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NIDC NATIONAL ISOTOPE DEVELOPMENT CENTER

Articles of Interest:

Astatine-211 Distribution: A Long Time Coming

D. Scott Wilbur, Ph.D.

The U.S. Department of Energy's Isotope Program recently announced a partnership between the National Isotope Development Center (NIDC) and the University of Washington to make astatine-211 (^{211}At) more widely available for research. The agreement marks the first of many planned to create a network of university-based isotope production centers capable of nationally supplying short-lived radionuclides like ^{211}At and addresses a recommendation in the Nuclear Science Advisory Committee Isotopes Subcommittee's 2015 Long-Range Plan for the DOE-NP Isotope Program.

University of Washington Cyclotron

Orders for ^{211}At may be placed now using the NIDC's online catalog. If you are interested in further information, please contact Dr. Wolfgang Runde, Associate Director for Production Planning and Customer Relations, NIDC. The following contribution by the team at the University of Washington is a brief overview of this unique alpha-emitting radionuclide.

Targeted alpha-emitting isotopes hold great promise for treatment of human diseases, particularly very difficult to treat disseminated and metastatic cancers. The promise that these isotopes provides comes from the high intensity radiation they deliver upon decay over very short distances, i.e. a few cell diameters. The result is incredibly effective killing of those cells targeted. Unfortunately, there are only a few suitable alpha-emitting isotopes. One of the isotopes that is particularly attractive for developing therapeutic radiopharmaceuticals is ^{211}At. It is appealing for three reasons: (a) a branched-chain decay resulting in 100% alpha-particle emission, (b) a short half-life (7.21h), which affords adaptation to a clinical setting, and (c) the absence of long-lived alpha-emitting daughters that can cause toxicity in the body by redistribution after ^{211}At decay. However, as a human-made isotope with a short half-life, ^{211}At must be produced on demand. First reported in 1940, the most common production method at both U.S. and foreign institutions is the ^{209}Bi(α,2n)^{211}At reaction conducted on cyclotrons capable of producing a 28-29 MeV alpha beam. This production route is also the most favorable as it provides ^{211}At free of other radioisotopic impurities.

The potential for using ^{211}At to fight bacteria, viruses and tumor cells was suggested over 60 years ago by Hughes and Gitlin, but the lack of availability of the isotope has greatly hampered development and evaluation of ^{211}At-labeled radiopharmaceuticals. The availability of on-site cyclotrons has allowed for pre-clinical development of ^{211}At-labeled monoclonal antibodies. Such work has been carried out at Duke University, the National Institute of Health (NIH), University of Washington (UW), the University of Pennsylvania and Johns Hopkins University. Duke researchers reported encouraging results from preclinical studies of ^{211}At-labeled monoclonal antibodies, which led to a Phase I Clinical Trial for treatment of glioblastoma.

Astatine-211 Distribution: A Long Time Coming (continued)

Preclinical research for the treatment of blood-borne cancers through conditioning for bone marrow transplantation was conducted at the Fred Hutchinson Cancer Research Center and at UW in Seattle. This has been successful and clinical trials are planned to begin later this year. Internationally, a Phase I Clinical Trial for the treatment of ovarian cancer was conducted in Gothenburg, Sweden.

It should be noted that chemistry studies involving astatine are challenging for several reasons. First, there are no stable isotopes of astatine and the longest-lived isotope, ^{210}At, has a half-life of only 8.1 hours. This makes characterization of labeled compounds very difficult, resulting in a larger number of studies being required to develop methods for radiolabeling compounds for use in the treatment of human diseases. Furthermore, ^{211}At cannot be directly labeled to most carrier molecules. Therefore, new labeling pendant groups that are specifically suited to the biologically active vector of interest are generally developed by research groups. Finally, the historical availability of ^{211}At has been highly-limited, largely due to the half-life and the lack of accelerators and cyclotrons capable of producing high-intensity alpha particle beams. This remains an issue as there are currently only a handful of cyclotrons in the US with such capabilities. Those facilities include UW, Duke University, the NIH, University of California Davis, the University of Pennsylvania, and Texas A&M University.

