Newsletter
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Reliable Supply of Actinium-227 for Cancer-Fighting Drug Ensured with New Contract

In one of its most significant contracts to date, the U.S. Department of Energy Isotope Program (DOE IP) has agreed to supply Bayer Consumer Care AG with a 10-year supply of actinium-227 (Ac-227) to support the anticipated market growth of its drug Xofigo®, used to treat male patients with prostate cancer that has metastasized to the skeleton. This advanced form of cancer can be quite painful for patients due to bone fractures and spine compressions, among other skeletal symptoms.

ORNL's Karen Murphy and David Denton conduct Ra-226 purification in hot cell. (Image courtesy of ORNL)

During the development phase, Bayer acquired the necessary Ac-227 stock needed for Xofigo® through multiple—yet sparse—channels, but once it achieved approval from the U.S. Food and Drug Administration in 2013, the need for a more robust supply chain grew significantly. After reviewing viable options, the DOE IP identified the Oak Ridge National Laboratory (ORNL) as an ideal entity for handling such a large Ac-227 production campaign given its unique facilities and extensive expertise in reactor-based isotope production.

With only two years allotted to prepare facilities and develop production capability, ORNL was faced with a daunting list of required checkpoints, starting with an extensive readiness review process. After receiving the green light to proceed, the team began recovering radium-226 (Ra-226) from obsolete medical devices used in brachytherapy and "disassembling" them mechanically, and then developed a multi-step chemical process to remove numerous contaminants. The highly purified Ra-226 was then fabricated into pellets for encapsulation into small targets before being subjected to neutron irradiation for 10–12 days in the ORNL High Flux Isotope Reactor. During this relatively short irradiation, a small portion of the Ra-226 is transmuted to Ac-227 and several other radioisotopes, including some fission products.

Researchers in the Nuclear and Radiochemistry Group in ORNL's Nuclear Security and Isotope Technology Division chemically separated and purified the resulting Ac-227 while recovering the unburned targets for recycling. Finally, the team delivered its initial Ac-227 samples in three shipments to Norway in late 2016, successfully demonstrating that the final product specifications met regulatory standards and that ORNL had the resources and know-how to consistently provide a long-term supply.

With regular shipments of Ac-227 from ORNL now established, Bayer will periodically extract Ra-223, the active ingredient in Xofigo®, from the decaying radioisotope and ship it to treatment facilities in approximately 50 countries where it is now approved.

FACILITY HIGHLIGHT: Argonne National Laboratory

CONTRIBUTIONS BY DAVID ROTSCH AND JERRY NOLEN, ARGONNE

When considering an expansion to its isotope development and production network, the DOE IP strategically searches for facilities that offer a unique blend of capabilities, expertise, and/or product offerings that will help further its mission to alleviate supply constraints for the Nation's critical isotopes. The extensive capabilities housed at Argonne National Laboratory's Low-Energy Accelerator Facility (LEAF) and the Argonne Tandem Linear Accelerator System (ATLAS) User Facility successfully met these criteria across the board.

ELECTRON LINAC

Housed at LEAF, Argonne's electron linear accelerator (e-Linac) provides a unique method for cost-effective, high-yield production of radioisotopes used for medical, national security, basic science, and industrial applications. This method, based on photonuclear reactions, also results in high specific activities needed for certain clinical applications that are not always achievable through research reactors or proton accelerators.

A modular target station is used to probe the activation of select targets. (Image courtesy of Argonne)

Originally built in 1969, Argonne's e-Linac was recently upgraded with National Nuclear Security Administration funding to enable R&D that supports domestic production of molybdenum-99. The e-Linac now delivers energies up to 53 MeV and average power over 25 kW from 25 to 35 MeV. Multiple beam lines allow for multiple target stations. The combination of these beam energies and power enable the production of radioisotopes with Curie-level activities in just 2- to 5-day irradiations.

The Argonne team recently designed, constructed, and commissioned a general-purpose isotope production station with support from the DOE IP. Currently, this station aids in the production and delivery of high-specific activity Cu-67, a valuable cancer-fighting isotope. Today's batches measure up to 200 mCi at end of bombardment (EOB) following benchtop processing but will increase to Curie levels by early 2019, once hot cell processing capabilities are implemented. The team plans to expand its medical isotope portfolio to include scandium-47 and actinium-225 (Ac-225).

