Fall/Winter 2007
Volume 2, Issue 1

Isotopes
For Medicine, Science and Industry

ISOTOPE NEWS

For additional information, see our website at http://www.isotopes@ornl.gov, or contact us at clinerl@ornl.gov.

Inside this issue

Newsletter of the
U.S. Department of Energy's
Isotope Program

Dear Isotope User Community:

In the spring/summer issue of *Isotope News*, John Pantaleo introduced the first changes in the U.S. DOE Isotope Program and its transition to contractor-based management. A key objective for the Isotope Program is to increase production capacity and the isotope portfolio. The Program's intent is to achieve a better balance between managing DOE's unique facilities and producing isotopes for commercial application, as well as low-volume isotopes critically needed by the scientific community for research.

We have taken early steps to identify future isotope needs and to develop new production of isotopes. We appreciate the feedback we received on the list of critical isotopes from the industry forum (CORAR), the Society of Nuclear Medicine's subcommittee on Radiopharmaceuticals. We have begun discussions with the National Cancer Institute (NCI) to help us identify additional critically needed research isotopes.

We will continue to expand and to integrate a network of production sites to serve the community with a dependable supply of isotopes and to increase the capacity of the Isotope Program to produce a wider variety of isotopes. In 2007, the accelerators at both Brookhaven National Laboratory and Los Alamos National Laboratory were operated in a dedicated mode in order to enable the year-round availability of accelerator-produced isotopes. We expect that a Hydraulic Shuttle Irradiation System at INL's Advanced Test Reactor will be available in FY 2009 for routine irradiation and isotope production services.

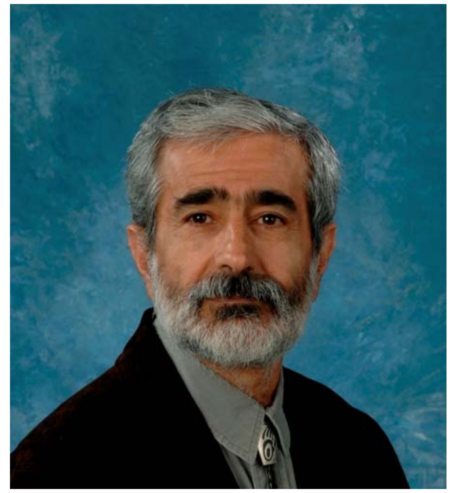
As noted in their recent report, *Advancing Nuclear Medicine Through Innovation* (2007), the National Research Council and the Institute of Medicine of the National Academies strongly recommended the cooperation between DOE and the National Institutes of Health. The program is committed to coordinate with other agencies, such as the NCI, in evaluating the most effective supply options. Meetings have started with the NCI to discuss future coordinated efforts and the need for a 70-MeV accelerator to reliably supply research isotopes.

The Isotope Program is considering several options to best serve its customers. The Isotope Program's management team is committed to take on the challenges to supply the range and volumes of necessary isotopes. With your support and participation, we will continue working toward strengthening the Department's ability to meet the national need for stable and radioactive isotope products. Representing the management team, we thank you for a productive year and wish you a peaceful and happy holiday season.

Wolfgang Runde
Program Manager

Brookhaven National Laboratory · INL Idaho National Laboratory · Los Alamos National Laboratory EST. 1943 · MURR · Oak Ridge National Laboratory · Pacific Northwest National Laboratory

ORNL's Mirzadeh Wins Seaborg Medal Award



Dr. Saed Mirzadeh, a senior scientist in the Oak Ridge National Laboratory's (ORNL's) Nuclear Medicine Program, was awarded the American Nuclear Society's 2007 Seaborg Medal, which is given in recognition of "significant contributions to the scientific basis for a wide variety of peaceful applications of nuclear technology." The award, established in 1983, is named for Glenn T. Seaborg, the Nobel Prize–winning nuclear chemist.

Dr. Mirzadeh's accomplishments have earned him a reputation as one of the most respected scientists in the fields of nuclear and radiochemistry; isotope production; and applications of isotopes in medicine, industry, and national security. This recognition was evidenced by more than 20 letters of endorsement in support of his nomination, and testimonials from colleagues at ORNL, other national laboratories, federal agencies, universities, and medical institutions around the world.

The depth of Dr. Mirzadeh's scientific contributions is demonstrated by his 73 peer-reviewed publications; 52 book chapters, reviews, monographs, and presentations; and 10 awarded patents. The breadth of this work is attributable to his rare combination of theoretical and practical command of his fields of endeavor and his mastery of science from first principles to practical applications.

