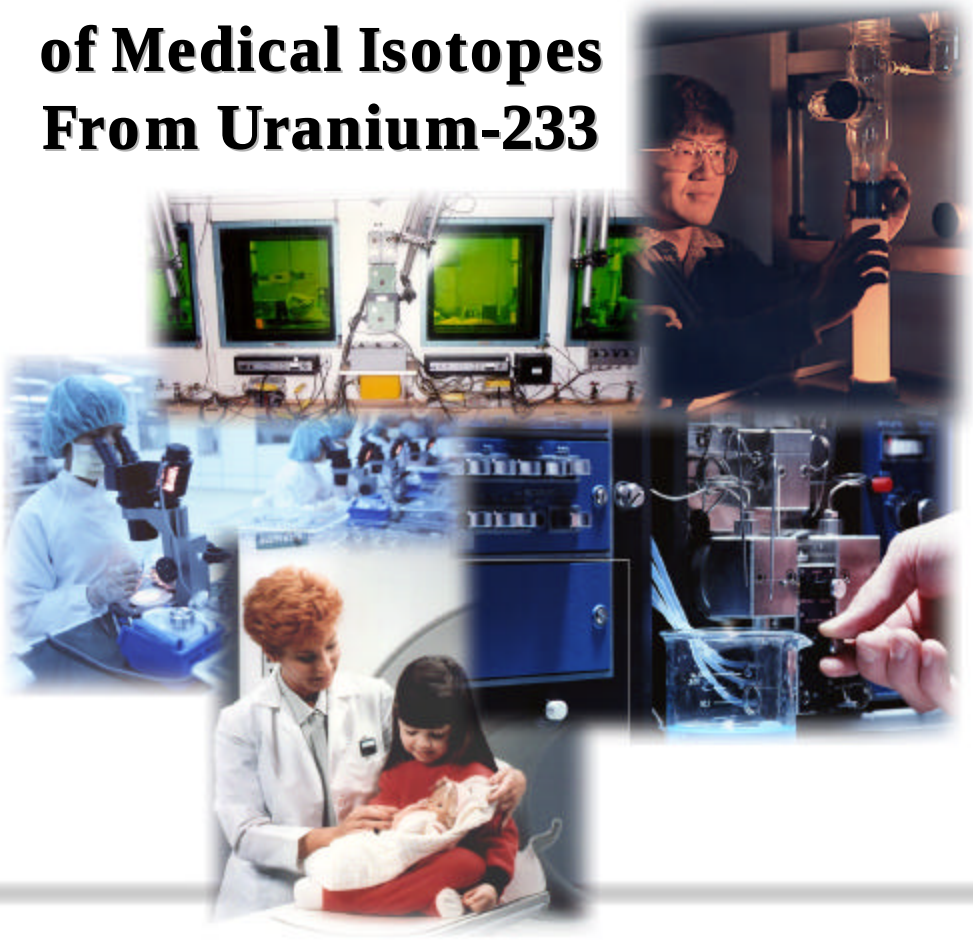
Report to Congress on the Extraction of Medical Isotopes From Uranium-233



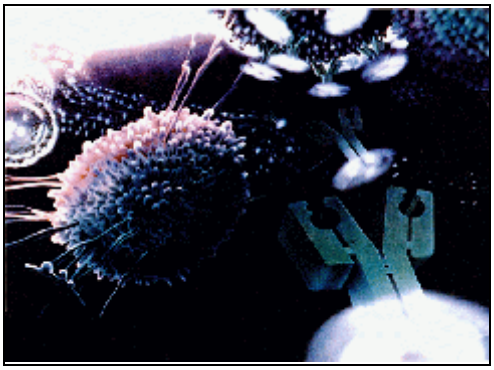
U.S. Department of Energy
Office of Nuclear Energy, Science and Technology
Office of Isotopes for Medicine and Science

March 2001

1. Introduction:

Medical isotopes save lives and reduce health care costs. Some of the more frequent uses of medical radioisotopes include diagnosis and treatment of several major diseases, sterilization of medical products, tissue grafts, nutrition research, and biomedical research into cellular processes. The Department of Energy supports the U.S. health care industry and medical research by producing these isotopes and through the support of fundamental isotope research. A class of medical isotopes -- alpha-emitting radioisotopes -- is of growing interest in the cure of cancer. To understand this interest, the Department sponsored a workshop on "Alpha-Emitters for Medical Therapy" in May 1996. As a result of the workshop, the Department, through the Office of Nuclear Energy, Science and Technology, undertook significant efforts and expended several million dollars in order to establish a domestic supply of the alpha-emitting radioactive isotopes actinium-225 (Ac-225) and bismuth-213 (Bi-213). Because of these efforts, researchers have made tremendous advances in the diagnosis and treatment of cancerous tumors in the human body using monoclonal antibodies and their molecular subunits in various forms as carriers for these radioactive isotopes.

