More Oncology Options:
Two New PET Imaging Agents Approved

Peter Gardiner, MB, CHB, MRCP, FFPNM—Vice President, Medical Affairs, and Karen E. Linder, MS, PhD—Senior Manager, Clinical Science and Medical Affairs, Blue Earth Diagnostics, Inc.; Stefano Buono—Chief Executive Officer of AAA and David W. Dick, PhD—Chief of Radionuclide Production and Clinical PET Radiochemistry, University of Iowa

The year 2016 proved to be very notable for the nuclear medicine and molecular imaging community, as two new products were approved by the Food and Drug Administration (FDA), immediately impacting two groups of patients desperate for improved diagnostic and management tools. The Clinical Trials Network (CTN) is privileged to have played a vital role in their approvals.

On May 27, 2016, the FDA approved Axumin™ (FDA label: fluciclovine F18 injection) for PET imaging in men with suspected prostate cancer (PCa) recurrence based on elevated PSA levels following prior treatment. PET imaging with 18F-fluciclovine may allow the detection and localization of such recurrence. Data submitted to the FDA included results from four clinical sites in the U.S., Italy and Norway. Overall, 18F-fluciclovine PET/CT was positive in 68% (403/595) of patients with biochemical recurrence. For PCa patients with PSA values in the lowest quartile (< 0.79 ng/mL, n=128), 53 (41%) had positive 18F-fluciclovine scans; 13 patients had prostate bed findings only; 16 showed pelvic lymph node involvement and 24 had extra-prostatic disease. This finding is highly relevant, as the location of disease recurrence can impact the selection of appropriate therapy.

Jonathan Allis, CEO of Blue Earth Diagnostics (BED), the company that commercialized Axumin™, comments: “We are extremely pleased with the FDA approval of Axumin for biochemically recurrent PCa and would like to recognize the contribution of the Society of Nuclear Medicine and Molecular Imaging (SNMMI) Clinical Trials Network, with whom we worked very closely during the development of Axumin™.” The involvement of CTN began in 2012, with the development of a proposal for a clinical trial in response to a Department of Defense grant call and continued with FDA discussions seeking guidance on the development program. The CTN also secured grant funding from the Movember Foundation for further evaluation.

The CTN has also assisted BED in the design of a robust reader training program, the conduct of a successful blinded image evaluation, completion of an imaging manual and design and evaluation of phantom studies. The SNMMI CTN website currently hosts the training program for the interpretation of Axumin™ images. BED is very grateful for CTN’s collaborative support of 18F-fluciclovine and for the many ways that they helped bring 18F-fluciclovine to the market for the benefit of patients with biochemically recurrent prostate cancer.
Additionally, on June 2, 2016, FDA approved NETSPOT™ (FDA label: kit for preparation of gallium Ga 68 dotatate injection) for the localization of somatostatin receptor–positive neuroendocrine tumors (NETs) in adult and pediatric patients with PET imaging. Developed and manufactured by Advanced Accelerator Applications (AAA), NETSPOT™ is the first approved PET imaging agent in the United States using gallium-68 as a radionuclide. AAA provides NETSPOT™ in two forms: as a kit for reconstitution using a 68Ga/Ga generator and as a patient-ready injection product. The injection product is prepared and delivered from a local radiopharmacy in selected metropolitan areas.

Neuroendocrine tumors are slow-growing tumors that develop in the hormone-producing cells of the body’s neuroendocrine system. They have receptors for somatostatin, a hormone that regulates the endocrine system. 68Ga-DOTATATE, a positron-emitting analogue of somatostatin, works by binding to these receptors. NETs are the second most common type of gastrointestinal malignancy—more prevalent than stomach and pancreatic cancers combined. Because NETs are often difficult to diagnose using traditional SPECT imaging agents, the approval of NETSPOT™ signals a vital paradigm shift for managing this disease.

NETSPOT™ dosing and imaging can be completed in a single two-hour visit, compared to the required 48-hour cycle associated with SPECT imaging. Additionally, radiation exposure to both patients and staff is reduced with this new PET agent. Confirmation of a positive diagnosis of NET may also require histopathology or other assessments before a course of action is implemented.

Liberon Marzella, MD, PhD, director of the Division of Medical Imaging Products in the FDA’s Center for Drug Evaluation and Research, noted in FDA’s approval letter that NETSPOT™ provides imaging Products in the FDA’s Center for Drug Evaluation and Research, noted in FDA’s approval letter that NETSPOT™ provides confirmation of the NETSPOT™ application to the FDA. In addition, the CTN leadership provided valuable guidance in the preparation and submission of the NETSPOT™ application to the FDA. In addition, the CTN developed and maintains an AAA-authorized reader training program on the SNMMI website for the interpretation of NETSPOT™ images.

