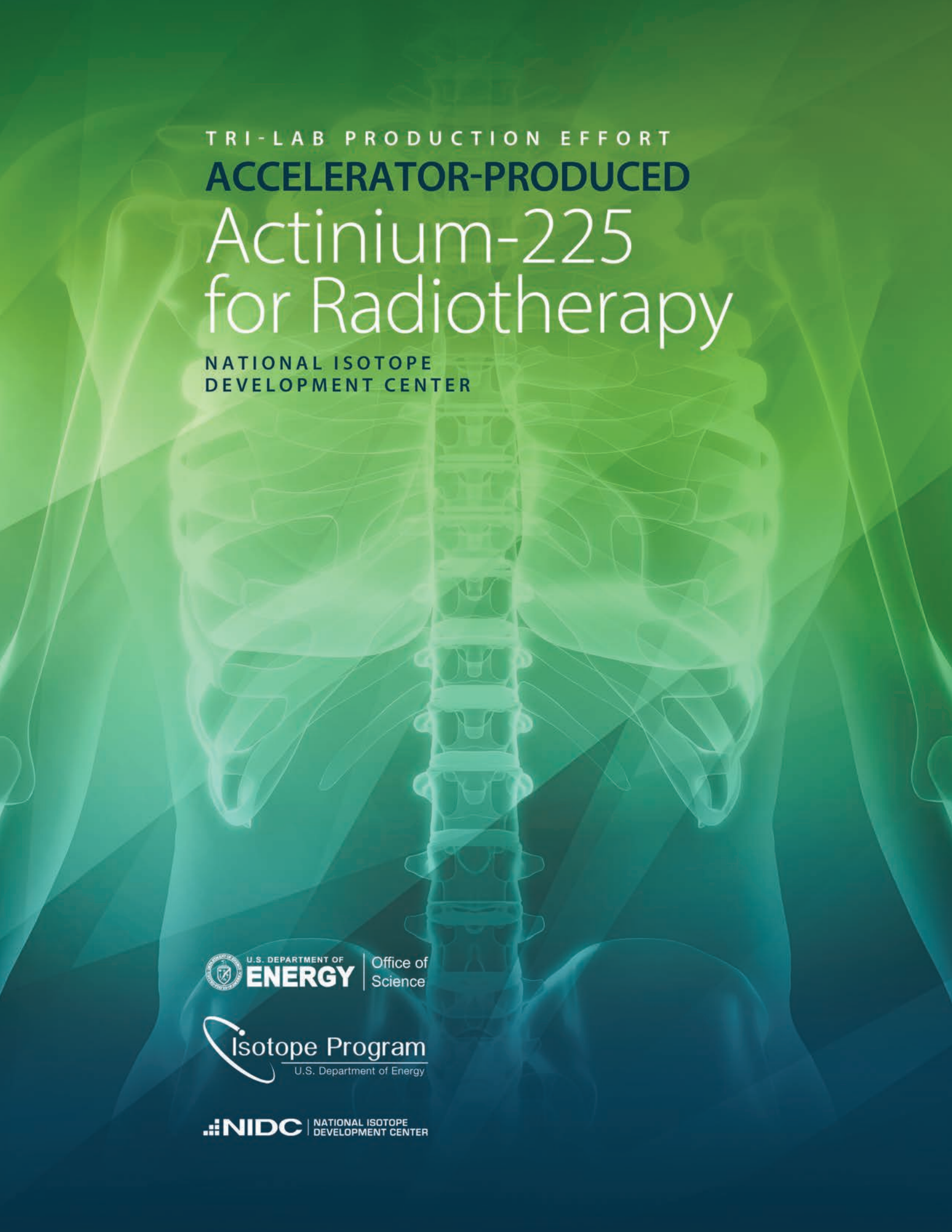


TRI-LAB PRODUCTION EFFORT

ACCELERATOR-PRODUCED Actinium-225 for Radiotherapy

NATIONAL ISOTOPE DEVELOPMENT CENTER

U.S. DEPARTMENT OF ENERGY | Office of Science

Isotope Program
U.S. Department of Energy

NIDC | NATIONAL ISOTOPE DEVELOPMENT CENTER

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, this joint "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 to produce accelerator-based Ac-225.