A highlight of Dr. Mirzadeh's work is his stimulation of the progress of research in radioactive isotopes that emit alpha particles, particularly in medical applications such as the treatment of cancer. He developed the chemistry for the separation of thorium-229 from uranium-233-bearing material at ORNL as well as the subsequent separations of the medically useful decay products. Radioisotopes supplied by Dr. Mirzadeh are used in many laboratory and clinical investigations in radiobiology and cancer therapy. At ORNL, he and his colleagues developed processes to attach these radioisotopes to antibodies and studied the efficacy of alpha-particle therapy for the treatment of cancer, a strategy that directly targets radioisotopes to cancer cells. This technique very effectively kills the cancer cells while minimizing the effects on healthy tissue. The ORNL work and other laboratory and clinical investigations under way (such as a clinical trial for leukemia therapy at Memorial Sloan-Kettering Cancer Center) have shown great promise for alpha-particle-based treatment strategies.

Throughout his career, Dr. Mirzadeh has been at the forefront of isotope production and applications research and development. In addition to his work with actinium, he developed the chemistry for radioisotope generator systems: tungsten-188/rhenium-188 and molybdenum-99/technetium-99*m* (for molybdenum-99 produced using molybdenum-98 targets).

His development of targets for tungsten-188 production and the tungsten-188/rhenium-188 generator system has facilitated the use of rhenium-188 in dozens of laboratory investigations and clinical trials worldwide.

Dr. Mirzadeh has also made seminal contributions to the production and use of radioisotopes for other medical, industrial, and national security applications as well as to the fundamental science of isotope production and nuclear physics. This includes the production of and subsequent research on astatine-211, germanium-68, tellurium-125*m*, yttrium-90, tin-117*m*, platinum-195*m*, nickel-63, promethium-147, barium-140, and thulium-170. His latest work has been an internationally recognized pioneering effort in the development of radiofullerenes, a unique approach to encapsulation of radionuclides in nanoscale structures.

Beyond his technical accomplishments, Dr. Mirzadeh has a tremendous interest in the education of the next generation of scientists and engineers. He has generously given his time to work with dozens of students, supervising 7 postdocs, serving as the advisor for 7 M.S. and 4 Ph.D. students, and mentoring more than 20 graduate and undergraduate students during summer internship programs and throughout the academic year.

The honor of being awarded the Seaborg Medal is particularly appropriate, given that much of Dr. Mirzadeh's work extends the fields of nuclear science and technology pioneered by the late Dr. Glenn Seaborg. Bestowing the award to a scientist who has made many contributions to the fields of isotope production and nuclear medicine serves as a tribute to Dr. Seaborg, who had a great interest in medical applications of radioisotopes.

Recent News

Nuclear Regulatory Commission Expands Definition of Byproduct: The NRC issued the final rule for the expanded definition of byproduct material in the *Federal Register*, Volume 72, Number 189, on October 1, 2007. The NRC amended its regulations to include jurisdiction over discrete sources of radium-226, accelerator-produced radioactive materials, and discrete sources of naturally occurring radioactive material. This new rule became effective November 30, 2007. The full text of the final rule can be found at www.access.gpo.gov/su_docs/fedreg/a071001c.html.

Review on State of the Science of Nuclear Medicine Published: The DOE and NIH commissioned a study to review the current state of the science in nuclear medicine, to identify future opportunities in nuclear medicine research, and to identify ways to reduce the barriers that impede basic and translational research. This study was initiated in response to discussions between DOE and the Office of Management and Budget about future R&D areas the DOE Isotope Program should focus on. The findings and recommendations were released on September 20 by the National Academy of Sciences and can be found on the website of the National Academies Press at http://www.nap.edu/catalog.php?record_id=11985#orgs.

Mo-99 Production Interrupted: An isotope supply crisis began when a scheduled shutdown of the National Research Universal (NRU) facility at Chalk River, Canada, on November 18 was extended until mid-January by owner-operator AECL. The extension was caused by outstanding upgrades of NRU's mechanical and safety systems. In an extraordinary sequence of events, the Canadian Parliament overruled the Canadian Nuclear Safety Commission (CNSC) and ordered the early restart of the NRU reactor. The NRU research reactor at Chalk River Laboratories, Ontario, was safely returned to service at 3:44 a.m. local time on December 16, 2007.

