Molecular Imaging 2020: Year in Review

John Sunderland, PhD, MBA; University of Iowa and Jonathan McConathy, MD; University of Alabama Co-Chairs, Clinical Trials Network

The year 2020 may long linger in our minds for a number of reasons, but some of those thoughts should be positive. The field of molecular imaging and nuclear medicine accomplished a phenomenal milestone: the U.S. Food and Drug Administration (FDA) approved three new molecules (FES, tau and PSMA), one new isotope (copper-64) and one new production method (cyclotron-generated gallium-68).

The development of new drugs and therapeutic biological products used to advance medicine and improve healthcare requires innovation, determination, team effort and, of course, money. But key to all of this is understanding the science about the diseases and conditions that new products are designed to treat, performing methodical testing to achieve reproducible and consistent results, establishing irrefutable quality control in manufacturing procedures and obtaining appropriate regulatory advice before new radiopharmaceuticals and therapeutics are approved for use in humans. The availability of these new drugs, biological products and manufacturing procedures often means desperately needed new treatment options can be made available to our patients—and what can be more positive than that?

2020 was indeed a year of “firsts” for PET tracers. Herein we provide a short review of these events in order of approval date.

Cerianna™ (fluoroestradiol F-18)

On May 20, 2020, the FDA approved the positron emission tomography (PET) imaging agent F-18 fluoroestradiol (Cerianna™, Zionexa USA) as the first F-18-labeled PET agent for detecting estrogen receptor (ER)–positive lesions as an adjunct to biopsy in patients with recurrent or metastatic breast cancer. This new agent will enhance therapeutic decision-making by providing total body information of the estrogen receptor status of tumors.1 “This approval is based on multiple single institution studies in the US and Europe, which are in the process of confirmation in multi-center trials now including EAI 142. These trials show that FES predicts clinical benefit with endocrine therapy,” said Hannah Linden, MD, Athena Distinguished Professorship of Breast Cancer Research at the University of Washington. “Like genomic profiling in earlier stage tumors, FES has the potential to reduce the use of cytotoxic agents in metastatic breast cancer by identification of which patients could benefit from ER-directed therapy. The emerging field of molecularly targeted synergistic agents makes this even more feasible.”

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A Decade of Growth
Molecular Imaging and Therapy

Cerianna is not indicated for imaging other receptors, such as human epidermal growth factor receptor 2 (HER2) and the progesterone receptor (PR). The ER status of a patient’s tumor and recurrence of breast cancer should be confirmed with tissue biopsy. When interpreting images, it is important to remember that the uptake of F-18 fluorodeoxyglucose depends on the ER density and function in tumors and physiologic tissue, including in the liver, ovary, and uterus. Tumors identified as ER-positive on PET/CT should be based on comparison with normal tissue background of organs without high physiologic uptake. 2

Tauvid™ (F-18 flortaucipir)
The FDA granted approval of Tauvid™ for intravenous injection to Avid Radiopharmaceuticals Inc. on May 28, 2020. It is the first tau diagnostic PET imaging agent used to assess adult patients with cognitive impairment who are being evaluated for Alzheimer’s disease (AD). Tau is one of two proteins, along with amyloid, recognized as a hallmark of Alzheimer’s disease. When diseased tau proteins develop inside neurons in the brain, neurofibrillary tangles (NFTs) are formed. Tauvid is indicated for brain imaging to estimate the density and distribution of these aggregated tau NFTs. It helps identify the presence of tau pathology by binding to sites in the formed. Tauvid is indicated for brain imaging to estimate the density and distribution of these aggregated tau NFTs. It helps identify the presence of tau pathology by binding(11,13),(991,990)

Detectetin™ (copper Cu 64 dotatate)
On September 8, 2020, RadioMedix Inc. and its commercial partner Curium announced FDA approval of Detectetin™ (copper-64 DOTANE injection). Detectetin is the first Cu-64-labeled PET agent indicated for the localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adult patients. The 12.7-hour half-life of Cu-64 allows for the increased availability across the U.S. through shipments from centralized production sites. 2

