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Addressing the Need for Ac-225: The US DOE Tri-Lab (ORNL, BNL, LANL) Research Effort to Provide Accelerator-Produced Ac-225 for Targeted Alpha Therapy

Kevin D. John, PhD, Contract Project Manager for the Tri-Lab Research Effort to Provide Accelerator-Produced Ac-225 for Radioimmunotherapy, Los Alamos National Laboratory

In April of 2015, the US DOE, Office of Science, Office of Nuclear Physics, Isotope Development and Production for Research and Applications (IDPRA) Program (http://science.energy.gov/np/research/idpra/ and https://isotopes.gov/) launched a multi-year research and development effort to develop the technological and logistical underpinnings associated with production proof-of-concept of large volumes of Ac-225. This effort was initiated in support of the growing demand for Ac-225 led by the targeted alpha therapy community's clinical research efforts. The US DOE tri-lab effort leverages the high-energy accelerator facilities at Brookhaven and Los Alamos National Laboratories, as well as the existing Ac-225 processing capabilities at Oak Ridge National Laboratory.

Ac-225 and its associated daughter Bi-213 are radionuclides that decay through the emission of high linear energy transfer alpha-particles and possess favorable, relatively short half-lives from a clinical application perspective. Furthermore, the ability to develop targeting moieties to bind to these isotopes increases specificity in radionuclide delivery to sites of diseased tissue, minimizing unwanted toxicities from nonspecific distribution of therapeutic agents. This renders Ac-225 and Bi-213 very attractive from the standpoint of treating a wide variety of metastatic cancers such as leukemia, lymphoma, melanoma, gliomas and neuroendocrine tumors.

In addition, the ability to couple the cytotoxic potential of alpha-particle emission with effective targeting vectors offers significant potential for combating an even wider variety of diseases. Multiple obstacles must be overcome by researchers and clinicians in order to realize the full potential of alpha-based therapy. Key among these current obstacles is the existing production capacity for Ac-225 and Bi-213, which limits the current level of research and clinical developmental efforts. The advancement of new production and process methods as outlined in this article will enable further research and application of Ac-225 and Bi-213, which will ultimately benefit larger patient populations.

Ac-225 was envisioned and developed at Oak Ridge National Laboratory (ORNL) in the early 1990s, and since 1994 ORNL has been the main supplier of pharmaceutical grade Ac-225. In 2009, the Isotopes Subcommittee of the Nuclear Science Advisory Committee (NSACI) made Ac-225 the highest-priority alpha emitter for new production approaches [1], and in 2011, the International Atomic Energy Agency (IAEA) addressed accelerator production of Ac-225 as a top research priority [2]. Table 5 of the Workshop Summary: *The Nation's Needs for Isotopes* [3] estimates that the annual usage for Ac-225 and/or Bi-213 based on known needs without new developments could be as high as 50,000+ mCi/year assuming that multiple Ac-225/Bi-213-based drugs receive FDA approval. This is in stark contrast to current worldwide, annual supply, which is estimated at approximately 1,000-2,000 mCi/year, capacity [4].

The current method of producing Ac-225 and its daughter Bi-213 depends on the supply of Th-229 extracted from fissile U-233 produced as a fuel for nuclear reactors or weapon applications [5]. In the 1960s, some U-233 was produced by the irradiation of Th-232 with neutrons using the Th-232(n,γ)

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Th-233(2β)U-233 reaction at the Hanford reactors. Some of these targets were later processed at Oak Ridge National Laboratory (ORNL), and some of the waste from U-233 chemical processing—which included Th-232 target material and Th-228 and Th-229 byproducts—was processed in the mid-1990s.

Although Th-229 was initially highly contaminated with Th-228 (t1/2=2 y), the 30-year decay period resulted in very pure Th-229. In the early 2000s, the Isotope Program supported extraction of ~35 mCi of Th-229 directly from U-233 stock. For the past 15 years, these purified batches of Th-229 have provided a limited but suitable source of Ac-225 and subsequently Bi-213. Until recently, ORNL and ITU were the only suppliers of pharmaceutical grade Ac-225; however, in a recently published review, the Institute of Physics and Power Engineering (IPPE), in Obninsk, Russia, was referenced as a third supplier [6].

An accelerator-based approach has recently been demonstrated at the Los Alamos National Laboratory Neutron Sciences Center (LANSCE) Isotope Production Facility (IPF) and at the Brookhaven Linac Isotope Producer (BLIP). This method utilizes thorium targets (monoisotopic Th-232) irradiated with high energy protons. Similar work has also been recently published by Zhuikov, at the Institute for Nuclear Research, Russian Academy of Sciences, in Troitsk, Russia [7]. The effort at LANSCE (using IPF and the Weapons Neutron Research facility) measured Ac-225 production cross sections for protons on Th targets from 56 to 800 MeV [8]. A 10-day irradiation at 200 MeV on an optimized target is projected to result in the production of approximately 1-2 Ci of Ac-225, which is roughly equal to the current annual global supply.

