Neurodegenerative conditions such as Alzheimer’s disease (AD) and chronic traumatic encephalopathy (CTE) are characterized by the pathological accumulation of tau aggregates. Human postmortem studies have shown that neurofibrillary tangles (NFT) density and not Aβ insoluble plaques are strongly correlated with neurodegeneration and cognitive impairment. Moreover, while age-related limbic NFT are frequently present in cognitively unimpaired individuals, neocortical NFTs are much less prevalent, in contrast with neocortical Aβ plaques that appear abundantly in some non-demented individuals. The fact that tau plays a key role in neurodegeneration has led to the development of specific therapeutic strategies for the treatment of AD and non-AD tauopathies, either by inhibiting tau hyper-phosphorylation, its aggregation or direct stabilization of microtubules.

In this context, there is a need to develop reliable diagnostic and prognostic biomarkers that can identify incipient focal or diffuse pathology that will allow, when available, early therapeutic interventions. To date, definitive diagnosis of these neurodegenerative conditions can only be established after postmortem examination of the human brain. Molecular imaging procedures are suited to overcome the need for a neuropathological examination in order to identify the underlying pathology of these diseases. While the last two decades have been focused on developing novel Aβ ligands for the non-invasive detection of Aβ deposition in the brain, only in recent years were efforts concentrated on developing selective tau imaging agents.

There are several obstacles to be surmounted to be able to image tau deposits in vivo (for in depth review see Villemagne et al). The greatest obstacle to be overcome by selective tau tracers is the co-existence of other misfolded proteins sharing the same β-sheet secondary structure, as is in the case of AD where tau and Aβ are both co-localized in grey matter areas. This particular issue is further complicated by the disparity between the brain concentrations of Aβ and tau aggregates in AD, where the concentrations of Aβ are, depending on the brain region, ~5-20 times higher than those of tau, requiring a radiotracer with high selectivity for tau over Aβ. In general, PET tracers should be non-toxic lipophilic molecules of low molecular weight (<450) that readily cross the blood-brain barrier (BBB), with rapid clearance from blood that are preferably not metabolized, with low non-specific binding whilst reversibly binding to its target in a specific and selective fashion.

It is also desirable that these novel tau tracers are labeled with isotopes with longer half-lives, such as fluorine-18 (F-18; half-life of ~2 hr) that allows centralized production and regional distribution, as currently practiced worldwide in the supply of F-18FDG.

Continued on page 2. See Tau Imaging.
TAU IMAGING TRACERS

While most of the proposed novel tau imaging tracers originated from research groups working on therapeutic tau anti-aggregation or defibrillation strategies, the most successful attempts come from research groups focused on screening novel or available chemical libraries to identify high-affinity selective PHF-tau compounds amenable to radiolabeling.

$^{18}$F-FDDNP (Figure 1) is a tracer reported to bind non-selectively to both extracellular Aβ plaques and intracellular tau in AD patients who presented with higher $^{18}$F-FDDNP retention than controls. $^{18}$F-FDDNP was also used in the assessment of adult Down syndrome patients, football players suspected of CTE, and in progressive supranuclear palsy patients. It has been shown that $^{18}$F-FDDNP also binds prion plaques in Creutzfeld-Jakob Disease (CJD) and Gerstmann-Sträussler-Scheinker disease. The lack of selectivity of FDDNP might preclude its use in most cases requiring the identification of the misfolded protein responsible for a specific phenotype.

$^{11}$C-PBB3 (Figure 1) is characterized by a π-electron-conjugated backbone that apparently allows binding to a broad range of AD and non-AD tau aggregates. While in vitro autoradiographic studies in AD brain sections showed substantial non-selective binding to both plaques and tangles, two-photon laser scanning fluorescence microscopy studies in a tau transgenic mouse model showed rapid clearance of the tracer with selective binding to tau tangles. Preliminary clinical studies in three healthy control volunteers and three AD patients assessed with both $^{11}$C-PBB3 and $^{11}$C-PiB showed a different pattern of brain retention between the two tracers suggesting that, at high specific activities, $^{11}$C-PBB3 binds selectively to tau.