The UW Medical Cyclotron Facility is a unique facility built to deliver fast neutron cancer therapy (one of only two sites remaining in the world). The Scanditronix MC50 compact cyclotron driving the facility is a fully tunable (with respect to beam energy and current) multi-particle instrument capable of accelerating proton, deuteron, ^{3}He, and alpha particle beams with varying energy and intensity. Production conditions at UW for ^{211}At are a 29 MeV alpha beam with 50 μA of beam current. In anticipation of clinical studies with ^{211}At-labeled antibodies, an external target station was designed and built at TRIUMF in Vancouver, Canada, specifically for producing the large quantities of ^{211}At required for that type of effort. To date, clinically relevant quantities (~125 mCi) of ^{211}At have been produced on the UW cyclotron in a 4-hour irradiation; larger quantities are possible with increased irradiation durations.

Meet a Laboratory Isotope Program R&D Staff Member

Roy performing Ra-226 experiments in the high-level alpha laboratory at ORNL.

Roy Copping joined the Medical Radioisotope Program at Oak Ridge National Laboratory (ORNL) as an R&D staff member in 2014. He is engaged in research related to the production and isolation of medical radioisotopes such as actinium-225, which can be used in alpha therapy applications for the treatment of cancer. He is also involved in a variety of projects that utilize the ORNL High Flux Isotope Reactor to produce radioisotopes from stable targets, which are chemically processed after irradiation to separate the important radioactive isotopes such as tungsten-188 and nickel-63.

Roy completed his PhD in Chemistry at the Center for Radiochemistry Research at The University of Manchester, United Kingdom in 2006. Before joining ORNL he worked at Los Alamos National Laboratory on the development of separation strategies for the recovery of molybdenum-99 from irradiated enriched uranium solutions. He has also held positions at Lawrence Berkeley National Laboratory and at the Commissariat à l'Énergie Atomique's Marcoule facility in France, focusing on the fundamental chemistry of uranium and neptunium.

Longer-lived Diagnostic Isotopes: ^{44}Ti/^{44}Sc Radionuclide Generator for PET

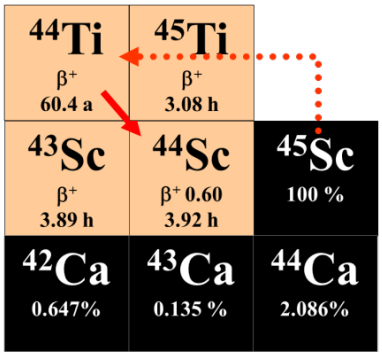

Figure 1. Production and decay pathway for the generator system ^{44}Ti/^{44}Sc.

Radionuclide generator systems are widely used in clinics largely because of their cost-effectiveness and independence from accelerator and nuclear reactor facilities. A radionuclide generator can be "milked" or eluted on a regular basis to provide diagnostic or therapeutic radionuclides on site and when needed.

During the past decade, as positron emission tomography (PET) imaging has improved, several generator systems have been of growing interest among researchers and clinicians. A notable example is the germanium-68/gallium-68 (^{68}Ge/^{68}Ga) system, which provides ^{68}Ga ($t_{1/2}$ 67.6 min, 88.9% β^+ branching ratio, $E_{<\beta+>}$ = 0.83 MeV) that can be attached to targeting biomolecules via bifunctional chelating agents. This isotope is of great interest for imaging of cancers and infection. In the case of ^{68}Ge/^{68}Ga, the parent radionuclide ^{68}Ge ($t_{1/2}$ = 270.8 d) continues to be produced for this application at Los Alamos National Laboratory (LANL) and Brookhaven National Laboratory (BNL) routinely.

Another generator system proposed for imaging purposes is the titanium-44/scandium-44 (^{44}Ti/^{44}Sc) pair (Fig. 1) to make available the PET isotope ^{44}Sc ($t_{1/2}$ 3.97 h, 94.27 % β^+ branching ratio, $E_{<\beta+>}$ = 0.63 MeV). This system is similar to ^{68}Ge/^{68}Ga, but there are salient differences. In particular, ^{44}Sc has a half-life almost four times that of ^{68}Ga. The longer half-life enables the tracking of slower biological processes and allows for more complex radiopharmaceutical preparations post-elution. The ^{44}Sc parent, ^{44}Ti, has a half-life of roughly 60 years, opening up the possibility for a long-term daughter radionuclide source. Such a long half-life, however, also creates economic and engineering challenges because of the large quantity of long-lived ^{44}Ti that must be secured on the generator column.