The Clinical Trials Network is proud to have been involved in working with the FDA and these companies on bringing new molecular imaging drugs to approval. These advancements assist treating physicians and molecular imagers by providing improved options for patients and caregivers in managing their care. We look forward to forming further collaborations with these and other companies aimed at bringing novel radiotracers into clinical trials and, subsequently, into the clinic. To access reader training to Axumin™ or NETSPOT™, click here.

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Axumin™ (fluciclovine F 18 PET/CT detected an 8 mm lymph node proximal to the rectal wall, rendering delivery of planned salvage radiotherapy problematic. The patient went on to receive hormone therapy.

References:
4. Stafano Buono, Chief Executive Officer of AAA, commented, “We are grateful for CTN’s support and assistance in bringing NETSPOT™ to approval and improving options for the diagnosis and management of NETs in adult and pediatric patients in the United States.”

Message from the Co-Chairs: CTN Identifies New Leadership

In late 2008, SNMMI launched the Clinical Trials Network (CTN) to expand the role of molecular imaging in bringing the right treatment to the right patient at the right time. Four co-chairs spearheaded programs designed to facilitate the integration, availability and performance of imaging radionuclides into critical care and manage improve image quality through standardization and education. Initial charges set forth for CTN leadership and committees have evolved over the years to meet the dynamic needs of the molecular imaging community and to address changes in the national and global regulatory arena for conducting clinical research.

At the CTN annual retreat in August 2016, we announced that John Sunderland, PhD, MBA, and Jonathan McConathy, MD, PhD, will be added as vice-chairs of CTN. In June 2017 at the SNMMI Annual Meeting, we will be stepping down as co-chairs, at which time they will assume the co-chair roles. John Sunderland is director of the PET Imaging Center and Small Animal Imaging Core at the University of Iowa and Jonathan McConathy is director of the Advanced Imaging Facility and the Division of Molecular Imaging and Therapeutics at the University of Alabama at Birmingham and recently served as president of CMIIT at SNMMI.

We are privileged and honored to have been involved in many projects during the past eight years that resulted in some monumental changes in nuclear medicine and molecular imaging research, education and PET image standardization. We have every confidence that John and Jonathan will make even greater strides in future endeavors, and we ask that you support them as you have supported all CTN co-chairs over the years.

In the NEWS

Joint Commission Standard for PET Scanner Performance

John J. Sunderland, PhD, MBA

The “Revised Requirements for Diagnostic Imaging Purposes,” published by The Joint Commission in January 2015, went into effect July 1, 2015, and—

for the first time—includes requirements specific to the practice of positron emission tomography (PET). These new quality standards impact the majority of hospital-based PET scanners in the United States, requiring each site to formalize and document safety, maintenance, quality control and scanner performance practices consistent with these new requirements.

Perhaps the most burdensome requirement for a site is the implementation of a phantom-based scanner performance evaluation that must include (1) image uniformity, (2) high-contrast resolution/spatial resolution, (3) low-contrast resolution/lesion detectability and (4) artifact evaluation. The Joint Commission does not specify which phantom/phantoms should be used, nor do they dictate acceptable criteria. These choices are left to the individual site, but common phantoms may be used to achieve the outlined requirements. Image uniformity is best assessed with a uniform 20 cm cylindrical phantom that extends beyond the axial extent of the scanner detector ring. High- and low-contrast resolution performance tests can be performed with the NEWA quality phantom, the SNMMI Clinical Trials Network (CTN) chest oncology phantom or the American College of Radiology (ACR) phantom, although standard phantom fill protocols and imaging procedures need to be modified to meet both the high- and low-contrast requirements of this new standard.