.

Operating Schedules of Isotope Production Facilities at ORNL, BNL, and LANL for FY 2008

In FY 2008 ORNL's High Flux Isotope Reactor (HFIR) resumed operation on November 14 following a cold neutron guide upgrade and planta reliability upgrades to begin a series of six operating cycles through the remainder of the fiscal year. Each cycle lasts 23-25 days. HFIR operates at a power of 85 MW as a high-flux neutron source for isotope production, materials studies, and neutron scattering research. Figure 1 shows the hydraulic rabbit tube facility at HFIR.

In FY 2007 HFIR had completed three full operations cycles after restarting on May 6 following completion of its new cold neutron source for neutron scattering research. Isotope irradiations provided for production of the commercial isotopes Cf-252, Fe-59, Ni-63, and Se-75, and of the research isotopes Ba-140, W-188, Lu-177, and Te-125*m*. During these three cycles, the HFIR neutron activation analysis (NAA) facility also produced ten small Yb-169 sources for use in gamma densitometry measurements at the Y-12 National Security Complex.

The normal operating schedule of LANL's Isotope Production Facility (IPF) spans from May/June to December 2008, while Brookhaven's Linac Isotope Producer (BLIP) will be operated February through May 2008. In order to compensate for reduced production at IPF in November 2007, the BLIP will be Operated in a dedicated mode in December and January 2008. Routinely produced isotopes at IPF and BLIP are Sr-82, Ge-68, Na-22. In 2008 IPF and BLIP will be experimenting to expand their capabilities to produce a greater variety of isotopes, including some research isotopes.

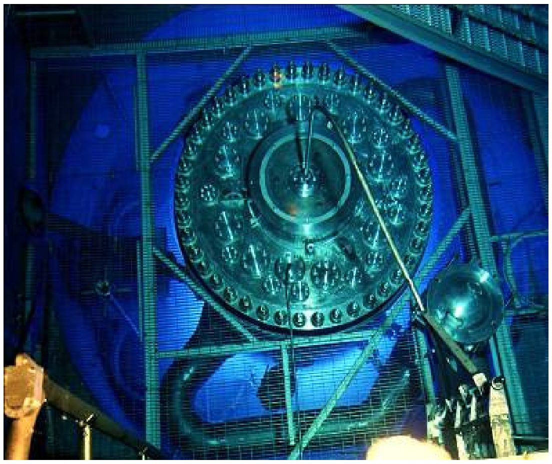


Figure 1. Top view of the HFIR pressure vessel with its hydraulic rabbit tube facility, which is used to insert and remove isotope capsules that require only short-term irradiation (hours or days). These short-duration irradiation capsules are generally used for the production of medical isotopes.

Stable Isotope Products and Services

Eva C. Hickman and W. Scott Aaron
Oak Ridge National Laboratory

The Isotope Research Materials Laboratory (IRML) and Chemistry Processing Operations maintains, processes, and distributes the entire DOE stable isotope inventory (valued at $360M) on materials priced at $0.87/mg to $18,681.14/mg and contained in over 2000 batches of some 225 stable isotopes from approximately 50 multi-isotopic elements (Figure 1). This article details services and products available through the Isotope Development Group at ORNL.

The Isotope Development Group (IDG) is part of the Nuclear Science and Technology Division. The IDG is divided into three primary functional areas:

(1) The Isotope Business Office (IBO), which negotiates contractual agreements with customers worldwide for ORNL; Brookhaven National Laboratory; BWXT-Y-12, LLC; Los Alamos National Laboratory; and Westinghouse Savannah River Company. The IBO arranges shipments and invoices for all stable and radioactive isotopes for the DOE Isotope Program.

(2) The Nuclear Medicine Program, in which research is focused on the development and processing of radioisotopes for applications in nuclear medicine.

(3) Stable Isotope Products and Services, which includes IRML, Chemistry Processing Operations, and surveillance and maintenance of the Calutrons.