High ^{44}Ti activities also require high particle beam currents and long irradiation times. LANL and BNL scientists have been investigating the production of parent ^{44}Ti at quantities to make pre-clinical and clinical evaluation of ^{44}Sc as a PET agent possible. Two proton beam irradiations of natural scandium metal targets were performed at the Isotope Production Facility at LANL during the 2014–2015 run cycle at lower proton energies ("C-slot" target position) (Fig. 2). These irradiations resulted in the combined formation of more than 10 mCi (~400 MBq) of ^{44}Ti, a significant amount compared with current global stocks of this rare radioisotope. In parallel, the BNL team has been working on the design and fabrication of additional proton beam targets for future bulk manufacturing of ^{44}Ti.

After irradiation, accumulated ^{44}Ti needs to be recovered chemically from the scandium target. For this pupose, the first target (containing ~5 mCi of ^{44}Ti) was used to develop chemical separation methods to isolate microgram quantities of ^{44}Ti from multiple-gram amounts of natural scandium. Based on recent experiments conducted by radiochemists at LANL and BNL, ion exchange column chromatography seems to be the most elegant and efficient strategy to attain this goal. Optimization of the chemical separation is currently underway.

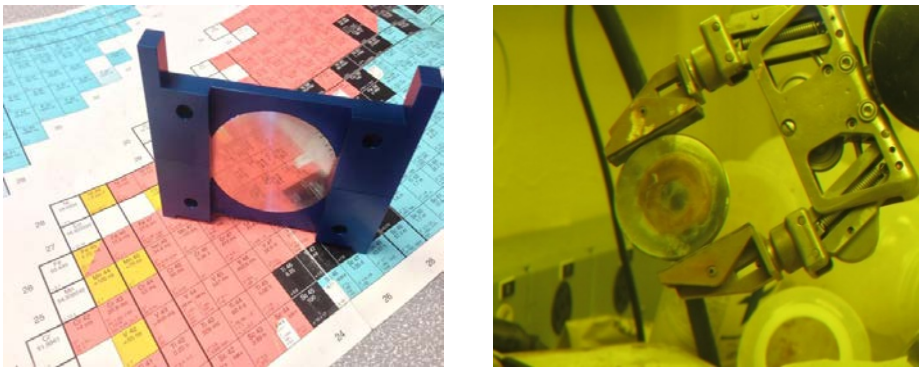

Figure 2. Scandium target before (left) and after (right) proton irradiation at LANL.

After isolation and purification from byproduct radionulides, long-lived ^{44}Ti will be fixed to a solid support for the repeated elution of the daughter radionuclide ^{44}Sc. Different extraction systems are under consideration to ensure long-term sorption of ^{44}Ti and near-quantitative recovery of the ingrown ^{44}Sc imaging isotope. Prototype sorption systems are slated for elution performance and ^{44}Ti breakthrough evaluation, the two main parameters detemining the quality of a radionuclide generator design. Once a successful system has been developed and demonstrated, test generators are expected to be available for ^{44}Sc labeling and biological studies. Please contact Dr. Wolfgang Runde, Associate Director for Production Planning and Customer Relations, during this product development period to discuss the availability of samples for evaluation.

Isotopes
For Science, Industry, and Medicine
U.S. Department of Energy

NIDC Quality Assurance Manager

Ariel Brown has joined the National Isotope Development Center (NIDC) as the NIDC Quality Assurance Manager.

She holds a Master of Science degree in Regulatory Affairs for Drugs, Biologics, and Medical Devices from Northeastern University and a Bachelor of Science degree in Chemistry from the University of Rochester. Prior to accepting this position, Ariel worked as a Radiopharmacy Quality Assurance Specialist in the Radiochemistry and Imaging Probes Core at Memorial Sloan Kettering Cancer Center.

In her role as NIDC Quality Assurance Manager, she will be working directly with the NIDC, DOE, and the Isotope Program (IP) Managers to develop, implement, and maintain a quality system to meet regulatory, operational, and customer specifications for all stable and radioisotope products produced by the IP.

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