As noted in the package insert, there may be a risk for image misinterpretation with Detectetin. Caution should be used, as a variety of other tumors also express somatostatin receptors. Increased uptake might also be seen in other non-cancerous pathologic conditions, in subacute inflammation, or as a normal physiologic variant (e.g., uncinate process of the pancreas). Additionally, a negative Detectetin scan in patients who do not have a history of NET disease does not rule out disease. 6

Cyclotron-Produced Gallium-68
On October 14, 2020, the University of Iowa received approval for cyclotron-produced gallium-68 (Ga-68) via a supplemental to their DOTATOC NDA, which was approved in 2019 for the localization of NETs in adults and children. Cyclotron-produced Ga-68 will allow for high-volume production. The newly approved process uses a liquid target filled with a zinc-68 solution to produce Ga-68 in the cyclotron. The target solution is transferred to a cassette-based synthesis module that purifies the gallium-68 and performs the chemistry process to manufacture the final drug product. Cyclotron-produced Ga-68 DOTATOC consistently results in production of 40-50 mCi of Ga-68 DOTATOC rather than the 10-25 mCi typically produced by a Ge-68/Ga-68 generator. The new process allows for multi-dose vials and provides a viable alternative to Ge-68/Ga-68 generators for facilities with cyclotrons. The FDA also approved cyclotron production of Ga-68 PSMA-11 at the University of California, San Francisco (UCSF). 7

Gallium 68 PSMA-11 (Ga 68 PSMA-11)
On December 1, 2020, the FDA approved gallium-68 PSMA-11, the first PET imaging agent for prostate-specific membrane antigen (PSMA)-positive lesions in men with prostate cancer. The approval was granted to the University of California, Los Angeles (UCLA) and UCSF following two prospective clinical trials involving a total of 960 prostate cancer patients. This approval process involved a great collaboration between the SNMMI Clinical Trials Network, two academic institutions, and the FDA that will hopefully serve as a model for future collaborations and radiopharmaceutical approvals. 8

Ga-68 PSMA-11 is indicated for patients with suspected prostate cancer metastasis who are potentially curable by surgery or radiation therapy and for patients with suspected recurrence based on elevated PSA levels. Once administered by intravenous injection, Ga-68 PSMA-11 binds to PSMA, allowing for the presence of PSMA-positive prostate cancer lesions to be imaged by PET. 9

The year 2020 certainly left some positive memories in the field of nuclear medicine and molecular imaging with the approval of three new molecules, one new isotope and one new production method. In fact, the past ten years have been an amazing era of growth for the field. Please review the timeline on pages 2 and 3 of this issue to follow the approvals of single photon tracers, PET oncology tracers, PET brain tracers, and radiopharmaceutical therapies that occurred over the past decade. It’s an amazing chronicle of innovation and progress.

References
2. DETECTETIN™ (Iodine I 131) Injection, for intravenous use. Prescribing Information. FDA Reference ID: 2588224.
5. Detectetin™ (copper Cu 64 dotatate injection) for intravenous use. Prescribing information. FDA Reference ID: 4661128.
Special Feature

FAP Agents

Fibroblast activation protein (FAP) is a membrane-bound enzyme that belongs to the DPP IV family of enzymes. In contrast to DPP IV, the name-giving enzyme of the family, FAP possesses not only DPP IV activity but also a unique endopeptidase activity, enabling it to cleave gelatin, collagen type I and α2-antiplasmin. Due to its expression in many tumors but also in benign diseases, there is considerable interest in the development of radiopharmaceuticals targeting FAP. Based on specific FAP inhibitors developed by Jansen et al., several radiolabeled FAP inhibitors (FAPIs) have been developed and characterized preclinically followed by first clinical evaluation. In general, FAPIs show rapid binding and internalization into FAP-expressing cells together with an equally rapid renal elimination. This results in high contrast images and allows early imaging of the patients.

The first clinical applications in patients with 28 different tumor entities revealed differences in tracer accumulation, with the highest SUVs in sarcoma, esophageal, breast, cholangiocarcinoma and lung cancer. Since FDG is currently used as the standard tracer in oncology, FAPIs were compared to FDG in up to 12 different tumor entities, revealing a higher detection rate and sensitivity for the FAP agents due to the higher contrast obtained with these tracers. This was especially the case for bone, liver and brain lesions and for peritoneal carcinomatosis.