The major isotopic impurity of concern reported in the accelerator studies was the longer-lived Ac-227 ($t_{1/2}$=21.7 years), which would be coproduced at about 0.1-0.2 percent of the overall radioactivity, at the end of the irradiation. Accelerator-produced Ac-225 needs to be clinically evaluated in order to assess the effect of the Ac-227 impurity in vivo. The impurity level is expected to be dependent on incident proton energy, target thickness, irradiation duration and the post-irradiation decay period.

Between the high-energy beams at IPF and at BLIP, it is estimated that up to fifty times the current annual global supply of Ac-225 could be produced, assuming year-round production at both sites, taking into account accelerator-scheduled downtime and maintenance. This magnitude of production would provide the means to expand research and development into the therapeutic applications of Ac-225 for a large number of patients. However, chemical processing and large-scale production methods are still under development, and they need to be in place before accelerator-produced, pharmaceutical-grade Ac-225 and generator-derived Bi-213 can reach their full potentials for research, clinical application and routine production.

Over the past year, the tri-lab effort has focused on the

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In the Literature

Each month, the CMIIT Editorial Board selects the top molecular imaging research papers from all papers indexed by PubMed. Below are recent papers on molecular imaging research. The links below go to these references, including their abstracts and links to the full paper on PubMed.

Gd-AAZTA-MADEC, an improved blood pool agent for DCE-MRI studies on mice on 1 T scanners
Longo DL, Arena F, Consolino L, Minazzi P, Geninatti-Crich S, Giovenzana GB, Aime S.
PMID: 26480471

Tumor-specific targeting by Bavituximab, a phosphatidylserine-targeting monoclonal antibody with vascular targeting and immune modulating properties, in lung cancer xenografts
Gerber DE, Hao G, Watkins L, Stafford JH, Anderson J, Holbein B, Öz OK, Mathews D, Thorpe PE, Hassan G, Kumar A, Brekken RA, Sun X. PMID: 26550540

A Practical One-Pot Synthesis of Positron Emission Tomography (PET) Tracers via Nickel-Mediated Radiofluorination
Zlatopolskiy BD, Zischler J, Urusova EA, Endepols H, Kordys E, Frauendorf H, Mottaghy FM, Neumaier B. PMID: 26478840

The use of dynamic nuclear polarization (13) C-pyruvate MRS in cancer
Gutte H, Hansen AE, Johannesen HH, Clemmensen AE, Ardenkjær-Larsen JH, Nielsen CH, Kjær A. PMID: 26550544

Comparison of Diagnostic Sensitivity and Quantitative Indices Between (68)Ga-DOTATOC PET/CT and (111)In-Pentetreotide SPECT/CT in Neuroendocrine Tumors: a Preliminary Report
Lee I, Paeng JC, Lee SJ, Shin CS, Jang JY, Cheon GJ, Lee DS, Chung JK, Kang KW. PMID: 26550047

Hybrid PET/optical imaging of integrin αVβ3 receptor expression using a (64)Cu-labeled streptavidin/biotin-based dimeric RGD peptide.
Kang CM, Koo HJ, An GI, Choe YS, Choi JY, Lee KH, Kim BT. PMID: 26518424

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development of scaled-up production targetry performance (Figure 1) and associated chemical processing details (Figure 2). As a result of these development efforts, the team has distributed over 150 mCi of material in the form of dry Ac-225 and Ac-225/Bi-213 generators to researchers for independent evaluation of the final, accelerator-produced material. These evaluations have been primarily aimed at assessing the efficacy and efficiency of radiolabeling relative to the Th-229-derived product.

Preliminary results have been promising for both direct Ac-225 and generator-derived Bi-213 applications. Future work will focus on detailed dosimetry and toxicity studies aimed at determining the impact of Ac-227 in the accelerator product, as well as continued optimization of targetry, chemistry and general logistical details, with the aim of positioning the tri-lab team to support clinical trials in a two-to-three-year time frame.

Figure 1. LANL/IPF-Irradiated Th target showing "scorching" associated with the rastered proton beam.

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Calendar of Events

Pacific Northwest Chapter SNMMI and Pacific Northwest Radiological Society's Joint Meeting
http://www.wrsnm.org
March 19-20, 2016
Bellevue, Wash.

Hybrid PET-imaging Symposium and Workshop 2016
http://www.diaradio.hku.hk
March 25-27, 2016
Hong Kong, China

GNYC Spring Symposium
www.gnycsnm.org
April 8-9, 2016
Atlantic City, N.J.

CAR 79th Annual Scientific Meeting—Imaging in an Era of Comparative Effectiveness: How to Stay Relevant
www.car.ca
April 14-17, 2016
Montreal, Quebec, Canada

MECSNM 46th Annual Spring Educational Conference and Exhibition
www.mecsnm.org
April 15-17, 2016
Linthicum Heights, Md.

BNMS Spring Meeting 2016
http://www.bnms.org.uk
April 17-19, 2016
Birmingham, United Kingdom

Australian and New Zealand Society of Nuclear Medicine Annual Scientific Meeting 2016
http://www.anzsnm2016.com
April 22-26 2016
Rotorua, New Zealand

International Conference on Medical Imaging & Diagnosis
http://www.omicsonline.org
May 9-10, 2016
Chicago, Ill.