Two novel benzimidazole pyrimidine derivatives, $^{18}$F-T807 and $^{18}$F-T808 (Figure 1) with high affinity for tau, were identified using in vitro autoradiography. First-in-human $^{18}$F-T807 PET studies in AD patients, mild cognitive impairment (MCI) patients and healthy participants have shown that cortical $^{18}$F-T807 retention follows the known distribution of PHF-tau in the brain where higher $^{18}$F-T807 cortical retention was significantly associated with increasing disease severity. While $^{18}$F-T808 showed better tracer kinetics than $^{18}$F-T807, substantial defluorination was observed in some cases.

Quinoline derivatives, THK-523, THK-5105 and THK-5117 (Figure 1) were radiolabeled with $^{18}$F and preclinically and clinically...
PET Reconstruct Harmonization for Clinical Trials: Update

John Sunderland, PhD

There is considerable interest by both pharmaceutical and FDA to use the information provided by PET imaging to help decrease the cost of drug development and the time it takes to bring these new drugs safely and effectively into the hands of physicians and patients. There is also considerable interest amongst the nuclear medicine community to bring new, promising PET radiopharmaceuticals out of the laboratory and through FDAs regulatory gauntlet into clinical practice. In both these instances, the FDA expects the PET scanners used in these clinical trials to generate accurate, reproducible and harmonious quantitative data, regardless of the manufacturer and PET scanner model used. However, significant differences in quantitative scanner performance have confounded these efforts. This scanner-dependent variability degrades the quality of clinical trials by requiring more subject accrual and/or leading to inconclusive results.

In September of 2012, in response to the need for better quantitative harmonization, the National Cancer Institute funded a five-year, $2.6 million initiative to identify optimized and harmonized PET reconstruction parameter sets for all recent model PET/CT scanners to generate quantitatively identical images for use in clinical trials. John Sunderland, PhD (University of Iowa), Paul Kinahan, PhD (University of Washington) and Joel Karp, PhD (University of Pennsylvania) are spearheading this project, now in the middle of its second year. Scientists and engineers from GE, Philips and Siemens are actively contributing to the project, and the CTN is playing a coordinating role.

Currently, the research team has collected data from 17 scanners representing 10 different scanner models. Academic PET sites participating in the project are imaging the NEMA Image Quality phantom using a modified protocol that includes 12 different sphere sizes from 8.5mm to 44 mm to characterize quantitative characteristics. The research team is in the process of identifying reconstruction parameter sets for each scanner that shows the most promise for universal quantitative harmonization. The investigative team is also measuring the noise characteristics associated with several scanner metrics (SUV_{max}, SUV_{mean}, SUV_{peak}) so as to assess statistical variance, another critical measurement parameter. PET imaging sites at the Universities of Washington, Pennsylvania, Iowa, Duke, Emory and Case Western Reserve have contributed data to this project thus far.

The research team is also working closely with the NCI’s Quantitative Imaging Network (QIN), providing carefully acquired “ground truth” phantom data sets designed to challenge novel region segmentation algorithms being developed by QIN members.

We anticipate that the majority of data collection will be completed in the coming year, with preliminary results being developed concomitantly.

In the NEWS

SNMMI 2014 Annual Meeting

CTN Preview

CTN Categorical: Saturday, June 7
8:00 AM – 4:00 PM

The SNMMI Clinical Trials Network (CTN) is excited to sponsor a full-day Categorical on “Molecular Imaging for Assessing Response to Therapy.” Participants will hear about the different response measurement criteria methods, metrics used when assessing response in different oncologic diseases, novel molecular imaging radiopharmaceuticals available for use, and the challenges within the pharmaceutical industry to incorporate molecular imaging in their oncology trials.

CTN CE Session: Tuesday, June 10
2:45 – 4:15 PM
The Status of DOTA Agents in Molecular Imaging. DOTA radiotracers have become a point of interest for many investigators seeking better imaging of neuroendocrine tumors. This session provides participants with some background information on the chemistry and the generators for making the agents, DOTA kits, and an update on the investigational trials underway using different DOTA agents.