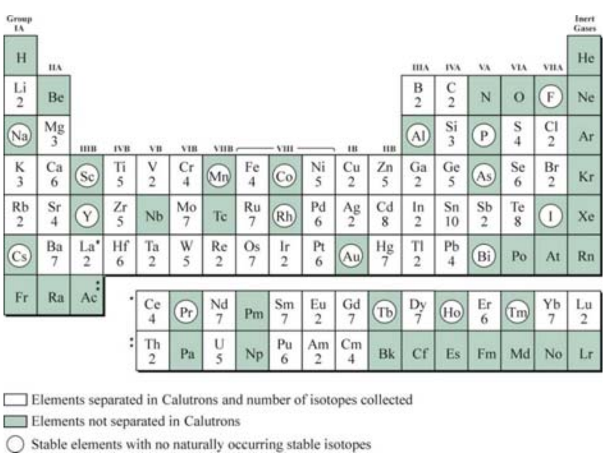


Figure 1. Isotopes enriched by the Calutrons.

Stable isotopes have been available in significant quantities since the end of World War II, when Calutrons previously used for uranium enrichment were redirected to separate or enrich stable isotopes. These isotopes have numerous medical, research, and industrial applications. The isotopes are stored in their most chemically stable form, typically as powders, and can be dispensed, packaged, and shipped to the customer in accordance with U.S. Department of Transportation/ International Air Transport Association regulations. Non-electromagnetic-separated isotopes (solids and gases) transferred to ORNL from Mound Laboratory are also dispensed. These include Ar, He, Kr, Ne, O_2, and Xe gases and N, Cl, Br, O, and S compounds.

Many applications require the isotope to be in a particular chemical or physical form. Conversions to alternate chemical forms are a routine service provided to customers. Metallurgical, ceramic, and vacuum processing is also used to provide custom physical forms. They include metal foils, ingots, wires, custom alloys, pressed and sintered or hot pressed metals and ceramics, and both supported and self-supported thin films.

Figure 2 illustrates those elements for which custom chemical and physical forms have been prepared by the IRML and Chemistry Processing Operations. The capabilities developed in regard to isotopes are also applied to support a large number of other programs including R&D and the Department of Homeland Security.

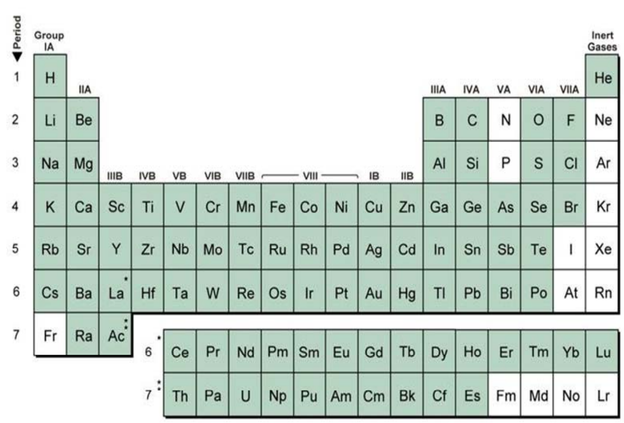


Figure 2. Custom chemical and physical forms are prepared for the elements shown in green on the periodic table.

The IDG has the equipment and staff expertise for the following materials processing capabilities:

1. Chemical processing and custom chemical conversions of inventory form to customer-requested forms. Wet-chemistry techniques are applied to the initial recovery and refinement of the Calutron-enriched isotopes and are also used to convert isotopes into custom chemical compounds and to reprocess stable isotope lease returns upon termination of the leases (Figure 3).

Figure 3. Chemical Processing Laboratory.

2. Conversions of isotopes to metal form. Hydrogen reductions, electrochemical reductions, and more-complex pyrochemical reductions are all performed to obtain isotopes in metal form. Pyrochemical reduction/ distillation techniques to convert rare earth and Group IIA oxides to high-purity metals involve reduction, typically using lanthanum metal, in a tantalum crucible or still under high vacuum using radio-frequency induction heating (Figure 4). Following reduction, the high-purity metal is vacuum distilled into a quartz dome for recovery. In some cases, the metal vapor pressures are too low to allow effective distillation, so a two-step process involving conversion of the oxide to fluoride followed by reduction to metal by calcium is performed.

Fig. 4. Magnesium beads grown by reduction/distillation. (a) magnesium beads, (b) tantalum still. (Note the blue calcium metal vapor exiting the top of the tantalum still.)

3. Melting and alloying metals into ingot forms for further processing or drop casting. Metal powders, trimmings, or other forms are melted in a water-cooled copper hearth by heating with an electric arc (Figure 5). Metals may be arc melted into an ingot for further processing or drop cast into special molds (Figure 6). Other metals such as lithium are melted in a crucible and then poured into molds. Vacuum melting with an electron beam, resistance, or radio-frequency induction heating is also possible.