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ISOTOPE AVAILABILITY NEWS

Newly Available

- *Actinium-225 (accel.-produced)*
- *Actinium-227*
- *Aluminum-26*
- *Americium-241*
- *Astatine-211*
- *Copper-67*
- *Lutetium-177*
- *Ruthenium-96*
- *Selenium-75*
- *Silicon-32*
- *Strontium-89*
- *Thorium-232*
- *Titanium-44*
- *Uranium-234*
- *Yttrium-86*

Coming Soon

- *Barium-133*
- *Cadmium-109*
- *Carbon-14*
- *Cerium-139*
- *Iridium-192*
- *Iron-55*
- *Iron-59*
- *Holmium-163*
- *Promethium-147*

Under Investigation

- *Gadolinium-153*
- *Heavy water (D_2O)*
- *Lithium-7*
- *Manganese-52*
- *Molybdenum-98*
- *Molybdenum-100*
- *Scandium-47*
- *Silicon-28*
- *Silver-111*
- *Tellurium-119*
- *Uranium-230*
- *Xenon-129*
- *Ytterbium-176*

Argonne *(Continued from page 2)*

SUPERCONDUCTING ION LINAC

Supported by the Office of Nuclear Physics, ATLAS is a DOE National User Facility capable of producing a wide variety of light and heavy ions that are useful for R&D and limited production of emerging isotopes using low-energy, ion-induced reactions. Ions available through ATLAS include protons, helium-3, helium-4, lithium-6, lithium-7, beryllium-9, as well as heavier options.

Relevant R&D conducted at ATLAS may include the exploration of production reaction yields via high-cross-section compound-nuclear reactions. Beam intensities available are well within the range required to produce research quantities of medical isotopes such as astatine-211 (At-211), and research towards the development of a Rn-211/At-211 generator has begun. Similar reactions enable development of a wide variety of Auger-electron emitting therapeutic and theranostic isotopes.

LABORATORIES

Argonne has a full array of conventional and radiological laboratories and radio-analytical counting equipment, including α-, β-, and γ-spectrometers; high-purity germanium (HPGe) detectors; multi-sample liquid scintillation; and NaI well detectors. Expertise and equipment to aid in the separation of radioactive material are also available.

For trace analysis and quality control, Argonne's analytical laboratory includes inductively coupled plasma mass spectroscopy (ICP-MS), inductively coupled plasma–optical emission spectroscopy (ICP-OES), and other instrumentation. Argonne recently purchased an Atomlab 500 dose calibrator for product distribution, a LabLogic Scan-RAM radio-TLC scanner for effective specific activity measurements, and an additional HPGe detector.

HOT CELLS

Two hot cells are designated for medical isotope processing activities on the hundred Curie-level scale. The first cell is adjacent to the e-Linac experimental hall, and the second, currently being outfitted for Cu-67 production, is in an adjacent building. Samples can be conveniently introduced and removed from these hot cells, and the interior equipment is fully customizable. Radiochemical laboratories are also available for processing of lower-activity samples, as well as for final chemical processing and quality assurance/quality control activities.

TEAM EXPERTISE

Through long-term and collaborative programs in physics, chemistry, and chemical and nuclear engineering, the Argonne team has developed extensive knowledge in technologies essential to research and production of radioisotopes. Their wide-ranging expertise includes:

- Accelerator design, engineering, and operations;
- Specialized target design and engineering;
- Chemistry and chemical engineering for isotope separation and purification;
- Nuclear engineering for shielding and design of targets with nuclear material;
- Engineering capabilities for the design and installation of hot cells and specialized equipment;
- Radiochemistry techniques; and
- Robotic handling to support the development of advanced remote isotope separation processing. ◇

The upgraded e-Linac housed at Argonne's Low-Energy Accelerator Facility has a maximum beam energy of 53 MeV and average power over 25 kW from 25 to 35 MeV. (Image courtesy of Argonne)

