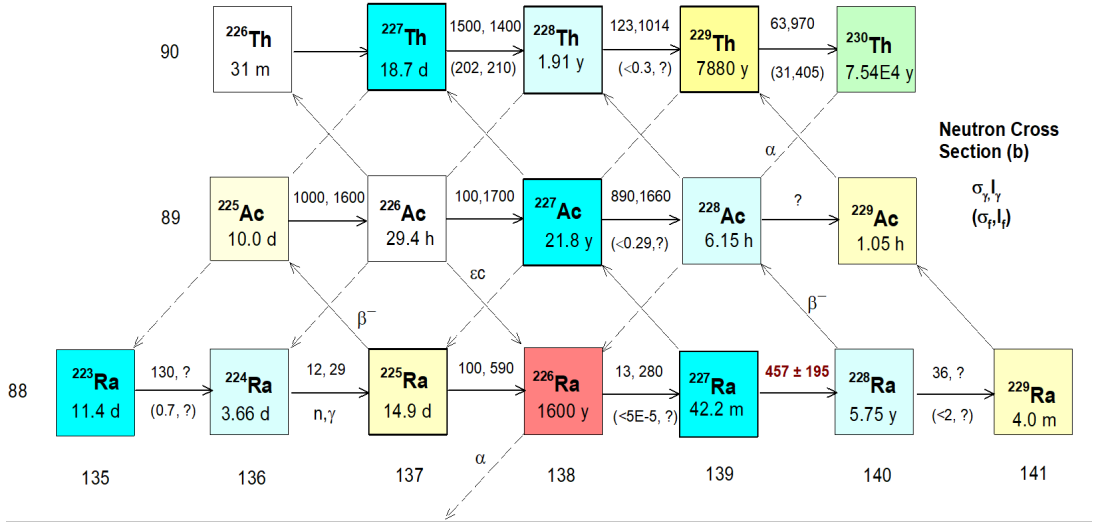
# Continuing Efforts to Increase Availability of $^{225}Ac$

- Monthly production, routinely achieving up to 50 mCi/batch at end of processing.
- Limited by processing capability and shipping transit times
- New local processing capability coming online at BNL and planned for LANL.
- For FY2022 to date: 307 mCi has been shipped (8 shipments to date).
- Building in processing capability redundancy to enhance reliability



# Alternative Routes of Production Under Investigation

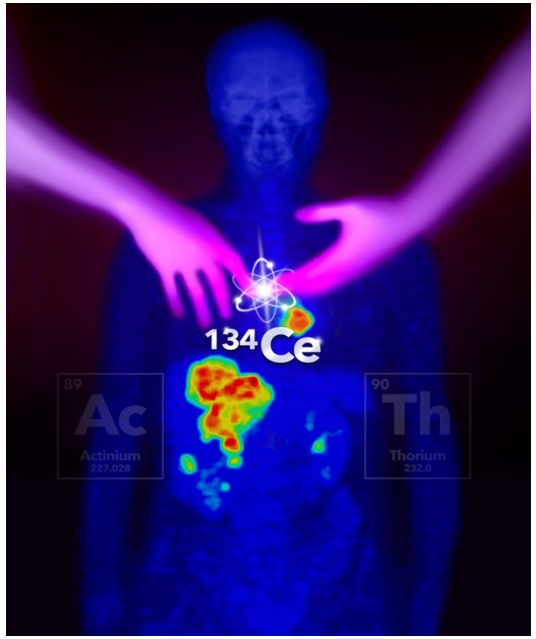
- ANL electron linac production route
  - $^{226}Ra(\gamma,n)^{225}Ra \rightarrow ^{225}Ac$
- BNL low energy cyclotron route
  - $^{226}Ra(p,2n)^{225}Ac$
- ORNL neutron production route
  - $^{226}Ra(3n,\gamma)^{229}Ra \rightarrow ^{229}Ac \rightarrow ^{229}Th$




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

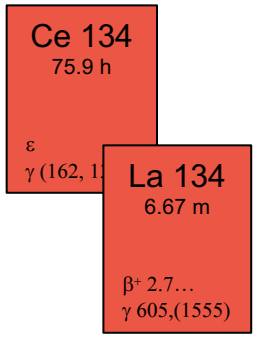
# Complementary Imaging Isotope Under Development

- $^{134}$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$^{IV}$).




$$^{134}\text{Ce} \xrightarrow{\varepsilon} {}^{134}\text{La} \xrightarrow{\beta+} {}^{134}\text{Ba}_{(stable)}$$

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




***Evaluation batches in progress!***

Ce-134 user group meeting September 19th

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

# 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 588 mCi of accelerator produced $^{225}$Ac to evaluators
- FY2022 to date: 307 mCi has been shipped.
- We are working with companies and research hospitals in preparation to support Phase I trials – responding to requests for Letters of Authorization
- $^{227}$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
- Increasing production and processing capabilities
- Continuing to scale up availability of this important isotope

# Thank You!

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

# Presentations & Agenda

**1:15 – 1: 30 PM** **Gary Kohanbash (**Dept. of Neurological Surgery at UPMC Children's Hospital of Pittsburgh)

**1:30 – 1: 45 PM** **Kevin Roland** (Fusion Pharma)

**1:45 – 2: 00 PM** **Ken Song** (RazyeBio)

**2:00 – 2: 15 PM** **Monideepa Roy** (Actinium Pharma)

**2:15 – 2: 45 PM** **Q&A & Discussion**