Figure 5. Arc melter for consolidation and metal casting.

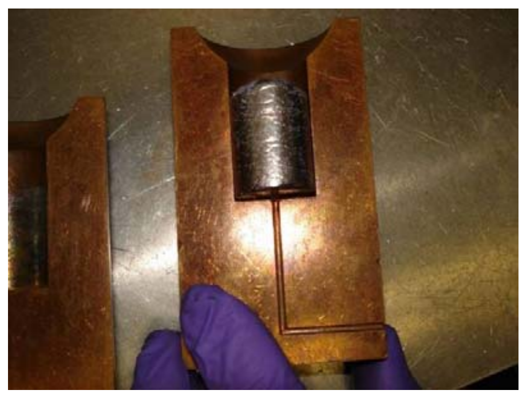


Figure 6. Drop-cast mold for a cylinder.

4. Hot and cold rolling of metals of millimeter-to-micron thicknesses, including cold rolling of reactive metals under argon atmosphere. Following conversion to metal and consolidation, many isotopes can simply be cold rolled, either directly or in a stainless steel rolling pack. Some metals require hot rolling, in which the metal is enclosed in an argon-filled rolling pack and sealed with a weld. The metal is heated to the appropriate temperature, rolled for several passes, and then placed back into the furnace.

This process is repeated until the appropriate thickness for further cold rolling is attained (Figure 7). At any stage, a radiograph can be taken of the rolling pack to determine location and condition of the rolled material. Many metals are too reactive to be handled in air, so cold rolling can be performed inside an argon glove box. Metal wires can be rolled (Figure 8), and for further size reduction in diameter, can be swaged or drawn to ~6 mils, depending on the material.

Figure 7. Rolling mill for hot or cold rolling**.**

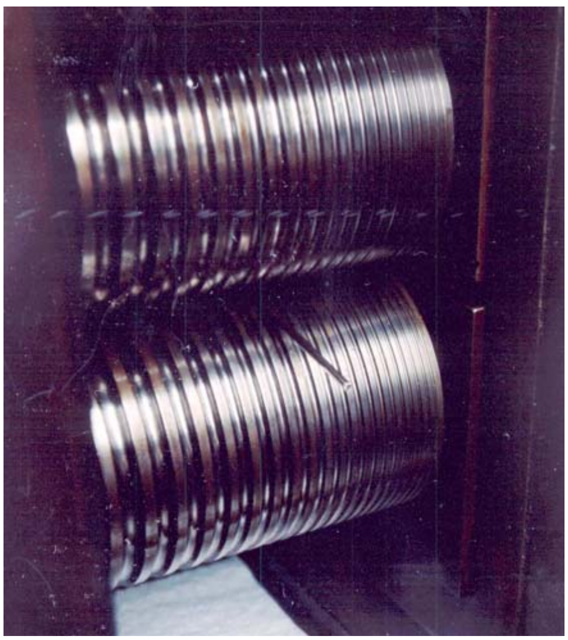


Figure 8. Wire-rolling mill.

5. Metal and ceramic powder consolidations using cold pressing. Metal or ceramic powders can be cold pressed to 40–50% theoretical density using a 50-ton hydraulic press. These cold compacts can be used as is, generally in a sealed holder or further consolidated by sintering. Powders can also be vacuum hot pressed at high temperature (~1800^{o}C) and pressure (up to 5000 psi) to nearly theoretical density.

6. Thin films and coatings. Thin films and coatings can be prepared by a variety of vacuum deposition techniques, including resistance, electron beam or radio-frequency induction heating (Figure 9). Plasma sputtering is also used. Both supported and self-supported thin films are often prepared for use as accelerator targets.

Figure 9. Evaporated aluminum foil**.**

Restoration of additional processing capabilities is under way:

• **Crystal bar reduction process, also known as the van Arkel–de Boer process**, for the preparation of silicon, titanium, zirconium, and hafnium metals

• **Electrodeposition** of metals such as zinc and chromium

The production and distribution of enriched stable isotopes is registered to the ISO 9001:2000 Standard, with initial certification achieved in 1996. The ISO 9001:2000 certification is an example of the IDG's commitment to excellence for its customers and sponsors.