Specifically, because alpha-particles deposit their energy over microscopic dimensions, antibodies "tagged" with this radioactive isotope deliver a potent dose of radiation directly to the cancer with minimal or no exposure of healthy tissue. In June 2000, former Secretary of Energy Richardson directed the Office of Nuclear Energy, Science and Technology to increase the supply of the isotopes Ac-225 and Bi-213 available to researchers through the processing of more uranium-233 (U-233) currently in storage at the Department's Oak Ridge National Laboratory (ORNL). This spring, the Department intends to further expand the supply of Ac-225 and Bi-213 by issuing a request for proposals for a contract that will, among other things, substantially increase the available supply of these isotopes to the research and medical community. In addition, the Department intends to undertake long-term activities concerning the production of Ac-225 and Bi-213.



Radioisotope-tagged monoclonal antibodies act as "Smart Bullets" by targeting malignant cancer cells for diagnosis and treatment

The Department is submitting this report on the status of its activities to process the U-233 in a manner that would retain and make available isotopes for beneficial use.

2. Background:

Nuclear medicine offers one of the safest ways to diagnose and treat several types of cancer, leukemia, heart disease, and other serious, life-threatening diseases. It does so without noticeable adverse effects on

normal organs and without the debilitating side effects and extended hospital stays associated with more common treatments. Each year, about one-third of the 30 million Americans hospitalized are diagnosed or treated with one or more nuclear medicine techniques, representing a $7-10 billion per year industry. Radioisotopes and radiopharmaceuticals, which are at the heart of nuclear medicine, are used in the United States alone for almost 40,000 procedures every day and in more than 100 million laboratory tests each year. The use of medical isotopes also reduces health care costs by improving the quality, efficiency, and effectiveness of patient care. Medical research using isotopes continues to promise new applications for fighting other diseases such as Huntington's and Alzheimer's. Adequate supplies of medical and research isotopes are essential to maintain U.S. effective diagnosis, treatment, and research capabilities.

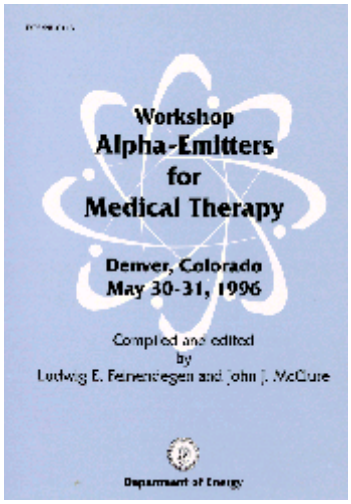
Over 90% of nuclear imaging utilizes Technetium-99, Thallium-201 and Fluorine-18 developed at the Brookhaven National Laboratory in the 1960's and 1970's

There is a long history, experience, and significant record of accomplishments in Department-supported radioisotope and radiopharmaceutical research, particularly at the national laboratories, going back to over three decades. Examples of developments are: technetium-99m (used annually for about 85 percent of all diagnostic nuclear medicine imaging procedures worldwide), thallium-201 ("gold standard" for myocardial tests - the so-called thallium stress test), iodine-123 (determination of thyroid disease), copper-67 (cancer therapy and imaging), tin-117m (promising agent for bone pain treatment and bone cancer therapy), and fluorine-18 (most sensitive radiotracer for detection and diagnosis of cancer). Our unique national laboratory facilities have made these accomplishments possible. These facilities include accelerators and nuclear reactors for the irradiation of target material and hot cell facilities for target processing and isotope purification. The Office of Nuclear Energy, Science and Technology relies heavily upon the operation of these facilities by other Department programs. The Department and its predecessors have thus provided the necessary combination of facilities and expertise to conduct isotope research and development starting with a basic concept or a medical need and going all the way to conducting limited pilot clinical trials in human patients.

