The exponential growth of radiopharmaceutical therapies (RPTs) over the last few years, ignited by the U.S. Food and Drug Administration (FDA) approval of three radiotheranostic pairs since 2018, is already improving the survival and quality of life of tens of thousands of patients. This success is leading to an explosion of investment in the field, with more than 60 new companies working on the development of new radiotheranostic agents, driven by newly available venture capital.

In addition to new drug development and industry investment in the field, the need to optimize our FDA-approved clinical therapies is driving investigator-initiated trials aimed at better understanding the many factors that affect therapeutic results and patient-specific toxicities. Personalized dosimetry is only one obvious area; in addition, among academically driven research studies are those focused on optimizing the timing of treatment cycles, dose-modification algorithms, and patient selection criteria.

With this sudden and exciting growth comes the need for support infrastructure for the coming tsunami of early-phase clinical trials and critical later-stage investigator-initiated trials. To meet this need, the Therapy Clinical Trials Network (TCTN) is being launched by the SNMMI to support and facilitate RPT research trials, mirroring the Clinical Trials Network, which has been a successful network since 2008, facilitating the use of molecular imaging radiopharmaceuticals in clinical trials.

Among the short-term goals of the TCTN are:

- Creating a network of highly qualified clinical trial sites with appropriate expertise and physical infrastructure to support complex early-phase therapy trials.
- Building a database summarizing the qualifications of sites performing RPTs. This builds on the efforts and data collected by the Radiopharmaceutical Therapy Centers of Excellence program; however, it will collect more in-depth information on the research infrastructure and readiness to perform complex early-phase RPT trials. This information will be used to help identify qualified sites capable of performing particular trials.

Continued on page 2. See The Launch of the Therapy Clinical Trials Network (TCTN).
Amyloid Image Library Now Available

Jonathan McConathy, MD, PhD

As noted in the article in this issue, “Amyloid PET in the Revolutionary Era of Amyloid Targeted Therapy for Alzheimer’s Disease,” nuclear medicine physicians will play a pivotal role in the diagnosis and treatment of patients with Alzheimer’s disease. In anticipation of an increased demand for clinical amyloid beta PET scans, the Clinical Trials Network (CTN) developed and launched an Amyloid Image Training Library to help physicians sharpen their skills by reviewing cases. This online resource contains full DICOM cases for all three approved amyloid beta imaging agents—florbetapir, flutemetamol, and florbetaben—along with correlative CT and/or MR scans. The library is intended to simulate the reading room and give physicians additional practice in interpreting real cases and supplements but does not replace training offered by the manufacturers.

The amyloid imaging agents were approved more than a decade ago. At that time, manufacturers offered their reader training programs online, and medical societies offered educational sessions at their meetings. However, with the lack of reimbursement, amyloid imaging was mostly relegated to the research space. Realizing that the majority of imaging physicians, including residents over the past 10 years, may have had limited exposure to clinical amyloid imaging, the CTN created this novel tool.

The library is located on the Brain Imaging Portal on the SNMMI website. It is free to all who register. Accessing the library opens a web page with links to the cases along with some basic instructions. Clicking on a case link will launch a viewer in a separate tab. The workflow will set up the images in the viewer. The user can set up each case in the approved format or have the workflow do it. The user can scroll through and manipulate the images. Each case includes the patient history, key findings, and a conclusion. The module contains positive, negative, and equivocal cases for each tracer. Multiple cases can be viewed in one session by toggling between the web page and viewer windows.

The library can be expanded to include tau PET, FDG PET, and additional amyloid cases. CTN is interested in receiving feedback on the product functionality, cases, and overall user experience. If well received, libraries for other imaging agents, such as PSMA imaging, could be developed on this platform. We believe that full cases that simulate interpreting studies in the reading room are an important resource for imaging physicians to develop and maintain their skills.

CTN would like to thank the University of Utah, the University of Alabama at Birmingham, and Life Molecular Imaging for the cases and Guido Davidzon, MD, SM; Phillip Kuo, MD, PhD; and Jonathan McConathy, MD, PhD, for the interpretation of the cases. Finally, CTN would like to thank MIMSoftware for partnering with us and hosting this novel training tool.

The Launch of the Therapy Clinical Trials Network (TCTN). Continued from page 1.