Leveraging its scanner validation experience and infrastructure developed over the past eight years, the CTN is developing standardized phantom fill and acquisition procedures, acceptance criteria and automated phantom analysis software so that procedures utilizing the CTN chest oncology phantom (in concert with the uniform cylindrical phantom) can fully meet The Joint Commission requirements for PET scanner performance.
Congenital hyperinsulinism (CHI) is the leading cause of persistent hypoglycemia in infants and children. Among the symptoms of CHI are life-threatening hypoglycemia attacks that can result in severe neurologic damage or even death. The most severe cases are caused by inactivating mutations of the pancreatic beta cell ATP-sensitive potassium channel (KATP), the site of action of diazoxide due to the inability to act on the K-ATP channel gene with loss of the site of action of diazoxide. Accordingly, patients with defects in the KATP channel genes (ABCC8 and KCNJ11) are identified by lack of response to therapy with diazoxide due to the inability to act on the K-ATP channel gene with loss of the site of action of diazoxide. Therefore, a skilled surgeon is essential for surgical planning. Co-registration of focal or diffuse lesions is pancreatic insulinomas, insulinomas, and insulinomas is characterized as a cluster of densely packed beta cells with irregular, non-encapsulated margins, often measuring less than 1 cm in size. The uninvolved pancreatic tissue has normal beta cells, thus resulting in a focal lesion results in a cure. Diffuse disease is characterized by enlarged islet cell nuclei throughout the pancreas. These patients usually require subtotal pancreatectomy for glycemic control. The detection of a focal lesion is where PET radiotracer fluorine-18-di-hydroxyphenylalanine (18F-DOPA) has great value as a diagnostic tool.

18F-DOPA PET/CT has become the test of choice used to differentiate focal from diffuse disease. Since 2006, 11 studies have shown the efficacy of 18F-DOPA for this indication. An independent analysis of these studies revealed a sensitivity and specificity of 92.5% (CI 85.8%, 98.1%) and 94.1% (CI 85.1%, 97.6%), respectively [1]. The reference standard for determining focal or diffuse disease is pancreatic histopathology. 18F-DOPA PET/CT is a valuable tool not only for diagnosis but also for localization of a focal lesion, essential for surgical planning. Co-registration with MRI or contrast-enhanced CT is used to create a roadmap for the surgeon [see figures]. The surgical approach for a lesion varies depending on the location of the lesion. Hence, a skilled surgeon is essential for successful treatment of these critically ill infants and neonates.

Currently, 18F-DOPA is made available by the FDA under an investigational new drug (IND) authorization, an option to apply to bill insurance for the direct costs associated with the imaging agent. The introduction of a nucleophilic method of synthesis with a higher specificity and automated kit-based synthesis may prove to be superior to the established electrophilic method. 18F-DOPA is approved for use in this indication in the European Union, and efforts are underway to explore the possibility of applying for a new drug application for this indication in the United States.

**SPECIAL FEATURE**

Using 18F-DOPA PET/CT to Diagnose and Localize the Focal Form of Congenital Hyperinsulinism

Lisa J. States, MD

Figure 1: Focal lesion in the pancreatic head requiring 18F-DOPA PET/CT with contrast-enhanced CT (CECT) biopsy. A 3-month-old girl underwent a subtotal pancreatectomy for glycemic control. 18F-DOPA PET/CT was used to biopsy the focal lesion, resulting in a cure. The radiotracer used for the biopsy was F-18 fluorodeoxyglucose (FDG) PET/CT.

Figure 2: Focal lesion in the anterior pancreatic body requiring 18F-DOPA PET/CT with contrast-enhanced CT (CECT) biopsy. A 3-month-old girl underwent a partial pancreatectomy for glycemic control. 18F-DOPA PET/CT was used to biopsy the focal lesion, resulting in a cure. The radiotracer used for the biopsy was F-18 fluorodeoxyglucose (FDG) PET/CT.

Figure 3: Focal exophytic lesion measuring 8 x 5 mm arising from the posterior pancreatic body required 60% pancreatectomy for glycemic control. A 3-month-old girl underwent a subtotal pancreatectomy for glycemic control. 18F-DOPA PET/CT was used to biopsy the focal lesion, resulting in a cure. The radiotracer used for the biopsy was F-18 fluorodeoxyglucose (FDG) PET/CT.
WHAT’S HAPPENING

RCPWiki: A Library of Radiochemistry and Radiopharmacy Protocols

In our varied and high-technology field, it can be difficult to find a reliable protocol for a new technique or to keep up with the latest developments for a common procedure. Recognizing this need, the Clinical Trials Network (CTN), in collaboration with the Radiopharmaceutical Sciences Council (RPSC) and supported by the Society of Nuclear Medicine and Molecular Imaging (SNMMI), has launched a new web-based initiative: the RCPWiki (RadioChemical and Pharmaceutical Wiki (www.rcpwiki.snmmi.org/)). A wiki is a website that can be edited by a group of people given access to the site. Our wiki uses the user-friendly WIX software and is maintained by SNMMI IT staff who monitor content to ensure its integrity and archive the information.

