NATIONAL ISOTOPE DEVELOPMENT CENTER

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Ac-225 Research Beginning To Produce Results

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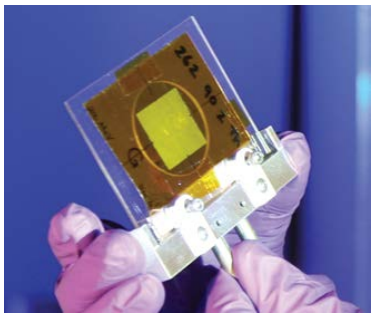


Thorium test foil target used to measure cross sections for proton production of Ac-225.

Since the discovery of radioactivity, there has been recognition that radiation can play a role in the treatment of disease. This was exemplified by the use of radium sources to treat patients with tumors. When artificial radioisotopes were discovered, the potential was expanded to include elements that compose molecules of biologic significance. One element, iodine, could be used in the atomic form, as iodide, when its affinity for thyroid tissue was discovered. After World War II, the use of radioiodine to treat thyroid cancer and hyperthyroidism was developed.

Many other isotopes have been explored, either for their natural affinity for tissue such as phosphate for bone or when formed into a molecule that has the right biologic behavior, e.g. iododeoxyuridine which incorporates into rapidly dividing tissue. At other times, physical means were used to direct the therapeutic isotope to its target as when colloids of phosphorous, gold or yttrium were used to either keep the radiation in a given space or to catch the isotope in the capillaries of the target.

In some instances, the interest shifted from beta emitters to alpha emitters. This became more interesting as the targeting molecules became more sophisticated and the uptake by the target was reduced. Unlike beta emitters, alpha emitters are cytotoxic regardless of the dose rate of the therapy. And, given their higher relative biologic effectiveness, they can be lethal at lower doses.

Work proceeded slowly on the application of alpha emitters for therapy. Challenges in the limited number of alpha emitters were the primary hurdle. Secondarily, the production of those alpha emitters presented technical challenges. One alpha emitter, astatine-211 (At-211), can be produced by a cyclotron that accelerates He-4. Most of the others are produced from longer-lived parent isotopes.

The second isotope of widespread interest has been bismuth-213 (Bi-213). Bi-213 is a decay product of a series of long lived alpha emitters, beginning with uranium-233 (U-233). U-233 decays to thorium-229 (Th-229). Th-229 decays to radium-225 (Ra-225) by alpha emission; Ra-225 decays to actinium-225 (Ac-225).

Adequate quantities of the Ac-225 have been difficult to generate because pure Th-229 is not readily available. Th-229 often co-exists with Th-228 which decays through a similar decay series but with the emission of high energy gamma rays that are hard to shield. One must wait several years for the separated Th-229 to exist without Th-228 present.

Ac-225 is then isolated on an ion exchange column that retains the Ac while enabling the Bi-213 to be separated. The challenge has been that Bi-213 has a 47 minute half-life which necessitates fast chemistry to bind it to a targeting molecule and then deliver it to the site of interest.

Actual target components for Ac-225 production – Al shell, 3 Al wrapped Th foils, and Cu disk for energy adjustment.

Ac-225 Research (Continued)

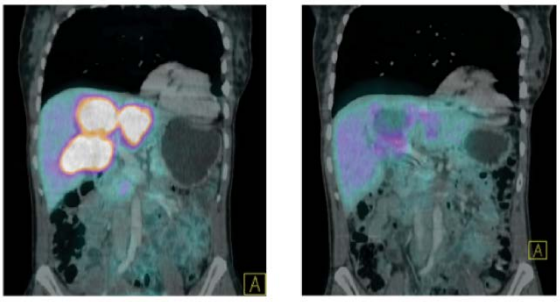
Some investigators are pursuing the use of Ac-225 instead. Its long half-life does not present any of the challenges that Bi-213 does for chemistry and targeting. But it does have a drawback in the form of its alpha emission. No molecule can hold it given the high recoil energy of the daughter nucleus. Research has been focused on developing chemical entities that retain the daughters and increase the radiation delivered to the target.