In addition to staging, the high-contrast images can also be used for radiation planning, which has been pursued in patients with glioblastoma, head and neck tumors and lower gastrointestinal tract tumors. For lower GI tract tumors, the TNM classification was changed in 50% of the patients, and classification changed in 47% of patients with metastases as new lesions were seen. Furthermore, in almost all patients, an improved target volume delineation was obtained when using the image information of 68Ga-FAPI PET/CT.

A therapeutic application using 225Ac-FAPI04 has been described in nude mice bearing human pancreatic cancer cells. Therapy resulted in a significant tumor growth delay compared to non-treated controls without a significant change in body weight. However, clinically, few data exist.

As mentioned above, FAP expression is up-regulated in a variety of benign diseases, such as myocardial infarction, fibrosis of several organs, rheumatoid arthritis and atherosclerotic plaques. For example, a discrimination between inflammatory and fibrotic activity seems possible in patients with IgG4-RD. Furthermore, fibrotic lesions showed a reduced response to anti-inflammatory treatment as compared to inflammatory lesions, indicating potential use of FAP agents for follow-up of individualized treatment strategies in these patients.

Myocardial infarction has been addressed in a preclinical study in rats showing FAPI uptake in the diseased myocardium, with a peak at six days after coronary ligation. The tracer was mainly localized at the border zone of the infarction. This finding indicated a significant impact of FAP agents on diagnosis and clinical management of patients with myocardial infarction.

Figure 1. Maximum intensity projections (MIP) of PET/CT scans in patients suffering from metastasized pancreatic cancer (A) and breast cancer (C). (B) Maximum tissue uptake of 68Ga-FAPI02 10 min, 1 h and 3 h after intravenous administration to a patient with metastasized breast cancer. me=metastases. Loktev A, et al. J Nucl Med 2018, 59(9):1423-1429.

Figure 2. Maximum intensity projections of FAPI-PET/CT in patients reflecting 8 different, histologically proven tumor entities. (CCC=cholangiocellular carcinoma; CUP=carcinoma of unknown primary; Ca=carcinoma). From Kratochwil et al. J Nucl Med 2019;60(6):801-805.

Continued on page 6. See FAP Agents.
Therapy Toolkit
Amanda Abbott, MS, CNMT, RT(N)(CT), PET

Your department has all the tools it needs to establish a successful radiopharmaceutical therapy program, but do you have a plan for implementation?

With funding from an Advanced Accelerator Applications educational grant, the SNMMI Clinical Trials Network (CTN) developed a Therapy Toolkit to help you prepare your institution to provide radiopharmaceutical therapies (RPTs), particularly focused on 177Lu-RPTs. The toolkit currently has five “compartments,” or sections, where one can find the latest updates and announcements and information on education, guidelines, technologist tools, and patient resources. The Therapy Toolkit lives on the new SNMMI Radiopharmaceutical Therapy Central website at therapy.snmmi.org/

Dive into the Education compartment for links to helpful webinars on regulatory considerations and site preparation when planning a therapy program. Browse through Guidance Documents for information on expanded access to investigational drugs for treatment and on charging for investigational drugs under an FDA Investigational New Drug (IND) application. Ensure your site is prepared by referring to the downloadable Therapy Implementation Checklist, which lists important components needed to prepare your hospital or clinic, faculty and staff, multidisciplinary team and patients. Search through the Tools for Technologists for learning modules, newsletter articles and publications that are specifically helpful for technologists. Read through helpful Publications regarding radiopharmaceutical therapies. Check back often, as more content and resources on coding and reimbursement, dosimetry and resident resources will be added to the Toolkit. This is your one-stop shop for the current and accurate information on developing a successful radiotherapy program.

First compartment: Therapy Toolkit

What’s Happening

CTN Education Committee Welcomes New Co-Chair
Amanda Abbott, MS, CNMT, RT(N)(CT), PET

Regan began her career in the field of nuclear medicine in 2002 at the Mayo Clinic in Arizona. She transitioned into molecular imaging research in 2007, with primary interests in dynamic PET/MRI imaging and clinical trials involving PET as it relates to molecular imaging. Currently, Regan is a research nuclear medicine technologist with the Martinos Center for Biomedical Imaging at Massachusetts General Hospital in Boston. Prior to moving to Boston, she spent seven years as the research associate for molecular imaging at the Huntsman Cancer Institute at the University of Utah under Dr. John M. Hoffman. Since her start in the field, Regan has been involved in everything from investigator-initiated imaging trials to NIH funded research trials to industry-sponsored trials. Regan states, “I’ve been working in dynamic PET/MRI imaging for the past 7 years and am learning more and more every day!”