CTN-Tech Section Joint CE Sessions:
Monday, June 9 • 3:00 – 4:30 PM

Imaging in Clinical Trials. This session focuses on fundamental concepts for operating in a clinical research environment. Becoming familiar with the unique “language” spoken by research staff is essential to successfully carrying out the requirements of a research study. Following the protocol and imaging manual are key in acquiring reproducible and usable images for the drug sponsor, and understanding how PET scans are used to assess response to treatment is basic to imaging in clinical trials. The session provides an excellent source of information for all imaging site staff to use when performing PET imaging in the clinical research domain.

Monday, June 9 • 4:45 – 6:15 PM
Imaging the Brain: A Guide for Technologists. With the introduction and use of new radiotracers for brain imaging, it is essential that technologists be trained on the basics of neuroimaging structure and function. The session, taught by John Hoffman, MD, and Satoshi Minoshima, MD, offers attendees valuable information on brain anatomy and how to apply it to achieve accurate positioning and appropriate scan acquisition parameters when imaging the brain.
Tau Imaging  Continued from page 2.

tested\textsuperscript{37,38}. Autoradiography analysis indicated that these tracers bind selectively to tau deposits at tracer concentrations\textsuperscript{38}. First-in-human PET studies showed significantly higher retention in the temporal, parietal, orbitofrontal and hippocampi of AD patients when compared to healthy controls, retention that was not associated with the retention of \textsuperscript{11}C-PiB, suggesting that these radiotracers bind selectively to tau and not to Aβ.

Furthermore, tracer retention was correlated with cognitive parameters, which is in agreement with postmortem studies showing a strong association of neurofibrillary pathology with dementia severity. In stark contrast with THK-5105 and THK-5117, THK523 retention in white matter was high, precluding clear distinction of the distribution of tau pathology by visual inspection of PET images\textsuperscript{39}. First-in-human PET studies with \textsuperscript{18}F-THK5105 showed a clear distinction between AD patients and healthy elderly controls. Moreover, \textsuperscript{18}F-THK-5105 retention, while correlating with dementia severity (Figure 2) and brain atrophy, was not associated with \textsuperscript{11}C-PiB retention in AD patients. Preliminary data from human PET studies indicate that \textsuperscript{18}F-THK5117 has better pharmacokinetics and a higher signal-to-noise ratio than \textsuperscript{18}F-THK5105.

These tracers will allow new insights into tau pathology in the human brain, facilitating research into causes, diagnosis and treatment of traumatic encephalopathy and major neurodegenerative dementias, such as AD and some variants of frontotemporal lobar degeneration, where tau plays a role. The field of selective tau imaging has to deal with several obstacles, mainly those related to the idiosyncrasies of tau aggregation that influence radiotracer design\textsuperscript{16}. Recent progress in the development of tau tracers is enabling the non-invasive assessment of the extent of tau pathology in the brain, eventually allowing the quantification of changes in tau pathology over time and its relation to cognitive performance, brain volumetrics and other biomarkers, as well as assessment of efficacy and patient recruitment for anti-tau therapeutic trials.

Funding Sources
This study was supported in part by ADDF Research Grant (20101208 AFTD), NHMRC Project Grant 1044361, the research fund from GE Healthcare, the Small Business Innovation Research (SBIR) program of Japan and the Grant-in-Aid for Scientific Research on Priority Areas “Integrative Brain Research” from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (20019006). The funding sources had no input into the design of this study, the analysis of data, or writing of the manuscript.

Victor L. Villemagne

Information on the authors and the complete list of references can be found on the CTN website.
The 1997 FDA Modernization Act (FDAMA) contained provisions that required the FDA to develop, among other things, current Good Manufacturing Practice (cGMP) regulations for PET drugs. The FDA completed the final FDAMA requirement on December 11, 2009, with the creation of cGMP regulations for PET drugs (21 CFR Part 212). According to the provisions in FDAMA, these regulations became effective two years later, on December 11, 2011. The FDA exercised regulatory discretion to extend this deadline to June 12, 2012. We have now entered the “post-FDAMA era” of PET drug production where all routine PET drugs, including those produced at academic institutions for internal use and those produced by commercial manufacturing sites for distribution within a regional area, must now be produced under cGMP regulations.