- Working toward the standardization and harmonization of the equipment across different institutions and vendors, including calibrating dose calibrators, as well as developing harmonized approaches to PET and SPECT scanner calibrations, in line with international efforts. This step is crucial in order to obtain accurate and reproducible quantitative measurements needed, particularly for imaging-based dosimetry.
- Developing standards of practice related to RPTs, including equipment calibration, therapy verification and administration, residual storage, etc.

The TCTN will work closely with other SNMMI groups, government entities, and contract research organizations, as well as our partners in industry, with the vision that we will help accelerate the development of both industry-sponsored RPT clinical trials and multi-institutional investigator-initiated trials.

We envision the TCTN and its member sites as a necessary tool to efficiently accelerate the development of RPTs through generating quality early-phase clinical trial data and sharing expertise among all stakeholders in the field. Although the TCTN necessarily will start as a small network, it is an explicit and necessary goal to support sites interested in building their capacities in this direction.
$^{89}$Zr-Girentuximab is a unique immunePET imaging approach for the detection of clear cell renal cell carcinoma (ccRCC) and molecular characterization of renal masses. About 70% of renal masses are discovered incidentally, and current conventional imaging methods are limited in their ability to distinguish benign versus malignant lesions (1).

Girentuximab is a distinct monoclonal antibody against an antigen target, an epitope of carbonic anhydrase found in more than 94% of human clear cell renal carcinomas (3) (Figure 1). Carbonic anhydrase-IX (CAIX) is a membrane-associated enzyme, known to be upregulated and overexpressed in response to tumor hypoxia in many tumor types, particularly ccRCC, while minimally expressed in normal kidney, making it a valuable drug target for both imaging and therapy (4, 5). Additionally, CAIX expression correlates with RCC type and grade, disease aggressiveness, and outcomes (6, 7).

Radiolabeled girentuximab (previously cG250) has been investigated as both a diagnostic and therapeutic agent in clinical trials. Initial studies were conducted using $^{131}$I- or $^{124}$I-radiolabeled girentuximab. A phase 1 imaging trial with $^{124}$I-cG250/girentuximab in 26 patients noted accurate preoperative characterization in patients with renal masses, with a sensitivity of 94%, negative predictive value of 90%, and 100% specificity and positive predictive value for the detection of ccRCC (8). Subsequent use of $^{89}$Zr-girentuximab in humans followed preclinical findings of prolonged trapping in the tumor relative to normal tissues, resulting in higher tumor uptake and sensitivity in the detection of ccRCC lesions compared to $^{124}$I-girentuximab (9).

Further studies with $^{89}$Zr-girentuximab have also shown high accuracy and incremental value in its ability to detect metastatic ccRCC as compared to FDG PET and CT imaging alone. Combined $^{89}$Zr-girentuximab PET/CT and CT evaluations detected 91% versus 56% compared to CT alone or 84% with combined CT and FDG-PET/CT (10).

In a recently completed study (NCT03849118), $^{89}$Zr-girentuximab imaging in 300 patients met all primary and secondary endpoints. Patients with a single indeterminate renal mass 7 cm or smaller in diameter (cT1) suspicious for ccRCC who were to undergo surgical resection were imaged with $^{89}$Zr-girentuximab. The co-primary end points were sensitivity and specificity of $^{89}$Zr-girentuximab versus histology, and key secondary end points were sensitivity and specificity of $^{89}$Zr-girentuximab in a cT1a (≤4 cm) subgroup. One hundred ninety-three patients (67%) had ccRCC, and 179 (62%) had cT1a lesions. Other lesions included papillary RCC (15.3%), chromophobe RCC (8%), oncocytoma (3%), spindle cell (1.4%), sarcoma (<1%), and other (5%). The average sensitivity and specificity were 86% [80%, 90%] and 87% [79%, 92%], respectively, across all three readers and 85% [77%, 91%] and 90% [79%, 95%], respectively, for key secondary endpoints. Of the 179 cT1a lesions, ccRCC was found in 65% of cases versus other renal lesions (35%), while in cT1b lesions (n = 109), ccRCC was noted in 71% of cases versus 29% of other renal lesions. $^{89}$Zr-girentuximab was well tolerated in patients with no major AE directly related to $^{89}$Zr-girentuximab. The grade 3 or higher treatment-emergent AEs noted in 18 patients (6%) had AE patterns consistent with post-resection complications related to nephrectomy (11).