The IBO received over 1000 inquiries this past fiscal year and shipped over 400 isotopes. For product information and technical services, please contact the IBO via web, e-mail, or phone:

http://www.ornl.gov/sci/isotopes/catalog.html
e-mail: isotopes@ornl.gov
Phone: (865) 574-6984

DOE-Sponsored Seminar on the Availability and Use of Rhenium-188 Radiopharmaceuticals and DOE-Supported Research on the Use of Tin-117*m* for Molecular Imaging and Targeted Therapy

F. F. (Russ) Knapp, Jr. (Oak Ridge National Laboratory) and Suresh Srivastava (Brookhaven National Laboratory)

The Second International Conference on Radiopharmaceutical Therapy (ICRT–2007) was held in Ulaanbaatar, Mongolia, September 3–7, 2007. The first meeting of this conference series, which is organized by the World Radiopharmaceutical Therapy Council (WRTC) of the World Federation of Nuclear Medicine and Biology (WFNMB), was held in Limassol, Cyprus, in 2005. The ICRT conferences provide a forum for radiopharmaceutical scientists and physicians to specifically discuss the development and use of therapeutic pharmaceuticals, as well as the status of clinical trials using these agents in nuclear medicine and oncology. The abstracts of ICRT-2007 have been published in the July 2007 issue of the *World Journal of Nuclear Medicine* (Vol. 6, Supplement 1). The Ulaanbaatar conference was held in association with the Annual Conference of Asia Regional Cooperative Council for Nuclear Medicine (ARCCNM), also a new organization focused on encouraging interaction and collaboration between Asian institutions.

Mongolia was chosen for the ICRT-2007 Conference because of the outstanding research of Professor P. Onkhuudai and his colleagues in the Nuclear Medicine Department of the First State Central Hospital of the Mongolian National Medical University in Ulaanbaatar. This group had made significant progress in the trial sponsored by the International Atomic Energy Agency (IAEA) for the treatment of refractory, inoperable liver cancer using rhenium-188 Lipiodol agents. The rhenium-188 was obtained from the ORNL tungsten-188/rhenium-188 generator system. Several papers describing the results of this IAEA-sponsored multicenter clinical trial will be published in *Seminars in Nuclear Medicine* in early 2008.

The Conference president was Professor P. Onkhuudai, M.D., who heads the Nuclear Medicine Department in Ulaanbaatar. Professor Onkuudai, the first physician fully qualified in nuclear medicine, completed his specialist training in 1972 at Karl Marx University, in Leipzig, Germany. He established in 1975, and has since led, the Nuclear Medicine Department in Ulaanbaatar. He established the first radioimmunotherapy laboratory, where over 20 studies per day are now performed. Since 2000, the Department has had the first SPECT Elscint camera, and myocardial perfusion imaging is routinely performed. The establishment of nuclear medicine and the opportunity to host ICRT-2007 were great accomplishments for Mongolia, which is a large isolated country with a small population of about 3 million. The use of nuclear medicine techniques in Mongolia began in 1974, initially with the evaluation of uptake of iodine-131 in thyroid disorders, nephrography for renal disorders, and the use of gold-198 sulfur colloid for liver cancer therapy. Selenium-75 in selenomethionine was used for the first time for pancreatic imaging using a Hungarian rectilinear scanner.

The Ulaanbaatar conference had 210 participants from 67 countries—compared with 80 participants at the initial Cyprus conference—and was truly an international meeting. The ICRT-2007 Conference included a total of 155 oral and poster presentations in 17 scientific sessions, including 45 invited lectures. The Mongolian colleagues were very kind and gracious hosts.

Dr. Russ Knapp (ORNL) and Dr. Suresh Srivastava (BNL) participated as representatives of the DOE national laboratories, presenting several invited papers and chairing technical sessions. Dr. Knapp also served on an eight-member panel, "Special Session on the World Radiopharmaceutical Therapy Council to Review Current Status and Discuss Future Perspectives," for discussion of issues affecting the use of therapeutic radiopharmaceuticals in developing countries. Discussions focused on the issues of cost and availability of therapeutic radioisotopes. He also led discussions at a DOE-sponsored seminar regarding the issues associated with the cost-effective utilization of the ORNL tungsten-188/rhenium-188 generator. In addition, he chaired and provided the opening lecture describing the DOE isotope production facilities in the United States.