ACS Symposium Honors Exemplary BNL Retiree

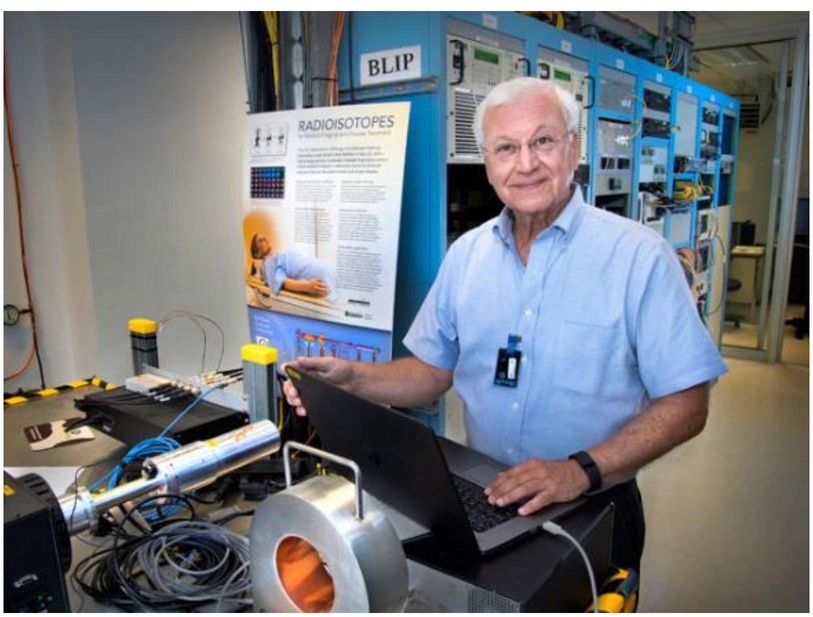
A symposium to honor Dr. Leonard Mausner was held at the American Chemical Society's (ACS) Fall 2018 National Meeting in Boston, Massachusetts. Mausner retired from BNL last year following thirty-six years of outstanding leadership and exceptional performance as a Senior Scientist and program manager.

Opening the session was Marc Garland, Deputy for the DOE IP and Program Manager for Isotope Operations, who shared how Leonard's creativity and technical skills have made a remarkable impact on BNL, the DOE IP, and the international isotope community. This includes his conception and implementation of several major facility upgrades at the Brookhaven Linac Isotope Producer (BLIP) that helped boost the availability of isotopes used in high-priority research and medical applications.

Next, a number of Leonard's close colleagues presented on a series of topics all directly tied to Mausner's career passions. These presentations ranged from medical radionuclide production with nuclear reactors and high-power accelerators to the ACS's Summer Schools in Nuclear and Radiochemistry, a program which he championed at BNL.

Bringing the session to a close was Leonard, himself, reflecting on some of his more memorable projects over the years as he contributed to the development of more than two dozen radioisotopes, all bridging his expertise in the fields of chemistry, nuclear physics, and mechanical engineering.

This symposium was organized by BNL's Cathy Cutler and the University of Missouri's Silvia Jurisson for the ACS' Division of Nuclear Chemistry and Technology.



Dr. Leonard Mausner (Image courtesy of BNL)

Isotope Spotlight

Accelerator-produced Actinium-225

Accelerator-based actinium-225 (Ac-225) is now routinely available through the DOE IP. The alpha-emitting radionuclide Ac-225 has attracted increased interest within the medical community for its radioimmunotherapy applications or its decay product bismuth-213 (Bi-213) from an Ac-225/Bi-213 generator.

The Ac-225 (half-life of 10.0 days) is produced with the DOE IP's high-energy accelerators at both Brookhaven and Los Alamos National Laboratories through the proton bombardment of natural thorium targets, and then separated and purified at ORNL. It has a theoretical specific activity of 5.8 x 10^4 Ci/g at EOB and a radionuclidic purity of ≥98% (~0.12% Ac-227 at EOB).

The DOE IP has completed accelerator production campaigns for Ac-225 every other month since early 2018, and the program plans to continue the bi-monthly schedule (depending on market demand) to ensure a reliable and abundant supply for research efforts and clinical trials.

Quotation requests for Ac-225 may be placed using the National Isotope Development Center's product catalog.

For further inquiries about the availability of Ac-225, please contact Dr. Wolfgang Runde, Associate Director for Production Planning and Customer Relations, NIDC.

Los Alamos Honors Isotope Program Achievements

Three teams whose work is supported by the DOE IP are recipients of 2017 LANL Distinguished Performance Awards:

1. **Isotope Production Team:** Acknowledges the core Isotope Production team and the significant production efforts for Sr-82 and Ge-68 last year
2. **Am-241 Oxide Production Team:** Acknowledges the successful completion of the first Am-241 oxide batch produced at LANL since the 1980's
3. **Isotope Production Facility (IPF) Accelerator Improvement Project Team:** Acknowledges the successful completion of the design and installation of the new beam transport system at IPF

Teams were recognized in September at the Los Alamos Large Team Distinguished Performance Awards Ceremony.