The imaging is performed with 37 MBq (1 mCi)/10 mg $^{89}$Zr-DFO-girentuximab injected intravenously followed by imaging of areas of interest 5 ± 2 days post-administration; the activity dosing is safe, well tolerated, and adequate for imaging (12). Biodistribution shows mild activity in the liver, spleen, and gastrointestinal tract and low uptake in normal kidneys in comparison to ccRCC lesions that show high contrast uptake (Figures 2 and 3).

Overall experience to date and recent phase III imaging study results highlight the potential of $^{89}$Zr-girentuximab imaging as a novel functional imaging probe to provide highly accurate, noninvasive characterization.
of renal masses, for detecting primary tumor as well as metastatic sites in the whole body, and the ability to assess heterogeneity of target expression across lesions. 89Zr-girentuximab imaging can be a critical clinical imaging tool to guide the management of patients for selection of surgical approaches such as sparing or partial nephrectomy versus a conservative approach for benign lesions or systemic treatment for metastatic disease. Advantages of 89Zr-girentuximab iPET is specificity, noninvasive assessment, avoidance of the need for biopsy procedures, and the ability to evaluate patients with contrast allergies or renal impairment who cannot undergo conventional imaging evaluation. Additional potential applications of 89Zr-girentuximab include imaging other malignancies that express CAIX and dosimetry assessments for optimization and development of targeted theranostics directed to CAIX (NCT02002312, NCT05239533, NCT05663710). References for this article can be found here.

Two Updated CTN Courses Are Now FREE

The Clinical Trials Network Education Committee develops a course curriculum as a resource for nuclear medicine professionals working in clinical research. Two of the most recently updated courses are now free to both members and nonmembers.

CTN Course 102, The Language of Clinical Trials, reviews common clinical research terms that will help participants be more accurate and effective in communicating with clinical trial sponsors and other research groups, increase efficiency in study start-up and ongoing trial management, and build a bridge between molecular imaging and other clinical research colleagues.

CTN Course 116, Imaging in Clinical Research: Elements for Success, reviews key elements for conducting clinical trials in accordance with Good Clinical Practice and federal regulations, including key terms, roles, and responsibilities, important trial documents, procedures for obtaining informed consent and reporting adverse events, and preparation for trial audits.

Courses are found in the SNMMI Learning Center and via the hyperlinks above.
In recent years, PET/CT imaging has become increasingly more prominent as the imaging modality of choice for oncological diagnosis. Among the attributes of PET/CT that contribute to its desirability are its promising contrast recovery coefficient and its capacity to detect lesions. It is necessary to create clinical phantoms to validate that these ever-improving technologies are effectively challenged and tested.

The new CTN PET phantom is a significant improvement on the CTN's previously employed anthropomorphic chest phantom. The size is larger now, approximating an adult chest. To optimize the phantom-filling process, the design elements have been updated to include a transparent base plate and a see-through chest cover. The new phantom is similar to its predecessor in that it has 12 spherical lesions varying in size from 7 mm to 37 mm dispersed throughout the phantom and two fill port screws at the top to fill the volume. However, in the updated phantom, each of the spheres’ lesions is attached to the underside plate to allow it to be filled and replaced as needed. Two asymmetrical lung inserts enclose some of the spheres with Styrofoam peanuts. The main volume of this body can store up to 17 liters of water.

We recently had the unique opportunity to test a prototype of the new phantom. We performed imaging acquisitions on the phantom using a Philips Vereos Digital PET/CT system, with an actual contrast ratio of 4.21:1, between the spheres activity and the phantom background activity. The imaging protocols and reconstructions employed were patient clinical protocols at our facility. Using the SNMMI Phantom Analysis Tool (PAT), we were able to get an SUV calibration of 0.99, which was within the recommended range of 0.9-1.10. Figure 2 shows the acquisition findings’ recovery coefficient curve, which showed good lesion detectability (Figure 1). These findings demonstrate the new CTN phantom’s ability to improve quality and standards.

