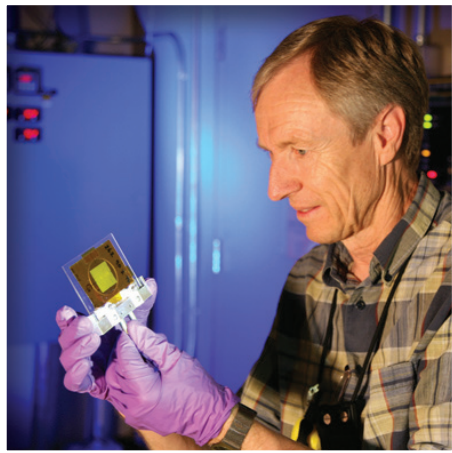
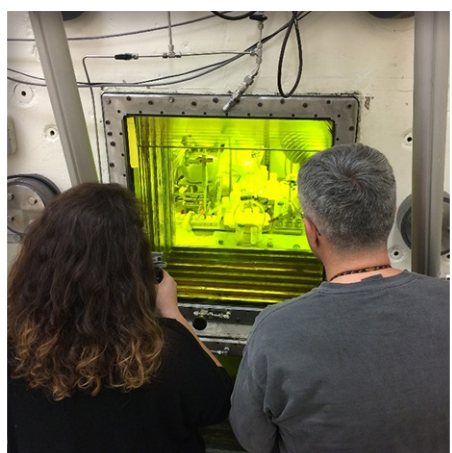
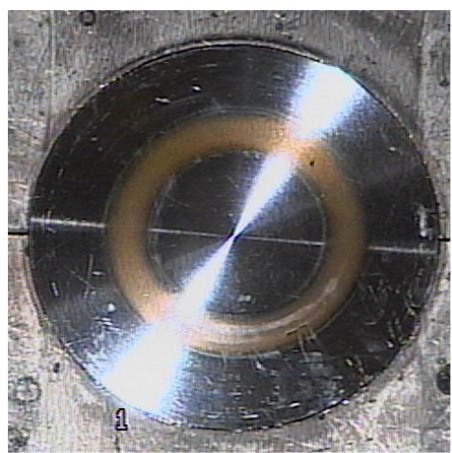




TRI-LAB PRODUCTION EFFORT ACCELERATOR-PRODUCED ACTINIUM-225 FOR RADIOTHERAPY



Isotope Program

U.S. Department of Energy



U.S. DEPARTMENT OF
ENERGY

Office of
Science

A Path Toward Abundant Supply

Three U.S. Department of Energy (DOE) national laboratories—Brookhaven National Laboratory (BNL), Los Alamos National Laboratory (LANL) and Oak Ridge National Laboratory (ORNL)—are making strides toward a robust and reliable supply of actinium-225 (Ac-225) for use in radiotherapy. Funded by the DOE Isotope Program, managed by the Office of Science for Nuclear Physics, this “Tri-Lab” effort leverages accelerator capabilities at BNL’s Brookhaven Linac Isotope Producer (BLIP) and LANL’s Isotope Production Facility (IPF) along with ORNL’s extensive experience with radioisotope processing in a joint effort to produce accelerator-based Ac-225.

The long-term goal of the Tri-Lab effort is to meet the growing worldwide demand for Ac-225 for direct and Ac-225/Bi-213 generator applications. With accelerator-based Ac-225 production, current annual supply could be matched with roughly a week of beam time, presenting an overall higher activity to end users. This approach finally provides a supply of Ac-225 that is capable of supporting clinical trials and applications.



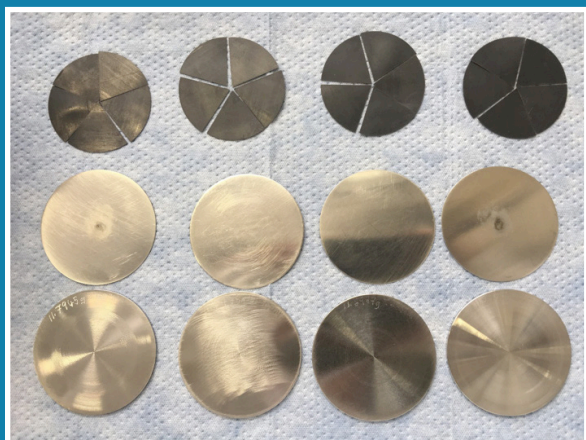
Actinium-225 final product, with blue glow from ionization of surrounding air by alpha particles



Los Alamos scientist Meiring Nortier holds a thorium foil test target for the proof-of-concept production experiments

Ensuring Product Quality and Applicability

Since the initiation of the U.S. DOE Tri-Lab Effort in 2015, the team has advanced production target development, chemical process methodology and general logistical considerations in order to evaluate the unique aspects of high-energy accelerator-based production approaches on the quality of both a final Ac-225 product and an Ac-225/Bi-213 generator. One of the key impacts assessed relates to the amount of Ac-227 (a unique co-product for the high-energy accelerator production method) in the final product (~0.12% at EOB) since the half-life of Ac-227 is about 22 years. Three independent dosimetry and toxicity studies have been completed, all concluding that the dosimetry impact of Ac-227 relative to Ac-225 is negligible.*

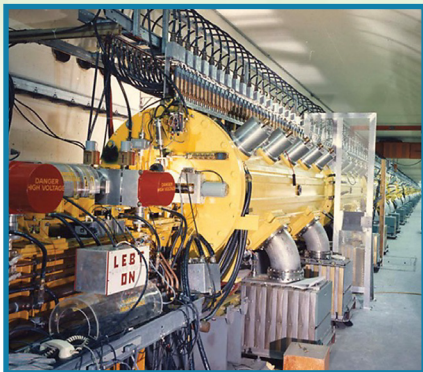


Target fabrication methods at LANL enable the Tri-Lab effort to fully explore and optimize targetry options for anticipated high-current Ci-scale production.

