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

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²²⁵Ac Supply and Demand

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

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

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

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

²²⁵Ac Supply Considerations

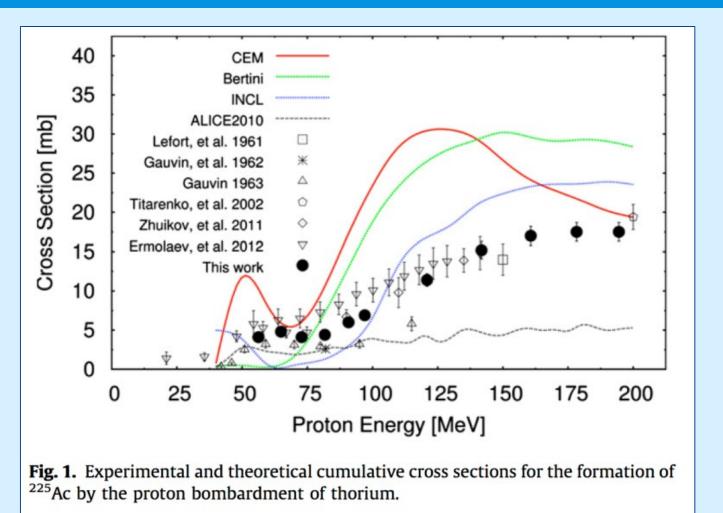
Projection of ²²⁵Ac demand assuming multiple, approved ²²⁵Ac and ²¹³Bi drugs and robust clinical R&D programs could be in the hundreds of Ci/year**

*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

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	Current s derived f ²²⁹ Th tha limited st New sou required based ph The high route is c leverage capabiliti
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)	232Th(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	

Accelerator Production of ²²⁵Ac



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

Facility	Antio Ac (1
LANL (100 MeV, 250-450 µA)	
BNL (200 MeV, 165 μA)	
* 71	

* 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

supply of ²²⁵Ac is from the decay of at was derived from stockpiles of ²³³U

urces of material are to support ²²⁵Acharmaceuticals

n-energy accelerator of interest as it es unique US facility

cipated Single Target -225 Yields at EOB 10 day irradiation)

1.3-2.3* Ci

2.2 Ci

The Tri-Lab Effort: Leveraging Unique **National Resources**



ORNL - Approximately 25 years of experience in the isolation of ²²⁵Ac from fissile ²³³U via ²²⁹Th

LANL Isotope Facility (IPF) at 100 MeV incident energy up to 275 μ**A for routine** production



Accelerator-Produced²²⁵Ac Overview

We've distributed over 275 mCi of acce produced ²²⁵Ac/²¹³Bi as part of the Tri-L effort

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

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

²²⁵Ac Materials Evaluation Campaigns

Accelerator-produced ²²⁵Ac/²¹³Bi gener performance is equivalent to generators produced from ²²⁹Th-derived ²²⁵Ac

Direct labeling studies of the accelerate derived ²²⁵Ac product are promising an equivalent to ²²⁹Th-derived ²²⁵Ac

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







Production LANSCE;