Primarily due to the Department's support, and in conjunction with the National Institutes of Health, the United States has become the world leader in the application of radioisotopes and radiopharmaceuticals for biomedical research. As a result, the benefits to patient healthcare have been immense. Despite our pioneering leadership, however, we have recently become dependent upon sources outside the United States for all of the technetium-99m and for many

radionuclides necessary to advance research in the health sciences and other areas. For the United States to continue contributions in the application of radioactive materials for biomedical investigations, it is essential that we establish a reliable source and supply of radioisotopes. Because of the uncertain supply of radioisotopes in the United States, many nuclear medicine researchers have become dissuaded from pursuing their ideas for new medical advances, threatening the future of nuclear medicine in the United States. To correct this gradual decline, the Department must continue to invest in dedicated, state-of-the-art facilities in order to reliably supply existing radioisotopes in use and develop new radioisotopes in sufficient quantity and year-long availability to support clinical research. Alpha-emitting radioisotopes are an example of this investment.

Moving into high gear after the Department's workshop on "Alpha-Emitters for Medical Therapy" held in May 1996, researchers increased their efforts using alpha-emitting isotopes and the use of monoclonal antibodies. Scientists are particularly interested in alpha-emitters, such as the Bi-213 isotope, for two reasons. First, alpha-emitters are extremely effective at killing cells through radioactive decay. Second, alpha-particles have a microscopic killing range, probably only a few cell diameters. Thus, if properly positioned, precise killing of cancer cells may be possible. Because of the short range of the alpha-emitter, few healthy cells surrounding the diseased cells will be harmed. Phase II human clinical trials for treatment of a type of leukemia using Bi-213 are underway at New York City's Memorial Sloan-Kettering Cancer Center. ORNL is studying Bi-213 for lung cancer therapy, and the National Cancer Institute is conducting studies to determine the value of this therapy in treating various cancers as well as transplant conditioning.



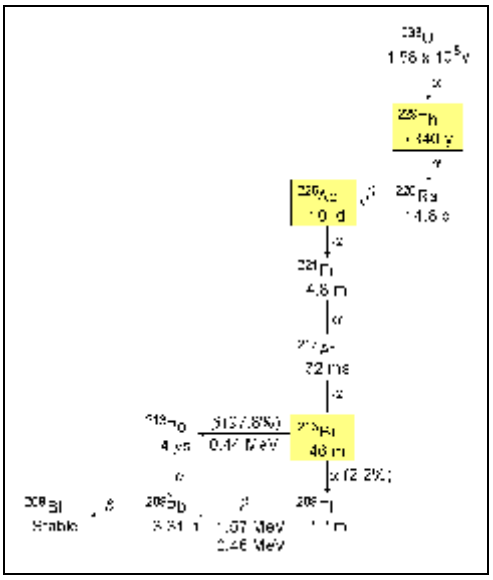
Additional workshops were held in June 1998 and at the June 2000 Society of Nuclear Medicine Conference

The Bi-213 isotope that is holding promise for medical treatment is produced through a complex process that starts with U-233. The key intermediates in this process are thorium-229 (Th-229) and Ac-225.

Ac-225 and Bi-213 are currently derived from purified Th-229 extracted from U-233 at ORNL. Theoretically, there are a number of ways to produce Bi-213 and Ac-225. The only practical way at present, however, is to derive these isotopes from the natural decay of Th-229. Th-229 is produced by the natural decay of U-233. Ac-225 is the product being shipped to medical facilities. Bi-213 is separated from the Ac-225 at the hospital and combined with the targeting agent.

The U-233 decay chain is the key to understanding the production of Ac-225. The decay chain shows that U-233 (with a half-life of 159,000 years) undergoes an alpha-decay to form Th-229. The U-233 nucleus is unstable and will eject an alpha-particle (i.e., a helium nucleus). The Th-229 daughter isotope is also unstable and will decay, producing another element. The last isotope in the U-233 decay chain, Bi-209, is stable and is not radioactive. The half-life is directly related to the rate at which the isotope decays (i.e., converts to another element). The shorter the half-life, the faster the decay. Bi-213 has a very short half-life of 45 minutes. After 45 minutes, only half of the Bi-213 is left. The other half will have decayed in this time. After another 45 minutes, one-half of the remaining Bi-213 will decay, leaving only one-fourth of the mass of the original Bi-213. After a number of hours, the amount of Bi-213 remaining will be undetectable. Ac-225 has a ten-day half-life and is used to produce the Bi-213.