New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs) have been submitted by US PET drug manufacturers. The exact number of PET drug applications and the number of FDA inspections are unknown. However, based on our best estimates, approximately 60 PET drug applications have been filed with the FDA and at least 70 inspections have occurred since the end of 2011. As of February 2014, at least 25 applications (both NDAs and ANDAs) have been approved by the FDA.

For many applicants, this is their first experience with FDA inspections. As a result, applicants have had to learn how to manage inspections with limited professional training. Likewise, many of the FDA investigators are new to the PET field and are experiencing the PET cGMP regulations for the first time. Thus, this is a shared learning experience for the FDA and the PET community during the first wave of inspections.

Herein we summarize the PET community’s current experience with FDA inspections, from the perspective of both academic institutions and commercial manufacturers, based on a recent SNMMI survey of the CTN Radiopharmaceutical Manufacturer’s database. Our goal is to continue the valuable dialog on this topic that has occurred in previous editions of this newsletter and in recent CE sessions held at the SNMMI Annual and Midwinter meetings.

The FDA has prepared a guidance manual for investigators to use during PET inspections of PET drug manufacturing sites. The manual is available from the FDA website and all PET drug manufacturers are strongly encouraged to obtain a copy, understand it, and use it to prepare for FDA inspections. The manual notes that “cGMP’s for PET drugs differ in significant ways from Part 211 (21 CFR Part 211 is the therapeutic drug cGMP rule).” It also states that investigators should “...schedule PET inspections in advance...” to allow an institution time to have the appropriate staff available. The manual describes six systems that form the core of each inspection:

- Quality
- Facilities and Equipment

The manual defines a “full” inspection as one that covers at least four of these systems. A “full” inspection is indicated for sites that, among other things, have never been inspected (i.e., a pre-approval inspection), have had a history of poor compliance, or have undergone significant changes in manufacturing or personnel. A “full” inspection is also completed every two years. An “abbreviated” inspection covers at least two systems and is indicated for sites that have been previously inspected with an adequate history of compliance.

In addition to the inspection guidance manual, the FDA has prepared a Guidance document entitled, “Media Fills for Validation of Aseptic Preparations for PET Drugs.” All PET drug manufacturers are strongly encouraged to obtain a copy of this manual and to use it to prepare for FDA inspections. Initial FDA inspections have focused on these areas:

- Media fill simulations
- Microbiology and environmental monitoring
- Electronic signature requirements (Part 11)
- Documented training (didactic and on-the-job)
- Inadequate investigations
- Continuous improvement and documented corrective/preventative actions
- Consistency and change control across a commercial network of manufacturing facilities

Regardless of the type of inspection, the inspection may close with the issuance of a Form 483, which is a summary of objectionable practices observed by the investigator. A proper response to 483 observations is critical. The response should be in the form of a written letter from the manufacturer. The response may include data to support certain practices and/or commitments to voluntarily correct objectionable practices.

Inspection standards and best practices for PET drug manufacturing are still in their infancy and will continue to mature through years of FDA inspections. As a PET community, we must continue to work together to ensure an orderly progression to effective practice standards that comply with FDA expectations, and are well-understood and well-communicated throughout the PET community.
FROM CLINICAL PRACTICE TO CLINICAL RESEARCH: MY JOURNEY
Matt McDonald, BS, CNMT

Until recently, my career as a nuclear medicine technologist had been fairly typical working in hospital nuclear medicine departments. Seven years ago, I decided to take a leap of faith and began working for an oncology center doing nuclear medicine and PET/CT for my soon-to-be mentor, Dr. Samuel Mehr. Dedicated oncologic nuclear imaging came with a new set of challenges, but also many perks (not being on call, for one!). I quickly learned that no patient in the oncology world was the same; for every patient scanned, I had to be adaptable to their unique situation. One patient may have just been diagnosed, another in remission and, sadly, many patients progress and die, some soon after completing a PET/CT study. These experiences made me realize that being flexible in a variety of situations was quite rewarding and an enjoyable part of my work in nuclear medicine and, more importantly, oncology.