Isotope Production Team at LANL (Image courtesy of LANL)

Workshop Addresses Need for Low-Radioactivity Argon

CONTRIBUTIONS BY HENNING BACK, PNNL

A diverse group of scientists and engineers gathered in March on the campus of Pacific Northwest National Laboratory (PNNL) for the inaugural Low-Radioactivity Underground Argon (LRUA) workshop to explore the worldwide need for low-radioactivity argon and the challenges associated with its production and characterization.

Argon derived from the atmosphere contains the radioactive isotopes Ar-42, Ar-39, and Ar-37, which are produced via cosmic-ray interactions. Although at exceedingly low concentrations, these radioisotopes are the leading backgrounds in some argon-based nuclear- and particle-physics experiments, as well as in other radiation detectors. In 2015, the DarkSide-50 experiment demonstrated that underground argon produced for their search for dark matter contained an Ar-39 concentration 0.073% of that in the atmosphere. This finding has sparked a global interest in a sustained supply of LRUA to support a broad range of disciplines from nuclear and particle physics to environmental studies and national security.

The LRUA workshop was funded by PNNL's Nuclear-physics, Particle-physics, Astrophysics, and Cosmology Initiative, a Laboratory Directed Research and Development Program. (Image courtesy of PNNL)

Currently, LRUA is not actively produced anywhere in the world, although a production plant to support the next-generation DarkSide-20k experiment is planned at the previous underground production site. Additionally, CO_2 wells in Hungary comparable to those used by the DarkSide collaboration have been identified and are thus a potential source of LRUA within Europe. In addition, cryogenic distillation is being pursued as a method to further reduce the concentration of Ar-39, and emerging technologies hold promise for reducing the size of these distillation columns from hundreds of meters to less than ten.

In the survey and characterization of new LRUA sources, predicting the production of argon radioisotopes and measuring their concentration is critical. Techniques for measuring Ar-39 are being leveraged from the environmental sciences community, which include radiometric methods, single atom counting, and accelerator mass spectrometry. Despite the Ar-39 focus, the far less abundant Ar-42 was of strong interest for workshop attendees. Understanding the details of the Ar-39 beta-decay were also presented, including the recent purification of Ar-39 provided by the DOE IP.

In lieu of conference proceedings, a single workshop paper is in preparation, and all presentations can be found online at https://zenodo.org/communities/lrua.

ISOtopics

FACILITY IMPROVEMENTS

The target processing laboratory (TPL) at BNL has received funding from the DOE Office of Science for hot cell refurbishments that will vastly expand the group's ability to handle higher levels and different types of radioactivity. The improvements will also serve as a new space for production under current good manufacturing practices (cGMP), a capability that is critical for supplying sufficient volumes of alpha emitters needed for clinical applications.

Originally slated for demolition, the updated space will feature three hot cells (with 4-foot magnetite concrete walls), six manipulators, and four leaded glass windows, and will be conveniently located near BNL's analytical labs. It will also benefit from a new ventilation system that will improve airflow throughout the entire facility. The new additions will help broaden DOE IP's isotope portfolio and, thus, serve an increased number of stakeholders.

STAFF PROMOTIONS

Congratulations to Dr. Kevin Hart for being named ORNL's new Isotope Program Manager. Kevin, a Distinguished Scientist at ORNL, previously led the Stable Isotope Group where his leadership was instrumental in re-establishing a domestic, enriched stable isotope production capability for the DOE IP.

FEATURED PUBLICATION

A LANL research team has published a comprehensive chapter entitled "Actinides in Medicine" as part of the Encyclopedia of Inorganic and Bioinorganic Chemistry (June 2018). Here, the team summarizes past, present, and future applications of actinides in medicine, particularly their role in medical imaging and therapy. Modes of production, medically relevant decay chains, principles of chelation, and target vectoring are also discussed in detail. In addition, a summary of actinides in preclinical and clinical trials, including Ac-225, Th-227, U-230, Th-226, and Bi-213, is provided.

Eva Birnbaum, Michael Fassbender, Kevin John, and former postdocs Tara Mastren (now at the University of Utah) and Maryline Ferrier (now at the University of Washington) co-authored this publication.

UPCOMING EVENTS

Annual Congress of the European Association of Nuclear Medicine, October 13-17, 2018, Düsseldorf, Germany

2018 American Society for Therapeutic Radiology and Oncology (ASTRO) Annual Meeting, October 21-24, 2018, San Antonio, Texas

2018 IEEE Nuclear Science Symposium and Medical Imaging Conference (NSS/MIC), November 10-17, 2018, Sydney, Australia

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