The RCPWiki provides an opportunity to resolve questions about protocols, reagents and instruments. Our aim is to make this wiki an invaluable database for our field by inviting the community to contribute new ideas and refine tried-and-tested protocols for general laboratory techniques, radiochemical syntheses, radiopharmaceutical drug preparation and other relevant approaches and information. Currently, the RCPWiki has separate sections for general protocols, basic science, radiochemistry and radiopharmacy, new sections will be added as the wiki grows. Following a simple application process, anyone can become an editor, log in to the site, enter and edit their content and publish it to the web in minutes—quickly and easily sharing their specialist knowledge. Complete instructions for navigating the RCPWiki are provided on the website.

Apply to become an editor by sending an email to rcp@rcpwiki.snmmi.org requesting an account, and the protocol you have developed will soon be online and available to the rest of the community—a permanent and vital contribution!

RCPWiki The RadioChemical & Pharmaceutical Wiki

Research Essentials for Techs

Translating Research into the Clinic: New PET Tracers

Many promising radiopharmaceuticals never make it to the clinic for a variety of reasons. However, the nuclear medicine and molecular imaging community saw success for two new radiotracers approved by the FDA in 2016. After years of research, these agents will be widely available through commercial distributors by January 2017 (See Lead Story in this issue). At the SNMMI 2017 Mid-Winter Meeting in Phoenix, Arizona, a special session for technologists is being held on Saturday, January 21. Speakers share key tips and demonstrate best-practice techniques to ensure that PET technologists are prepared to make this new knowledge available to the rest of the community—a permanent and vital contribution!

SESSION INFORMATION:
Saturday, January 21 - 7:45 to 8:45am

- Imaging with Azumim™: Hands on and How to
  Fenton Ingram, CNMT, PET, RTRH-Emory Healthcare
- Imaging with NETSPOT™: Hands on and How to
  Rebecca Kim Smith, BS, CNMT, NCT-Vanderbilt Medical Center

This unique session demonstrates the successful translation of clinical research into the clinical setting and broadens the knowledge base for all imaging personnel.

Tech Talk

Bridging the Gaps in Clinical Imaging Research

Amanda Abbott, CNMT, RT(N)(CT), PET

Technologists have an important frontline role to play in clinical imaging research to ensure that scans obtained in the context of clinical trials are acquired in an accurate, standardized and reproducible fashion. This may require refresher training, prescreening of protocol patients prior to the day of arrival, adherence to required protocol parameters and guidelines and proper documentation to facilitate consistency in longitudinal imaging testing.

The team at the SNMMI 2017 Mid-Winter Meeting in Phoenix, Arizona, will demonstrate the successful translation of research into clinical practice. All technologists are invited to attend this session and actively participate in the discussion about the future of clinical imaging research.

Research Subjects Made Simple

Sarah Frye, MBA, CNMT, PET, NCT, CCURP

- Be prepared – have protocol information, participant history and equipment ready BEFORE the participant arrives. Consult with the referring physician if needed.
- Follow the protocol – review protocol requirements in advance. Be sure there is time for discussion prior to beginning any study procedures.
- Keep the participant content – do the little things to ensure a good experience for the participant, e.g., escort the participant to the research department from a designated meeting place. Avoid unnecessary delays.
- Answer questions – review events of the day with the participant. Confirm that a signed, current informed consent form is obtained and placed in the research file.
- Write it down – complete source documentation as events occur and accurately transfer information to the case report form. Make a note to file with participant specifics, and always include your name or initials and today’s date.

Tech Tip

Follow-up – check in with the participant at a designated time post-scan to record any adverse events.

Adjust on the fly – if unsure, get last-minute assistance from other staff and physician investigator to avoid repeat scans. Be flexible!
CTN Offers Services for Academic Clinical Research

The Clinical Trials Network offers a variety of services to assist academic investigators with their clinical research.

- Trial design using PET imaging
- Protocol and study document development
- Expert analysis of PET images
- Scanner validation and QC troubleshooting
- IND/ANDA preparation for FDA review
- Access to information on investigational PET agents for use in clinical trials
- Reader training program for Axumin™ and NETSPOT™ PET images

Contact CTN for more information at ctnadmin@snmmi.org.

Save the Dates

The 38th Annual High Country Nuclear Medicine Conference
February 25–March 1, 2017 • Vail, CO

2017 ASCO Annual Meeting
June 2–6, 2017 • Chicago, IL

SNMMI 2017 Annual Meeting
June 10–14, 2017 • Denver, CO

53rd DIA Annual Meeting
June 18–22, 2017 • Chicago, IL

World Molecular Imaging Congress 2017
September 13–16, 2017 • Philadelphia, PA

2017 NANETS Symposium
October 19–21, 2017 • Philadelphia, PA

30th Annual Congress of the European Association of Nuclear Medicine
October 21–25, 2017 • Vienna, Austria