International Conference on Nuclear Medicine & Radiation Therapy
http://www.omicsonline.org
June 9-10, 2016
Cologne, Germany

SNMMI 2016 Annual Meeting
http://www.snmmi.org/AM2016
June 11-15, 2016
San Diego, Calif.

A Summary of the MWM Industrial Partners Circle Meeting

Jonathan McConathy, MD, PhD, and Buck E. Rogers, PhD

The 2016 Industry Partners Circle (IPC) meeting was recently held at the 2016 SNMMI Mid-Winter Meeting in Orlando, Florida. This half-day meeting brought together board members from the Center for Molecular Imaging Innovation and Translation (CMIIT) and the Radiopharmaceutical Sciences Council (RPSC) with experts in companies involved in molecular imaging to discuss challenges and opportunities in the field. The IPC is intended to provide industry perspective to help guide CMIIT and RPSC for future programming at SNMMI meetings and to prioritize current and new initiatives.

The discussion was centered around the following five questions:

- What types of training in academia will be most valuable to industry in the next 5-10 years?
- What is the role of molecular imaging in clinical trials (e.g., subject selection, surrogate endpoints, companion diagnostics)?
- What is the outlook for FDA-approval and CMS reimbursement of molecular imaging agents?
- What are the prospects for non-nuclear molecular imaging agents for clinical use?
- How can academic centers leverage their capabilities for small volume tracers and the use of research tracers for clinical trials?

Topics of substantial discussion included the training of molecular imaging professionals; the need for academia, industry, and professional societies like the SNMMI to continue engaging the Food and Drug Administration and payers; the advantages and limitations of non-radioactive agents, including fluorescent and MRI-based technologies for routine clinical use; and the importance of molecular imaging in early decision-making in clinical trials.

The IPC attendees are in the process of summarizing key discussion points, which will be made available to CMIIT and RPSC members through MI Gateway when completed. It is anticipated that several action items will be identified that will aid in the future planning of CMIIT and RPSC activities.

MI In the News

MI Gateway presents a sampling of research and news of interest to the community of molecular imaging scientists. More molecular imaging news is available daily at www.snmmi.org/cmiit.

PET/CT beats CT and bone scans for detecting metastatic prostate cancer: study

DotMed

A recent study published in The Journal of Nuclear Medicine shows that a PET/CT scan using the radiotracer F-18-DCFBC to target prostate-specific membrane antigen (PSMA) is more sensitive for detecting metastatic prostate cancer than the imaging modalities currently in use, which could hold the key for providing more timely treatment.

Results for Lu-Dotatate in Patients With Midgut NETs Continue to Impress

OncLive

For patients with advanced midgut neuroendocrine tumors (NETs), the peptide receptor radionuclide therapy Lu-Dotatate (Lutetium-177 DOTATATE; Lutathera) continues to confer a major therapeutic benefit, reducing the risk of disease progression or death by 79% and signaling an improvement in overall survival as well.

Deadly fungal lung infection transplant or leukaemia patients could now be treated faster

Western Daily Press

A deadly fungal lung infection that affects transplant or leukaemia patients could soon be treated faster thanks to a new test using a combination of PET and MRI imaging that was developed by British scientists.

PET/MRI Plus CT Helps Determine Colorectal Cancer Treatment

Diagnostic Imaging

Use of integrated whole-body PET/MRI may aid in the selection of treatment strategies for patients with colorectal cancer, according to a study published in the American Journal of Roentgenology.

How Blasts Affect the Brain

The Scientist

Using PET scans, researchers found that repeated exposure to explosions can damage the cerebellum in combat veterans and mouse models alike. The study was published in Science Translational Medicine.

Study Confirms PET-CT as Modern Standard for Staging Hodgkin Lymphoma

Cancer Therapy Advisor

Positron emission tomography-computed tomography (PET-CT) is the modern standard for staging Hodgkin Lymphoma and response assessment using Deauville criteria is robust, according to a study published online ahead of print in the journal Blood.

New protease-activated imaging agent successfully fluoresces tumors

Health Imaging

Work is underway around the world to better localize and visualize cancer cells using fluorescence. Now, researchers at Duke Medicine report they have tested the first fluorescent imaging agent activated by a protease enzyme and proven safe in humans.

Lipoprotein nanoplatelets important for imaging biological molecules and cells

News-Medical

An interdisciplinary research team from the University of Illinois at Urbana-Champaign has developed a new material composite derived from quantum dots. These lipoprotein nanoplatelets are rapidly taken up by cells and retain their fluorescence, making them particularly well-suited for imaging cells and understanding disease mechanisms.

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Figure 2. BNL/BLIP-Irradiated Th foils being prepared for dissolution at ORNL.

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CENTER FOR MOLECULAR IMAGING INNOVATION AND TRANSLATION

1850 Samuel Morse Drive
Reston, VA 20190
P: 703.708.9000
F: 703.708.9020
www.snmmi.org/CMIIT

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