In June 2013, I accepted a new position at The Urology Cancer Center and GU Research Network. Dr. Luke Nordquist, a medical oncologist specializing in urologic cancers and clinical research, decided to establish a nuclear medicine lab at his clinic in 2013. Radium-223 Xofigo® was recently approved for treatment of patients with prostate cancer and symptomatic bone metastases, and Dr. Nordquist needed a nuclear medicine technologist to administer this drug on-site. He sought me out for that need, and also asked me to learn about and assist in clinical research. With the success of the nuclear program and the high volume of nuclear scans required for clinical research, our clinic decided to add on a gamma camera in May 2014.

Our site has nearly 30 active clinical trials for prostate, bladder, and kidney cancers, and we are working with several drug companies in developing investigator-sponsored studies, including projects using Xofigo®. Our vast experience with Xofigo® has also led to the publication of three abstracts, one of which I presented at the SNMMI 2014 Mid-Winter Meeting.

Although a nuclear medicine technologist by training, I am becoming more involved in clinical research in a number of different roles. The key to this successful transition has been my adaptability skills. I discovered that if one is open to change, the results can be very rewarding.

Research Essentials: Who’s Who in Clinical Research

Successful clinical research trials require a team of dedicated, experienced individuals who strive to determine the safety and effectiveness of medications, devices, diagnostic products and treatment regimens intended for human use. Depending on the trial, the team may consist of the following members:

- **Sponsor**: Someone who takes responsibility for the initiation and management of a clinical trial; can be an individual investigator or academic institution, a pharmaceutical company, private organization, or government agency.

- **Contract Research Organization (CRO)**: A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of the trial-related duties and functions. Such obligations may include protocol design, selection of monitors or investigators, data analysis, and preparation of materials to submit to FDA. In some cases, an Imaging CRO may be hired to specifically oversee imaging components/activities in a study.

- **Clinical Research Associate (CRA)**: An individual, hired by the sponsor or CRO, who is responsible for managing the study-specific activity at clinical research sites to ensure the study is conducted according to regulations and verify that subject data collected by the sites are accurate.

- **Principal Investigator (PI)**: An individual who actually conducts a clinical investigation under whose immediate direction a test article is used on a human subject. If an investigation is conducted by a team, the PI is the responsible leader of the team.

- **Clinical Research Coordinator (CRC)**: A person who handles most of the administrative responsibilities of a clinical trial on behalf of a site investigator and acts as liaison between the site and sponsor.

- **Study Subject**: the most important member of the team - a living individual about whom an investigator obtains data through intervention or interaction with the individual. Most clinical trials involve patients with a specific disease or medical condition, but some studies enroll healthy volunteers.
Tech Tip

THE ABC’S OF HANDLING A QUERY

Bryan Kerr, AS, CNMT, PET, NCT, RT(N)(CT)(ARRT)

When a sponsor checks data that have been submitted for a trial, there may be an item that is not clear to the sponsor. This situation then prompts a “query” to the site. When handling a query, it is necessary to follow these ABCs to resolve the query appropriately.

A: assess the information or issue the query calls into question. Refer to your records to ensure you have the correct data that corresponds to the query.

B: believe - but verify - a query from the sponsor. Keep accurate records to ensure that a query is resolved correctly. We all like to think we don’t make mistakes - including the sponsor/CRA - but it is very easy to enter a data point incorrectly or not review data accurately.

C: correct the mistake. Work with the sponsor’s monitor to make the required changes and resolve the query in a timely manner.

Clinical Trials Network

2014 WEBINAR SERIES

CTN offers opportunities to earn valuable CE credit at a nominal fee. There are four remaining webinars in our 2014 series, so plan on joining us for one - or more - of them. If unable to attend the live webinar, purchase the recorded session through the SNMMI Learning Center.