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

	<i>molecules</i> <i>Molecules</i> 2019 , 24, 1921; doi:10.3390/molecules24101921
	Article Optimization of Cation Exchange for the Separation of Actinium-225 from Radioactive Thorium, Radium-223 and Other Metals
lerator	Jonathan Fitzsimmons ^{1,*} , Bryan Foley ^{2,†,‡} , Bryna Torre ^{3,†,‡} , Megan Wilken ⁴ , Cathy S. Cutler ¹ , Leonard Mausner ¹ and Dmitri Medvedev ¹
_ab	Talanta 175 (2017) 318–324 Contents lists available at ScienceDirect Talanta ELSEVIER journal homepage: www.elsevier.com/locate/talanta
sed e	Radiometric evaluation of diglycolamide resins for the chromatographic separation of actinium from fission product lanthanides Valery Radchenko ^{a,b} , Tara Mastren ^a , Catherine A.L. Meyer ^a , Alexander S. Ivanov ^c , Vyacheslav S. Bryantsev ^c , Roy Copping ^d , David Denton ^d , Jonathan W. Engle ^{a,e} , Justin R. Griswold ^d , Karen Murphy ^d , Justin J. Wilson ^{a,f} , Allison Owens ^d , Lance Wyant ^c , Eva R. Birnbaum ^a , Jonathan Fitzsimmons ^g , Dmitri Medvedev ^g , Cathy S. Cutler ^g , Leonard F. Mausner ^g , Meiring F. Nortier ^a , Kevin D. John ^a , Saed Mirzadeh ^d , Michael E. Fassbender ^{a,*}
ition to	 ^a Chemistry Division, Los Alamos National Laboratory, P.O. Box 1663, Los Alamos, NM 87545, USA ^b Life Science Division, TRIUMF, 4004 Wesbrook Mall, Vancouver, BC V6T 2A3, Canada ^c Chemical Sciences Division, Oak Ridge National Laboratory, Oak Ridge, TN 37831, USA ^d Nuclear Security and Isotope Technology Division, Oak Ridge National Laboratory, Oak Ridge, TN 37831, USA ^d Department of Medical Physics, University of Wisconsin, Madison, WI 53705, USA ^f Department of Chemistry & Chemical Biology, Cornell University, Ithaca, NY 14853, USA ^g Collider-Accelerator Department, Brookhaven National Laboratory, Bldg 801, Upton, NY 11973, USA
e	Applied Radiation and Isotopes 118 (2016) 366–374 Contents lists available at ScienceDirect Applied Radiation and Isotopes journal homepage: www.elsevier.com/locate/apradiso
ts	Large scale accelerator production of ²²⁵ Ac: Effective cross sections for 78– 192 MeV protons incident on ²³² Th targets [*] J.R. Griswold ^{a,b,*,1} , D.G. Medvedev ^c , J.W. Engle ^d , R. Copping ^a , J.M. Fitzsimmons ^c , V. Radchenko ^d , J.C. Cooley ^d , M.E. Fassbender ^d , D.L. Denton ^a , K.E. Murphy ^a , A.C. Owens ^a , E.R. Birnbaum ^d , K.D. John ^d , F.M. Nortier ^d , D.W. Stracener ^e , L.H. Heilbronn ^b , L.F. Mausner ^c , S. Mirzadeh ^a
	 ^a Nuclear Security and Isotope Technology Division, Oak Ridge National Laboratory, Oak Ridge, TN 37831, United States ^b Department of Nuclear Engineering, University of Tennessee, Knoxville, TN 37996, United States ^c Collider-Accelerator Department, Brookhaven National Laboratory, Upton, NY 11973, United States ^d Los Alamos National Laboratory, Los Alamos, NM 87545, United States ^e Physics Division, Oak Ridge National Laboratory, Oak Ridge, TN 37831, United States
	Current Radiopharmaceuticals, 2018, 11, 215-222 RESEARCH ARTICLE In vivo Evaluation of Free and Chelated Accelerator-produced Actinium- 225 - Radiation Dosimetry and Toxicity Results
ator S	Zewei Jiang ¹ , Ekaterina Revskaya ¹ , Darrell R. Fisher ² and Ekaterina Dadachova ^{3,*} ¹ Department of Radiology, Albert Einstein College of Medicine, Bronx, NY, 10461 USA; ² Versant Medical Physics and Radiation Safety, Richland, WA, USA; ³ University of Saskatchewan, Saskatoon, SK, S7N 5E5, Canada "Our data demonstrates that accelerator- produced ²²⁵ Ac is suitable for the development of the pre-clinical and
r-	clinical targeted radionuclide therapy."
d are	0.19% 0.17% 0.15% 0.13%
s to	0.17% U.15% 0.13% 0.13% 0.05% 0.05%
	40 60 80 100 120 140 160 180 200

Accelerator-Produced ²²⁵Ac 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

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

- trials

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

Summary and Acknowledgements

The Tri-Lab effort is routinely producing ²²⁵Ac 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 ²²⁵Ac to evaluators

²²⁷Ac 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**



LA-UR-19-25067

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

- reliable, consistent and routine production

 $\sqrt{}$ - large quantities for meaningful impact to preclinical studies and clinical

- experience with GMP production and regulatory compliance (as demonstrated by our ⁸²Sr production)