Her 18 years of experience in dynamic PET and PET/CT as well as hands-on experience with radiotracer development brings unique insight and guidance to the very busy Clinical Trials Network Education Committee. We look forward to working with Regan on this important committee!

Updated CTN Courses – Be on the Lookout in 2021!

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

What’s Happening

Regan Butterfield, BS, CNMT, AR(CT)

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Vital Signs, ECGs, and Physical Measurements in Clinical Trials

CTN courses include detailed information on the conduct of clinical research. These pathways include continuing education sessions at the SNMMI Annual and Mid-Winter meetings, webinars each year on timely topics and a comprehensive curriculum that offers unique training options in clinical research for nuclear medicine technologists. Several of these courses are currently being updated and will be posted online in the SNMMI Learning Center in 2021.

Imaging in Clinical Research: Elements for Success

This course provides a foundation for working in clinical research, especially the use of basic terms and definitions. It describes the organizations and entities that have in ensuring study compliance. Additionally, key documents used in clinical trials and the basic elements required for obtaining informed consent and recording or reporting adverse events and serious adverse events are discussed.

Pharmacokinetics of PET Tracers

This course provides a foundation for understanding the pharmacokinetics of PET tracers, an important component to consider when designing and implementing clinical trials.

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Artifacts in PET Imaging: Examples and Explanations

This course reviews common artifacts seen in PET/CT imaging, identifying and categorizing the types of artifacts and their causes. It covers the implications of these artifacts on data analysis and report generation, and provides strategies for minimizing or mitigating their impact.

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The Language of Clinical Trials

Improve your knowledge on how to communicate with clinical trial sponsors, contract research organizations (CROs), institutional review boards (IRBs), the Food and Drug Administration (FDA) and other groups by reviewing important terms and acronyms that are routinely used in clinical research.
FDA Approves Cyclotron-Produced Ga-68 DOTATOC and Ga-68 PSMA-11

Cyclotron-Produced Ga-68 Provides Alternative to Generators

David W. Dick, PhD; Department of Radiology, University of Iowa

On October 14, 2020, the University of Iowa received approval from the Food and Drug Administration (FDA) for a new process to produce gallium-68 (Ga-68) DOTATOC, which localizes neuroendocrine tumors (NETs) in adult and pediatric patients. On December 1, 2020, the University of California at Los Angeles (UCLA) and the University of California at San Francisco (UCSF) received FDA approval for the production of gallium-68 (Ga-68) PSMA-11, which localizes primary and metastatic prostate cancer. Both applications utilize cyclotron-produced Ga-68, which allows for higher-volume production. The newly approved processes use a liquid target filled with a zinc-68 solution to produce gallium-68 in the cyclotron. The target solution is transferred to a cassette-based synthesis module that purifies the gallium-68 and performs the chemistry process to manufacture Ga-68-labeled radiopharmaceuticals.

The advantage of cyclotron-produced Ga-68 radiopharmaceuticals is the consistent production of 40-50 mCi of the Ga-68 drug rather than the 10-25 mCi typically produced by a Ga-68/Ga-68 generator. The new drug applications (NDAs) are for multi-dose vials, which allows multiple patients to be injected per vial. In addition, the new process provides a viable alternative to Ga-68/Ga-68 generators in facilities with cyclotrons. The University of Iowa has waived exclusivity for the Ga-68 DOTATOC NDA and encourages everyone to file abbreviated new drug applications (ANDAs) based on this NDA. For details on the Chemistry, Manufacturing and Controls (CMC) section of the NDA, contact David Dick (david.dick@iuwawa.edu) at the University of Iowa. UCSF has waived exclusivity for the Ga-68 PSMA-11 NDA and encourage everyone to file ANDAs based on this NDA. For details on the Chemistry, Manufacturing and Controls (CMC) section of the NDA, contact Robin Lippisch (robin.lippisch@ucsf.edu) at UCSF.