JUNE 26
PET Imaging of the Brain for Technologists
Speaker: Adam Opanowski, CNMT, PET, NCT, RT(N)

AUGUST 21
Using FACBC to Image Recurrent Prostate Cancer
Speaker: David Schuster, MD

OCTOBER 23
Updates on 68Ga: Outlook for the Future
Speaker: David Dick, PhD

DECEMBER 11
Coverage with Evidence Development for Amyloid Imaging: Current Status
Speaker: Maria Carrillo, PhD, Alzheimer’s Association

For the complete list of webinar titles and speakers please view CTN’s educational offerings at www.snmmi.org/ctn.

Message from Co-Chairs Continued from page 2.

course topics developed and presented by physicians, physicists, and other scientists. Also, the CTN will continue to offer a validation phantom program along with maintaining a comprehensive registry of clinical imaging sites and radiopharmaceutical manufacturers to help with drug development clinical trials.

• Work towards the use and approval of new radiopharmaceuticals
The CTN is uniquely positioned with the FDA, NCI, industry, and the academic nuclear medicine community to assist in defining the pathways toward regulatory approval of new radiopharmaceuticals. As such, we can collaborate in the broader SNMMI initiative of the FDA Task Force, develop plans to move non-proprietary agents forward, and assist biomarker developers with advancing their proprietary radiopharmaceuticals.

• Facilitate access to investigational PET radiopharmaceuticals for multicenter clinical trials
One step in improving access to these PET agents is to obtain FDA-approved centralized INDs for investigational PET radiopharmaceuticals. To date, SNMMI holds an IND for FLT and will consider applying for others as community needs dictate. The CTN has developed a comprehensive set of template forms for non-proprietary radiopharmaceuticals that can be provided to eligible investigators for site-specific adaptation. These templates include case report forms, informed consent for IRB approval and image acquisition and reconstruction guidelines. Additionally, proper Chemistry, Manufacturing and Controls (CMC) documentation suitable for FDA-acceptance can be prepared for investigational radiopharmaceuticals. We also have developed, and update regularly, a comprehensive database of PET radiopharmaceuticals produced and developed at commercial and academic sites in the US and have included cyclotron information and regulatory status of RPs.

CTN’s vision is to take a leadership role in advancing the use of radiopharmaceuticals and optimizing the use of molecular imaging in clinical trials and dissemination into clinical practice. Its mission is to advance the use of molecular imaging radiopharmaceuticals in clinical trials through standardization of chemistry and imaging methodology. This includes using imaging agents during the course of drug development, as well as bringing new radiopharmaceuticals to regulatory approval.

We recognize that continuity in an organization is fundamental in achieving success. Like other volunteer-oriented groups, the CTN relies on SNMMI members and other professional personnel to provide the leadership and guidance that makes programs successful. The CTN internship program initiated in 2011 was set up to help cultivate the next group of PET clinical researchers by providing them with guidance and exposure to the many nuances of clinical research. The future is bright, but we must continue to find ways to grow the ranks within this area and establish a plan to bring new members into the CTN so leadership and committee members can continue to function at, and above, the level of success we have achieved thus far.
During the past 12 months, the CTN Radiopharmaceutical Manufacturers’ Committee moved forward with both on-site and desktop audits of the radiopharmaceutical manufacturing sites supplying FLT for a study that cross-referenced the SNMMI-held IND for FLT. Although not specifically required by the FDA as part of the IND approval, the CTN made a decision at the time of approval to perform its own audits to ensure that quality product was being manufactured and administered to study subjects.

Approximately 25% of the manufacturing sites were audited: 5 were desktop audits and 2 were to be done on-site (one is pending). Representatives from this Committee were randomly assigned a site to review. Those doing desktop audits reviewed batch records, and the on-site auditor visited the manufacturing facility and reviewed records and manufacturing procedures. All auditors completed audit reports that were then reviewed by all committee members. Results of the audits were very positive. Two sites had to clarify a couple of items and provide additional information not provided in the batch records, but all sites eventually received a passing score.

The Committee intends to perform these audits annually, with results being included in the Annual Report to the FDA for the FLT IND.