Dr. Srivastava presented two plenary lectures. In his presentation on "The Role of Electron Emitting Radiopharmaceuticals for Therapeutic Oncology," he highlighted recent advances in molecular biology that have led to better understanding of cancer and other diseases, including parallel promising research on various biological vehicles that can deliver cell-killing radiation to tumors in a highly localized fashion. The second lecture, "Potential of Conversion Electron Emitter Tin-117*m* for Application to Cardiovascular Therapies," focused on the DOE-supported research on the merits and uses of the conversion electron emitter tin-117*m* for diagnostic (molecular imaging) and therapeutic applications, in particular for cardiovascular diseases.

The Third International Conference on Radiopharmaceutical Therapy will be held in Cartagena, Colombia, in November 2009.

Upcoming Conferences in 2008:

- 8th International Symposium on Radioactive Isotopes in Clinical Medicine and Research, Jan. 9–12, Bad Hofgastein, Austria, www.nucmed-gastein.at
- 6th International Conference on Isotopes, May 12–16, Seoul, Korea, http://www.intl-isotope-soc.org/events/2008/5/12/148
- Annual Congress of the European Association of Nuclear Medicine, Oct. 11–15, Munich, Germany
- Nuclear Medicine Tomorrow – Cite Internationale des Congres de Nantes, March 30–April 2, Nantes, France, www.nmt2008.org
- Society of Nuclear Medicine 55th Annual meeting, New Orleans, Louisiana, USA, June 14–18, http://interactive.snm.org

Availability of HFIR-Produced High-Specific-Activity Lutetium-177 from ORNL

The restart of the ORNL High Flux Isotope Reactor (HFIR) in May 2007 has permitted resumption of production of several important radioisotopes for medical and industrial applications, including high-specific-activity (HSA) lutetium-177.

The goal has been to provide samples of this important therapeutic radioisotope to several collaborators for radiolabeling studies in order to assess the global interest in the potential routine availability of HSA lutetium-177 from ORNL. Lutetium-177 decays with the emission of a relatively low energy beta particle (0.497 MeV), which is most well suited for deposition of energy to kill small tumor sites such as micrometastases, which are encountered in later stages of many cancers. Lutetium-177 has a half-life of 6.7 days, which permits international distribution. The specific activity depends on the thermal flux of the reactor and other irradiation parameters, and currently commercially available lutetium-177 is produced in lower-flux reactors with a specific activity of <20 Ci/mg Lu.

Because of its very high maximal thermal flux of ~2 x 10^{15} $n \cdot cm^{-2} \cdot s^{-1}$, use of the HFIR offers an important and unique opportunity to provide to the research and clinical communities much higher specific activity lutetium-177, with a specific activity exceeding 60–70 Ci/mg Lu. The availability of this new product is important for instances in which the mass levels of the carrier molecules—usually a peptide or antibody—that target the cancer cells following intravenous administration must be minimized because of the limited binding sites or potential toxicity.

Following HFIR Cycle No. 410, lutetium-177 was processed and provided to several collaborators for analysis. If broad interest and thus a potential market for HFIR-produced HSA lutetium-177 develops, then the decision to add lutetium-177 to the ORNL portfolio of radioisotopes that are routinely produced and distributed will be assessed, as well as the possibility of developing the current Good Manufacturing Practice (cGMP) Quality Program and submission of a Drug Master File to the U.S. Food and Drug Administration.

Silicon-32 to Be Available in 2009

DOE produced silicon-32 (half-life of 100 years) at its Los Alamos accelerator by spallation of potassium chloride targets at 800 MeV [Cl-37(p,α2p)→Si-32] until 1998, when the 800-MeV beam was discontinued. In 2006, DOE exhausted its supply of silicon-32, which is used as an environmental tracer in oceanographic research and in waste vitrification tests. Discussions were begun with Tri University Meson Facility (TRIUMF) to use its 475-MeV proton facility in Vancouver, B.C., Canada, to irradiate potassium chloride targets for subsequent processing at Los Alamos National Laboratory (LANL). The targets have been fabricated and will be inserted into the TRIUMF 475-MeV proton source as soon as the Safety Analysis Report is approved. We expect to make silicon-32 available to researchers in 2009.

We're on the Web!

See us at

http://www.ornl.gov/sci/isotopes/catalog.htm

ISOTOPE BUSINESS OFFICE
P.O. BOX 2008
BLDG. 5700, ROOM R111
OAK RIDGE, TN 37831-6158

The newsletter is also available on our website at http://www.ornl.gov/sci/isotopes/catalog.htm. If you are not currently receiving our newsletter and wish to do so, you can add your electronic mail address by following the instructions at this link: https://email.ornl.gov/mailman/listinfo/isotope-newsletter.