CTN Welcomes a New Intern for 2023–2025

CTN welcomes our new intern, Molly Martin, PhD, PharmD, BCNP. Dr. Martin graduated from Augustana College and completed her PhD in Pharmacy (Medicinal and Natural Products Chemistry) and Doctor of Pharmacy at the University of Iowa (UI), where she is currently a nuclear pharmacist in the Department of Radiology. Dr. Martin’s career spans 15 years, with experience in designing methodology for radiolabeling of peptides and antibodies, preparing and dispensing radiopharmaceuticals, and working as a radiation safety officer. Currently Dr. Martin is also responsible for investigational radiopharmaceuticals used in nuclear medicine, participates in site qualification and initiation visits to discuss medication preparation and dispensing requirements of upcoming clinical trials, and manages recordkeeping as required by study sponsors and the U.S. Food and Drug Administration. Dr. Martin provides support to the UI Theranostic Radiopharmaceutical Manufacturing Facility for regulatory compliance with good manufacturing practice for manufacturing processes and procedures, development of standard operating procedures, and preparation of investigational New Drug applications. Dr. Martin’s professional goals include expanding the theranostics program at UI to investigate new cellular targets and theranostic isotope pairs and promoting the field of nuclear pharmacy. The CTN is very excited to work with Dr. Martin during this time of launching the Therapy Clinical Trials Network (TCTN) and creating new CTN database fields to expand data collection for theranostic and dosimetry studies. (See pages 1 and above for articles on the TCTN and Database, respectively.) Dr. Martin’s expertise is valuable for these new endeavors with the CTN. Welcome, Dr. Martin!

The CTN thanks Patricia Edem, PhD, for her 2021–2023 internship and wishes her continued success in her radiochemistry career.
An Update and Expansion of the Clinical Trials Network Database

Peter J. H. Scott, PhD and Suzanne E. Lapi, PhD

Radiopharmaceutical manufacturing is a complex process that requires advanced technology and expertise in various fields, including radiopharmaceutical chemistry, and an understanding of the complex regulatory environment. The implementation of advanced radiopharmaceutical imaging procedures has only recently been available beyond large academic centers. Key to the advancement of these techniques is communication between manufacturing and imaging sites to share best practices, find collaborations, or initiate new clinical trials focused on either new radiopharmaceuticals or the use of established radiopharmaceuticals to understand response to therapeutics.

Since its creation in 2008, the CTN has maintained a database and a Database Reporting Tool (DaRT) that allows users to search radiopharmaceutical imaging and production sites by geographical location, disease targets, availability of different radionuclides, or equipment types, including synthesis modules, cyclotrons, and PET/CT or PET/MR scanners. The database currently includes information pertaining to both production of radiopharmaceuticals and imaging capabilities. With the exponential growth in radiopharmaceutical use for imaging and radiotherapy, in both the research and clinical areas, there is a need to update and expand this impactful tool.

The goals for the database 2.0 include an update on the information for existing sites, to expand the number of sites listed and to expand the information for each site, including therapeutic/theranostic programs and training opportunities. This will encompass the manufacturing and use of diagnostic and therapeutic radiopharmaceuticals and imaging infrastructure and treatment capabilities, including SPECT/CT and well-counter equipment information for dosimetry capabilities. In addition, the inclusion of training programs will provide an opportunity to connect with potential students looking for graduate schools or technical degree programs, as well as points of contact for those looking to recruit recent graduates from programs relevant to the field.

The plan is for the next version of the site to be accessible also to the general public to enhance the impact of this initiative.

An additional focus of the database will be to increase the inclusion of international sites. An expansion of the global nature of the database will provide additional information to those looking to collaborate with partners in different regions, allowing for access to different expertise, technologies, and regulatory environments. SNMMI is exploring a potential collaboration with the International Atomic Energy Agency to facilitate the globalization of the information housed in the database/DaRT.

The overarching goal of the database is to include research institutions with cutting-edge radiopharmaceutical synthesis and imaging facilities, contract manufacturing organizations that specialize in radiopharmaceutical drug production and distribution, and where possible pharmaceutical companies with experience in research and development or approved radiopharmaceutical manufacturing.

By providing this updated database as an important resource to the radiopharmaceutical community, CTN aims to strengthen existing collaborations and provide opportunities for new initiatives.

Reference: http://ctndart.snmmi.org

Step-by-Step Radiopharmaceutical Therapy Procedural Competencies for Technologists

Deborah Barrickman, FSNMMI-TS, MEd, CNMT (N)(CT)(PET)

Due to the evolving complexity of nuclear medicine, employee competencies have become increasingly critical. Nuclear medicine technologists have never before been so involved in monitoring patient considerations, symptom management, and oncologic emergencies. Several federal institutions have developed a tool for radioligand therapy competencies for technologists to ensure patient safety and staff competency.

Patient safety is established by introducing a concept, understanding the sequence, and building on the knowledge base. Each layer of a process builds upon the next to reinforce precision and safety. This is especially critical when providing instruction, testing, and finally administering therapeutic procedures. Each step must possess multiple points to allow duplicating safety stops and prevent mishaps.