The very short half-life of Bi-213 and its daughters provides an advantage to practitioners. Once administered, Bi-213 will quickly convert to stable bismuth-209. After about a day and a half, Bi-213 and its daughters should not be detectable in the patient. Bi-213 appears to be very potent, so only a very minute quantity may be needed to treat a patient. The amount of Bi-213 that is currently used in the experimental treatments is very minute, on the order of 0.000000001 grams (a billionth of a gram). Th-229 has a long half-life, 7,340 years. Thus, only a very small fraction is converted to Ac-225 and Bi-213 during a one-year



Uranium-233 Decay Chain

period. Once purified, Th-229 will reliably produce a limited amount of Ac-225 and hence the Bi-213 per year indefinitely.

The extraction of the Th-229 from the U-233 stored at ORNL is complicated due to several factors: 1) the approximately 40 grams of Th-229 is contained in approximately 450 kilograms of U-233; 2) the U-233 is contained in approximately 1,400 kilograms of other uranium isotopes in various forms (metals and oxides) stored in approximately 1,200 packages of varying configurations (tin cans, aluminum cans, stainless steel, glass, etc.); 3) the U-233 also contains U-232 contamination up to 220 parts per million, which after a series of decays, decays into thallium-208, which in turn emits a very energetic 2.6 MeV gamma, a significant radiation hazard during processing and handling; and 4) the U-233 is currently stored in Building 3019A, Radiochemical Development Facility, which was built to support the Manhattan Project, and has effectively exceeded its useful life.

On January 8, 2001, former Under Secretary of Energy Moniz signed Excess Material Deposition Decision Memorandum No. 2, which established the path forward for managing the U-233 stored at ORNL. Specifically, this memorandum determined that there is no programmatic use for the U-233 currently in storage at ORNL other than as a possible source of medical isotopes. The memorandum directed that a Request for Proposals (RFP) be issued that will require a contractor to:

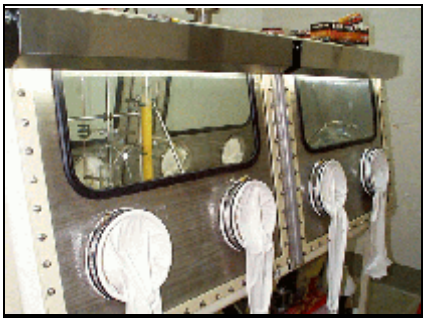
- process the U-233 to extract Th-229 for use as a source of medical isotopes;
- further process the U-233 to eliminate current concerns regarding criticality, stability in storage, and provision of safeguards and security; and
- remove the U-233 material from Building 3019A, allowing the building to be deactivated.

The memorandum further identified the responsibilities of the various program offices, including the responsibility of the Office of Nuclear Energy, Science and Technology, for issuing the RFP and subsequent management if a contract is awarded. These activities were assigned specifically to the Office of Nuclear Energy, Science and Technology's Office of Isotopes for Medicine and Science, whose mission is to serve the national need for reliable supply of isotope products and services for medicine, industry, and research..

3. Current Activities:

   a. Short Term

The Office of Nuclear Energy, Science and Technology's Medical Isotope Program has undertaken several actions designed to increase the quantity of Ac-225/Bi-213 available to researchers and the medical community. The current inventory of Th-229 is approximately



These gloveboxes are being modified to support larger Ac-225 shipments required by human clinical trials

100 milli-curies. In fiscal year (FY) 2001, an additional $350,000 has been provided to support the extraction of an additional 35 millicuries of Th-229 from the U-233. This additional material will allow ORNL to supply individual shipments of up to 35 millicuries of Ac-225 to major researchers as well as continuing to support other research centers with smaller quantities at their historical levels. However, the major research centers are currently requesting deliveries of 50 millicuries of Ac-225 per month to support human clinical trials as well as additional growth in the research community at large. In response to this demand, the Medical Isotope Program

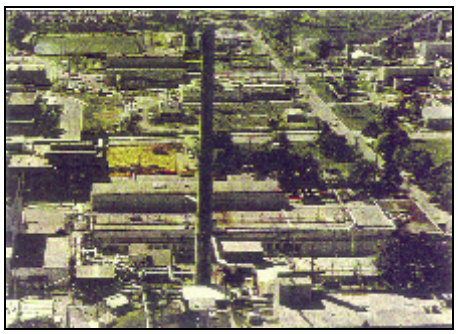
has redirected an additional $500,000 to ORNL to upgrade the processing facilities in order to support the processing of these larger shipments and to improve radiological health and safety.