Target Optimization

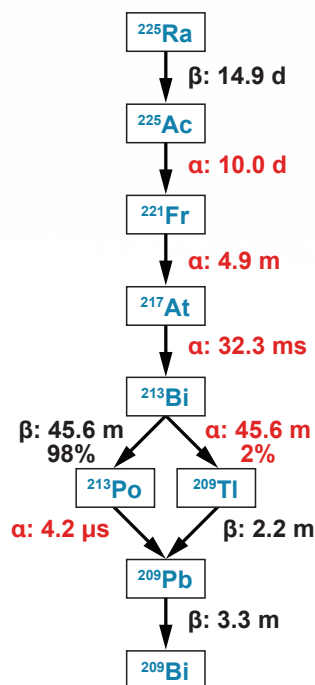
An inventory of radioactive thorium-232 (Th-232) metal has been established at LANL to support manufacturing of targets for routine production, as well as for advanced targetry development. The Tri-Lab effort has leveraged existing capabilities at LANL for processing and machining of Th-232 and developed protocols to support preparation of immediate and future target designs. Fabrication methods include arc melting, rolling, electroplating and electrical discharge machining. In addition, methods have been validated for e-beam and tungsten inert gas welding of the target encapsulation, and LANL is pursuing laser welding and hot pressing operations.

*see E. Dadachova et al., Current Radiopharmaceutical, 2018, 11, 215-222 for more details.



Left photo: BLIP—165 μ A intensity H⁺ beam delivered to targets at incident energies ranging from 66-202 MeV.

Right photo: IPF—100 MeV incident energy H⁺ beam delivered up to 275 μ A for routine production.



Ac-225 decay scheme

In addition, accelerator-produced Ac-225 product and Ac-225/Bi-213 generators were made available to researchers and clinicians to evaluate the applicability of the accelerator-produced material relative to the current route of separating Ac-225 from decaying Th-229.

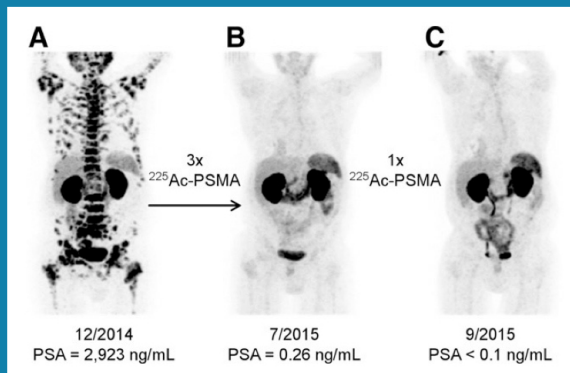
Forward Outlook on Production

Current efforts are focused on ramping up to full-scale production capabilities, with the goal of making enough Ac-225 to support expanded clinical trials and a variety of approved drugs. At present, we routinely produce 20-40 mCi batches every 6 weeks with the short term goal to increase capacity to 100 mCi batches. Long term, DOE plans to scale to 1,000 mCi batches to support potential Ac-225 approved drugs and/or Ac-225/Bi-213 generators at multiple locations. In addition to scaled-up production activities, we are focused on submission of a supporting Drug Master File for the accelerator product in 2019.

Clinical Trial Support

Holding great promise for cancer therapy, treatments containing Ac-225 or Bi-213 are under development at numerous institutions and hospitals. Specifically, targeted molecular antibody and peptide vehicles containing these isotopes offer selective binding to biomolecules that attach to certain malignant cells found in acute myeloid leukemia, non-Hodgkin's lymphoma, brain tumors, gastric, prostate, bladder, ovarian, pancreatic cancers and melanoma.

Other diseases also under investigation include HIV infection, viral cancers, fungal infections and emerging drug-resistant pathogens.



Patient PET/CT scans show pretherapeutic tumor spread (A), 2 months after third cycle of Ac-225 drug (B), and 2 months after one additional therapy (C). Note: Ac-225 used in this study was derived from Th-229 and not created as part of the Tri-Lab effort. (J Nucl Med December 1, 2016 vol. 57 no. 12 1941-1944)

Front Cover Captions: From top: Los Alamos scientist Meiring Nortier holds a thorium foil test target for the proof-of-concept production experiments (image courtesy of LANL); thorium target irradiated at IPF, with path of the proton beam clearly visible on target face (image courtesy of LANL); thorium target processing in ORNL hot cell (image courtesy of ORNL)

Other Photo Credits: Inner pages, clockwise from top left: actinium-225 vial (image courtesy of ORNL); proton accelerator at BLIP (image courtesy of BNL); LANL IPF (image courtesy of LANL); patient PET/CT scans (image courtesy of the Journal of Nuclear Medicine); thorium target samples (image courtesy of LANL); and LANL scientist holding thorium foil (image courtesy of LANL)

ORNL 2019-G00227/DLR

**Accelerator-produced Ac-225 is available.
For more information on availability, please contact
the National Isotope Development Center.**

www.isotopes.gov

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