Whether one uses Bi-213 or Ac-225, supply of the Ac-225 is critical to being able to meet demand for a clinically useful application. At least one of the clinical trials with Bi-213 has been challenged by the amount of isotope they can administer to the patient.

As the isotope program transitioned from the Office of Nuclear Energy to the Office of Nuclear Physics, a subcommittee of the Nuclear Science Advisory Committee reviewed isotope needs across the landscape. It became clear that the supply of alpha emitters was the number one priority for the isotope program with special reference to the medically useful isotopes.

To help meet this priority, a research program has been initiated that involves efforts at Brookhaven National Laboratory (BNL), Los Alamos National Laboratory (LANL) and Oak Ridge National Laboratory (ORNL). Accelerators at BNL and LANL are being proposed to produce Ac-225 by high energy proton irradiation of thorium targets.

The cross section measurements conducted to date have demonstrated that an irradiation of a few days could match the current annual production of Ac-225 by a different route.



Case II: Response of multiple liver lesions after i.a. therapy with 14 GBq Bi-213-DOTATOC

This approach is not without challenges, however. The high energy protons also produce fission in the target which makes processing much more complicated. The high radiation levels require processing to be done in a hot cell. The actinium is separated from the thorium and fission products by chemical manipulations that still leave some lanthanides in the mix. Due to the chemical similarity, it is much harder to separate lanthanum from actinium. The high radiation levels also pose hurdles for transporting the material from BNL or LANL to ORNL. Heavy shields are required to keep the dose levels low enough for safe transport.

Recent results from clinical trials have kept interest in the work at a high level. At the 2012 Society of Nuclear Medicine meeting, investigators from Germany presented a paper demonstrating the therapeutic effect of a biologic molecule labeled with Bi-213. A patient with a neuroendocrine tumor received treatment and the results of the treatment were demonstrated in the image shown here.

The bright spots in the image above are tumors in the patient's liver. After treatment, the image on the right shows the dramatic response to the radiation. Little evidence of the tumor is present in the later images.

Several questions have to be answered before the Ac produced by accelerators can be used clinically. Unlike the current production method, the accelerators produce other isotopes of actinium. The effect of these isotopes has to be determined.

As the process is scaled up from irradiated foils to larger targets, there will also be challenges in processing the targets to remove the actinium from the other isotopes. There is particular concern about isotopes of lanthanum as the chemistry is so similar to actinium. Finally, the isotope has to be shown to behave similarly to the actinium or bismuth produced currently to ensure that labeled molecules will behave the same in patients.

IDPRA Research and Development

Dennis Phillips

In 2009 the Isotope Development and Production for Research and Applications (IDPRA) program was established in the Office of Science/Office of Nuclear Physics of the U.S. Department of Energy. Its mission is to provide within technical and fiscal constraints isotopic materials for research and applications that are not yet commercially viable and thus available in limited supply in the private sector. A competitive Research and Development program was funded to investigate new and improved technologies in the production of radioactive and enriched stable isotopes and to facilitate training of personnel to create the next generation of expertise in production, purification and distribution of isotopic materials. To date about $22,000,000 has been invested in peer-reviewed research and development projects at national laboratories, universities and companies with appropriate expertise and/or facilities. Several of the grants have involved collaborative efforts and have engaged students at both the undergraduate and graduate levels, as well as postdoctoral research associates, thereby providing unique training opportunities. Furthermore, additional grants have been provided to small businesses to support research aimed at commercial development of isotope products and technologies through the Office of Science's Small Business Innovative Research (SBIR) program. The spectrum of supported projects closely coincides with recommendations made to the program by the DOE/NSF Nuclear Sciences Advisory Committee. Specific work supported has included:

- Research into the production of therapeutic alpha emitters (Ac-225, At-211, Th-229)
- Research into the production of isotopes for positron emission tomography (As-72, Cu-62, Cu-64,Y-86, Zr-89)
- Production of heavy elements for research and applications (Bk-249, Cf-252, Am-241)
- Development of technologies to produce therapeutic beta-emitters (Cu-67, Re-186, Rh-105, Pr-143)
- Development of new radioisotope extraction/separations technologies
- Development of advanced targetry for accelerator and reactor isotope production
- Development of concepts and requirements for isotope harvesting at the Facility for Rare Isotope Beams (FRIB)
- Development of new technologies for stable isotope enrichment
- Activities in workforce development (undergraduate, graduate, and post-doctoral training)

Upcoming Meetings

April 2013: 245th American Chemical Society National Meeting and Exposition
New Orleans, Louisiana **(Drop by the DOE/NIDC Booth #1136 at the exhibit hall.)**
April 7 - 11, 2013

May 2013: International Society Radiopharmaceutical Sciences
Jeju Island, Korea
May 12 - 17, 2013

June 2013: Society of Nuclear Medicine and Molecular Imaging Annual Meeting
Vancouver, BC, Canada **(Drop by the DOE/NIDC Booth #1334 at the exhibit hall.)**
June 8 - 12, 2013

Noted Research Chemist, and Professor Alun G. Jones Remembered

Professor Alun G. Jones, Harvard Medical School, died late last year at the age of 71. His impact on the field of nuclear medicine was quite significant. A nuclear chemist in the Nuclear Medicine Section of Radiology at Harvard Medical School in Boston for more than 40 years, Dr. Jones contributed to the advancement of nuclear medicine by his careful study of the chemistry of radioisotopes and technetium-99m in particular. He is also remembered for his warm and welcoming demeanor, wry sense of humor and generous spirit. His leadership and mentorship was especially important to the field of radiopharmaceutical chemistry.

Born in Wales, Dr. Jones earned a PhD in Nuclear Chemistry from the University of Liverpool and completed additional training at the Institute for Nuclear Physics Research in Amsterdam before emigrating to the U.S. in 1969. After a year at the University of Maryland, Dr. Jones accepted an assignment at Harvard Medical School in 1971 to conduct research with Brigham and Women's Hospital's Nuclear Medicine Section, choosing cardiovascular imaging applications of technetium-99m as his area of focus.

Over the course of his time at Harvard, he developed a very fruitful collaboration with Professor Alan Davison of the MIT Chemistry Dept. The collaboration introduced intellectual rigor into the development of Tc-99m labeled compounds. In 1984, Dr. Jones, Dr. Davison and then graduate student Michael Abrams discovered a chemical compound that could attach to the technetium-99 isotope and deliver it to the heart. They administered the new radiotracer to a human subject and used a nuclear medicine camera to take the first ever high-resolution, clinically valuable images of the subject's heart using Tc-99m. The subject suffered no ill effects, and the team's discovery was deemed a success. He shared the discovery's patent with Davison and Abrams.

In 1992, Dr. Jones and Dr. Davison received the Method to Extend Research in Time (MERIT) Award, one of the National Institutes of Health's most prestigious awards. Less than 5 percent of NIH-funded investigators receive this award. A succession of graduate students shuttled between Jones' and Davison's labs developing and testing new ligands for Tc-99m, Rhenium radioisotopes and other radiopharmaceuticals.

"I worked alongside Dr. Jones for more than 40 years," said former Nuclear Medicine Section Head Jim Adelstein, MD. "Not a day went by that Alun was anything less than a supremely talented and committed scientist. His work was a major step in advancing cardiac diagnostics and treatments, and the chemical compounds his team discovered are used on a daily basis with thousands of patients around the world. I cherish those many years spent working with my colleague and friend."

Dr. Jones is survived by his wife, Anne K. Serrell-Jones, and sons, Andrew and Timothy Jones. A memorial service was held at the Harvard Faculty Club in Cambridge on December 1. Contributions may be made to the Bourne Conservation Trust of Bourne, Massachusetts, or the Alun G. Jones Student Scholarship Fund at Harvard Medical School.