Lastly, research begun in FY 2000 with $75,000 from the Medical Isotope Program is being completed that will improve the Th-229 to Ac-225 extraction process in order to shorten the time needed to complete the process and therefore decrease the amount of product loss through decay.

b. Mid Term

On January 31, 2001, the Department released draft RFP No. DE-RP05-00OR22860, for the disposition of the Department's inventory of U-233 stored at ORNL. The draft is available at http://www.oakridge.doe.gov/u233seb. The services to be acquired consist of:

- processing and repackaging the U-233 inventory in Building 3019A to render it suitable for safe, long-term, economical storage including elimination of the need for criticality and safeguards and security controls;
- extracting Th-229 from as much of the inventory as practicable in an effort to increase its availability to support cancer research and treatment;
- operation of Building 3019A during contract performance; and
- placing Building 3019A in a safe, stable shutdown mode.



Building 3019A, Radiochemical Development Facility, currently stores the U-233 to be processed under the Request For Proposal

As part of this effort, the Department intends to lease the Th-229 to the contractor for beneficial use; i.e., the contractor will extract the Ac-225 from the Th-229 and distribute the material to researchers and the medical community.

The draft is the Department's preliminary approach to achieving the Department's objectives to make medical isotopes widely available and identify requirements for the project. The RFP was sent out as a draft seeking comments from interested parties on all aspects of the RFP in order to ensure that the final product reflects the most effective approach for obtaining the required services. The Department anticipates that the services will be acquired using the negotiated process as described in Part 15 of the Federal Acquisition Regulation.

The current schedule calls for industry comments on the draft RFP to be submitted by March 2, 2001, with the final RFP issued in late spring 2001.

The Department anticipates that a contract award could be made this calendar year.

c. Long Term

As noted in the Background section of this report, Ac-225 and Bi-213 are currently derived from purified Th-229 that is produced by the natural decay of U-233. All of the Ac-225/Bi-213 currently available is from Th-229 originally extracted from the ORNL inventory of U-233. The Department is in the process of exploring additional long-term sources of Ac-225/Bi-213.

Presently, the Department is in the process of seeking research and development sources for cost-shared research of new technologies and processing methods for the reuse or recycling for another Department stockpile of U-233 including the extraction of Th-229 for Ac-225/ Bi-213. This stockpile, located at the Idaho National Engineering and Environmental Laboratory (INEEL), is leftover material from the Light Water Breeder Reactor Program and is heavily mixed with thorium-232. However, even with the added Ac-225/Bi-213 that might be available from the INEEL U-233, the supply of Ac-225/Bi-213 available as U-233 decay products will be inadequate if therapeutic applications for leukemia become even moderately successful and will become woefully inadequate if successfully applied to other types of cancer including prostate, breast, lymphomas, and various forms of brain cancer. Alternate sources of Ac-225/Bi-213 will be required to meet the increased demand.

Preliminary research indicates that Ac-225/Bi-213 could be produced through accelerators and/or reactors. Alternative methods include producing Th-229 directly as opposed to obtaining it by decay of U-233; producing radium-225, which decays into Ac-225; and producing Ac-225 directly. While each of these methods eventually results in a supply of Ac-225 for use in a Bi-213 generator, they all require additional chemical processing and/or separation steps that are yet to be determined and will likely increase production costs. In anticipation that the Ac-225/Bi-213 demand will increase, the Department plans to issue a Notice of Program Interest for development and demonstration programs for long-term improvements in accelerator and/or reactor production of Ac-225/Bi-213 with the purpose of providing financial assistance awards through cooperative agreements.

4. Path Forward:

The success of cancer treatments utilizing Ac-225/Bi-213 may be contingent upon the Department's ability to simultaneously work on the short, mid, and long-term issues. Improvements to the short-term supply are on track and should be completed by September 30, 2001. Mid-term activities involve the anticipated issuance of an RFP and award of a contract in calendar year 2001 that will result in a substantial increase in the availability of Ac-225/Bi-213 for cancer treatments and research. In the event

that the Department is unsuccessful in awarding a contract, additional discussions will be needed in order to accomplish the Th-229 extractions and downblending of the leftover U-233. Long-term activities will begin in FY 2001 through the anticipated award of cooperative agreements to explore alternate production approaches for providing Ac-225/Bi-213.