US DOE Tri-Lab Production Effort to Provide Accelerator-Produced ^{225}Ac for Radiotherapy: 2019 Update

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^{225}Ac Supply and Demand

^{225}Ac is a promising isotope for the treatment of cancer used in emerging Targeted Alpha Therapy (TAT) applications

Current worldwide supply of ^{225}Ac is estimated at 1200-1700 mCi/yr* derived from ^{229}Th/ ^{225}Ac generators

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

- ^{225}Ac: 0.3-5 μCi per patient kg
- ^{213}Bi: 1 mCi per patient kg

*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. 24-28 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

^{225}Ac Supply Considerations

Facility	Nuclear Reaction
Reactor (thermal neutrons)	^{226}Ra(3n,γ)^{229}Ra →^{229}Ac→^{229}Th ^{228}Ra(n,γ)^{229}Ra →^{229}Ac→^{229}Th
Accelerator (electrons)	^{226}Ra(γ,n)^{225}Ra→^{225}Ac
Accelerator (low energy particles)	^{226}Ra(p,2n)^{225}Ac ^{226}Ra(α,n) ^{229}Th ^{226}Ra(p,pn) ^{225}Ra→^{225}Ac ^{232}Th(p,x) ^{229}Th
Accelerator (high energy protons)	**^{232}Th(p,x)^{225}Ac** ^{232}Th(p,x)^{225}Ra→^{225}Ac
Accelerator (high energy neutrons)	^{226}Ra(n,2n) ^{225}Ra→^{225}Ac
Hot Cell Facility (^{233}U processing)	^{229}Th decay to ^{225}Ac

Current supply of ^{225}Ac is derived from the decay of ^{229}Th that was derived from limited stockpiles of ^{233}U

New sources of material are required to support ^{225}Ac-based pharmaceuticals

The high-energy accelerator route is of interest as it leverages unique US facility capabilities

Accelerator Production of ^{225}Ac

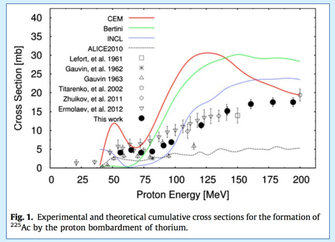


Fig. 1. Experimental and theoretical cumulative cross sections for the formation of ^{225}Ac by the proton bombardment of thorium.

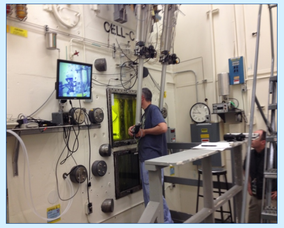
^{225}Ac yield curve based on measured cross sections show that Ci-scale production is feasible at LANL and BNL

Facility	Anticipated Single Target Ac-225 Yields at EOB (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.

*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*

The Tri-Lab Effort: Leveraging Unique National Resources



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

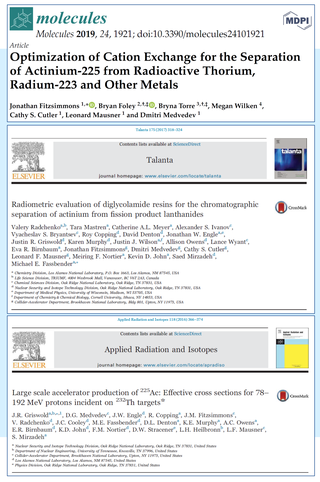
BNL Linac at the Brookhaven Linac Isotope Producer (BLIP) 165 μA intensity to targets at incident energies ranging from 66-202 MeV

Accelerator-Produced ^{225}Ac Overview

We've distributed over 275 mCi of accelerator produced ^{225}Ac/^{213}Bi as part of the Tri-Lab effort

19 separate batches have been processed (since the start of the effort) with multiple shipments per batch resulting in distribution to 15 different customers/evaluators

The Tri-Lab effort has generated multiple publications and patents (see US patents 9,951,399 and 9,555,140)



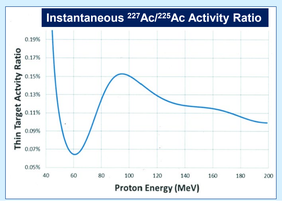
^{225}Ac Materials Evaluation Campaigns

Accelerator-produced ^{225}Ac/^{213}Bi generator performance is equivalent to generators produced from ^{229}Th-derived ^{225}Ac

Direct labeling studies of the accelerator-derived ^{225}Ac product are promising and are equivalent to ^{229}Th-derived ^{225}Ac

Supported three biodistribution/dosimetry/toxicity studies to assess impact of ^{227}Ac ($t_{1/2} \cong 22$ years)

"Our data demonstrates that accelerator-produced ^{225}Ac is suitable for the development of the pre-clinical and clinical targeted radionuclide therapy."



Accelerator-Produced ^{225}Ac Current Focus

General focus on increasing production frequency and volume in support of clinical R&D and clinical trials

Continued improvements to the design and preparation of thorium targets and radiochemical processing optimization

Continued improvement of shipping capabilities and shipping performance

Submittal of a Drug Master File to inform the FDA - helps our customer base, and protects our process

Starting to execute facility vision with eye toward Stage 3 large scale production

Continued focus on stakeholder and customer interactions

Approach to Routine Production for Use in Approved Drugs

We have positioned ourselves to ensure a strong, reliable supply that meets the quality requirements and quantities needed for clinical application

- ✓ - reliable, consistent and routine production
- ✓ - large quantities for meaningful impact to preclinical studies and clinical trials
- ✓ - experience with GMP production and regulatory compliance (as demonstrated by our ^{82}Sr production)

Please see US DOE Isotope Program booth # 467 for additional details

Summary and Acknowledgements

The Tri-Lab effort is routinely producing ^{225}Ac and ***product is available*** for end users and shipments to multiple users have been completed [please contact the National Isotope Development Center at (865) 574-6984 or see their website https://www.isotopes.gov/ for more details]

We have distributed over 275 mCi of accelerator produced ^{225}Ac to evaluators

^{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

We are working with companies and research hospitals in preparation to support Phase I trials - DMF development is underway

This research is supported by the U.S. Department of Energy Isotope Program, managed by the Office of Science for Nuclear Physics