Competency is a person’s actual performance; a person needs competence before he/she can achieve competency. It is through consistent and repetitive instruction that personnel are able to prove whether they are competent or need additional training. To manage competency effectively, a healthcare organization must understand the difficulty of measuring and improving competence.

Continued on page 7. See Step-by-Step Radiopharmaceuticals.
Amyloid PET in the Revolutionary Era of Amyloid Targeted Therapy for Alzheimer’s Disease
Phillip Kuo, MD, PhD

The recent approval of two anti-amyloid antibodies, aducanumab and lecanemab, has finally provided us breakthrough therapies that target the mechanism of Alzheimer’s disease (AD) rather than just treating the symptoms. The accelerated approval was based on the antibodies’ removal of amyloid from the brain as measured on serial amyloid PET. However, the use of amyloid PET as an imaging biomarker for approval generated much controversy, especially since the first antibody, aducanumab, did not definitively show clinical benefit. The question was rightfully asked, “Is reduction in brain amyloid an appropriate surrogate endpoint to predict a clinical benefit to patients?” Any discussion of benefit also needs to include discussion of risk. Both antibodies can cause amyloid-related imaging abnormalities (ARIA) detected on MRI. ARIA can be symptomatic and present as brain edema (ARIA-E) or hemorrhage (ARIA-H).

The second anti-amyloid antibody, lecanemab, not only reduced amyloid in the brain but also slowed (but did not stop) decline, according to the clinical dementia rating scale. The U.S. Food and Drug Administration (FDA) is currently reviewing the clinical data for potential full approval of the drug. For patient selection, the prescribing information states to confirm the presence of amyloid beta pathology prior to initiating treatment. Nuclear medicine physicians play a critical role in confirming the presence of the amyloid target and therefore ensuring the correct patients receive therapy. This high-stakes role is familiar to us given the success of theranostics-targeting somatostatin receptor and prostate-specific membrane antigen for neuroendocrine and prostate tumors, respectively. For both neurology and cancer, we are diagnosing the molecular pathology that is the critical “nostics” component of theranostics.

We currently have three FDA-approved 18F-labeled amyloid PET radiopharmaceuticals: florbetapir, flutemetamol, and florbetaben (in order of approval). The potential full approval of lecanemab has generated new hope that the Centers for Medicare and Medicaid Services will grant reimbursement status to these amyloid tracers. While each tracer has its own specific guidelines for image interpretation that should be utilized, they all share the same basic principles for image interpretation. Negative scans show a white matter pattern of uptake, whereas positive scans show uptake in both gray and white matter and thus loss of the white matter pattern.

The SNMMI is providing new resources to sharpen your skills and prepare you to provide optimal interpretation of amyloid PET as we charge into this new era of amyloid-targeted therapy for AD.
Attention Clinical Trial Sponsors:

Ensure that you are getting the best qualitative and quantitative imaging data for your studies with our PET/CT validation and SPECT/CT scanner calibration programs!

**PET/CT Validation:**
- CTN phantom with concentration and acquisition protocols customized for your radiopharmaceutical
- Quantitative assessment for scanner calibration, coefficient of variation, PET/CT alignment, lesion detectability, and recovery coefficient assessment
- Harmonized reconstructions for all scanners across your study

**SPECT/CT Calibration:**
- Quantitatively robust method to help ensure the quantitative veracity and comparability of data between sites and scanners
- Provides the therapeutic radioisotope-specific calibration factor to be used for radiation dose calculations
- CTN anthropomorphic chest phantom is used to assess resolution and measure contrast recovery

A) Tissue-equivalent SPECT/CT calibration phantom with plastic bottle insert
B) CTN chest phantom (left); PET/CT image of a CTN chest phantom (right)
C) Sample PET/CT validation report

Contact us today to learn how we can help with your studies! [ctnadmin@snmmi.org](mailto:ctnadmin@snmmi.org)

**Save the Dates**

**36th Annual Congress of EANM**
September 9-13, 2023
Vienna, Austria

**The SNMMI Fall Therapeutics Conference**
September 21-23, 2023
Baltimore, MD

**RSNA 109th Scientific Assembly and Annual Meeting**
November 26-30, 2023
Chicago, IL

**2023 SNMMI Mid-Winter & ACNM Annual Meeting**
February 1-3, 2024
Orlando, FL

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