The goal of the Tri-Lab effort is to meet the growing worldwide demand for Ac-225 for direct and actinium-225/bismuth-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 provides a supply of Ac-225 that is capable of supporting clinical trials and applications.

Actinium-225 final product, with blue glow due to phosphorescence of the glass vial by alpha particles.

A drug master file for accelerator-produced Ac-225 was accepted by the U.S. Food and Drug Administration in January 2020. For more information, contact the NIDC.

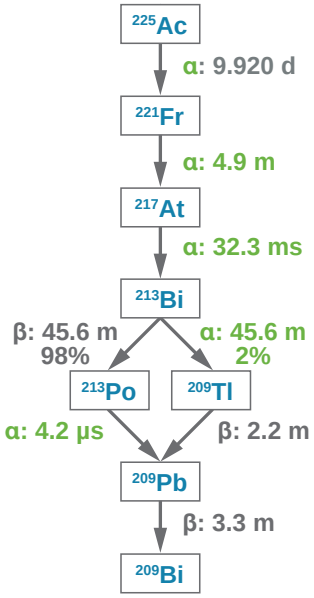
Ensuring Product Quality and Applicability

Target stack assembly used for the BNL/ORNL 100 mCi batch.

Since the initiation of the DOE Isotope Program Tri-Lab effort in 2015, the team has advanced production target development, chemical process methodology, and general logistical considerations 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 End of Batch) between 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.* 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 purifying Ac-225 produced in the decay of Th-229.

***See E. Dadachova et al., *Current Radiopharmaceuticals*, 2018, 11, 215–222 for more details.**

Left photo: BLIP—165 μA intensity H+ beam delivered to targets at incident energies ranging from 66 to 202 MeV. Right photo: Cathy Cutler with BNL leads a user group session focused on Ac-225 at the 2019 Society of Nuclear Medicine and Molecular Imaging annual meeting



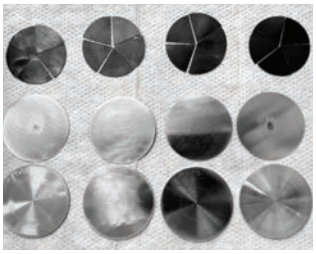
Ac-225 decay scheme

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 provide 40–50 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 Ci batches to support potential Ac-225 approved drugs and/or Ac-225/Bi-213 generators at multiple locations. The program will of bring additional hot cell processing capability on-line in late 2020 with the anticipated completion of the BNL All-Purpose Hot Cell project. Additional Ci-scale facility investments are planned for LANL and ORNL.

Target Optimization

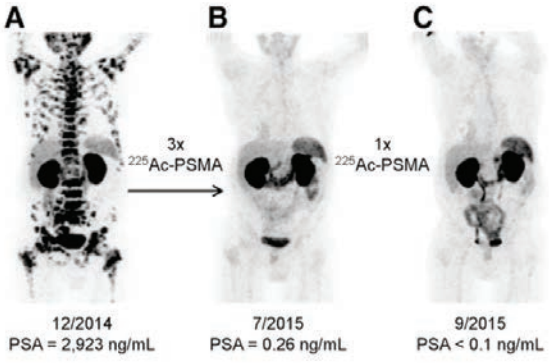
An inventory of radioactive thorium-232 (Th-232) metal has been established at LANL to support manufacturing of targets for routine production, and for advanced targetry development. The Tri-Lab effort has leveraged existing capabilities at LANL for processing and machining of Th-232 and developed protocols 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.



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

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; melanoma; and gastric, prostate, bladder, ovarian, and pancreatic cancers. Other diseases also under investigation include HIV infection, viral cancers, fungal infections, and emerging drug-resistant pathogen-related infections.



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.)

Accelerator produced Ac-225 is available for purchase now.
For information on availability and specifications, please contact:

National Isotope Development Center

www.isotopes.gov

EMAIL: contact@isotopes.gov • **TELEPHONE:** (865) 574.6984 • **FAX:** (865) 574.6986