Yale University
Positron Emission Tomography Center

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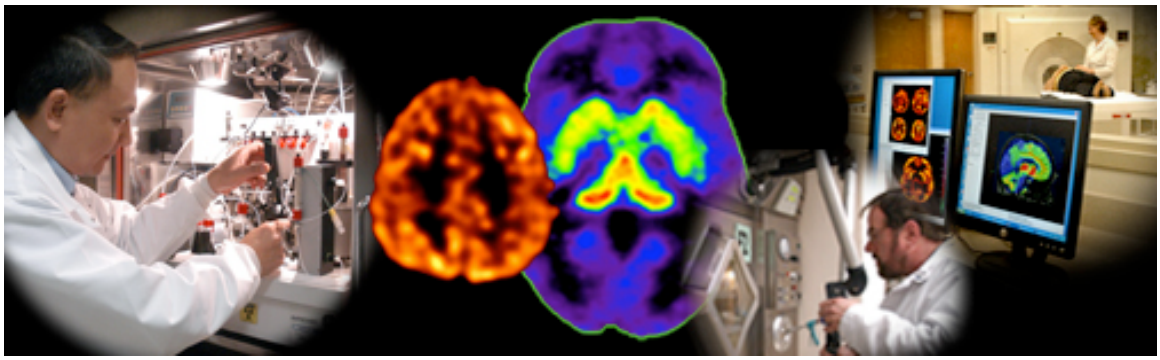

Overview of PET Center Resources and Capabilities

- New, state-of-the-art facility operational since Spring 2006
- Expert faculty; experienced technologists/staff
- Research nurse on-site; physiological monitoring
- GE PETtrace cyclotron, targetry for producing C-11, F-18, N-13, 0-15
- HRRT high-resolution scanner for imaging brain/small animals (one of 18 in the world)
- CTI HR+ whole body scanner
- State-of-the-art motion correction
- Radiochemistry laboratory with modules to produce a wide variety of radiotracers
- Chemistry SOPs – high quality standards for safety, production, use
- cGMP (Good Manufacturing Practices compliant)
- High specific activity and support for studies
- Fully equipped laboratory for blood and metabolite analyses
- Image analysis laboratory and image analysis software applications
- Rapid turn around of data (automatic)
- Collaborative opportunities (close proximity to other Yale School of Medicine Departments, Research Centers, Yale-New Haven Hospital)

Background

In 2004, Yale University broke ground for a new, state-of-the-art Positron Emission Tomography (PET) Research Center dedicated to providing the highest quality of nuclear imaging research. Located on Howard Avenue in New Haven, with close proximity to other Yale School of Medicine departments, this impressive 22,000 sq. ft. facility has been established to advance the interests of Yale clinicians, scientists, and students in molecular imaging research.

The PET Center is comprised of a technologically advanced radiochemistry laboratory engaged in the development and use of a complete line of PET radiopharmaceuticals labeled with the most common PET isotopes (11C, 15O, 13N, and 18F); a physics and data analysis section that oversees scanning procedures and optimizes data acquisition and analysis; and a biological section involved in the evaluation and validation of molecular tracers. It is anticipated that the PET center will grow over time to include approximately 45 clinician scientists, basic scientists, technicians, and students.

PET is a non-invasive diagnostic scanning technique that provides researchers and clinicians with visual images of organ function. PET scans can detect biochemical changes in body tissues before structural damage occurs from disease. This information allows clinicians to be proactive in their treatments and enables researchers to detect early biomarkers of disease that can aid diagnosis and advance drug development.

The Yale University PET Center collaborates with other School of Medicine departments to provide educational opportunities for doctoral and postdoctoral trainees. Collaborations with industry partners are serving to advance the use of molecular imaging in new medication discovery and the development of new diagnostic PET radiopharmaceuticals. Current research interests focus on disorders of the central nervous system (CNS), oncology, and cardiology.

Mission

Our mission is to create a collaborative molecular imaging research environment to advance the interests of Yale clinicians and scientists; to provide educational opportunities for undergraduate students, doctoral candidates, and post-doctoral trainees; and to develop new PET radio-pharmaceuticals to advance disease diagnosis and medication discovery.

Faculty

Richard E. Carson, PhD, *Professor of Diagnostic Radiology and Biomedical Engineering, Director of Yale PET Center*

Yu-Shin Ding, PhD, *Professor of Diagnostic Radiology, Director of Radiochemistry, Co-director of Yale PET Center*

Henry Huang, PhD, *Associate Professor of Diagnostic Radiology, Co-director of Radiochemistry*

David Labaree, PhD, *Associate Research Scientist, Department of Diagnostic Radiology*

Nabeel Nabulsi, PhD, *Associate Research Scientist, Department of Diagnostic Radiology*

James Ropchan, PhD, *Lead Production Radiochemist, Associate Research Scientist, Department of Diagnostic Radiology*

Facilities & Equipment

The Yale University PET Center is a state-of-the-art molecular imaging facility. Resources include a GE PETtrace cyclotron, with targetry for producing positron-emitting isotopes such as C-11, F-18, N-13 and 0-15; a radiochemistry laboratory with modules for the production of a wide variety of radiotracers; a CTI HR+ whole body scanner; and a Siemens HRRT scanner for imaging the brain and small animals. The Center also has a fully equipped laboratory for blood and metabolite analyses and an image analysis laboratory for investigators, with several workstations running image analysis software applications. Details for each of these resources follow:

Radiotracer Chemistry Laboratories
The Radiotracer Laboratory Complex at the PET Center, Yale University School of Medicine, is fully equipped for radiotracer synthesis with 4 mini hot cells, 4 full size hot cells, and automated or remote synthesis devices for preparation of radiotracers labeled with C-11, F-18, N-13 and O-15. There is a water target (H216O) for the production of N-13 ammonia and a water target (H218O) for the production of [18F] fluoride, as well as nitrogen gas targets for the production of carbon-11 and oxygen-15, and an automated system for the production of [11C]cyanide. The lab is also equipped with several automated synthesis modules from GE Medical Systems, including Microlab for the production of [11C]methyl iodide, two FXc-Pro methylation boxes for synthesis of various C-11 tracers, an FDG synthesis machine and two F-18 synthesis modules (nucleophilic substitution box and electrophilic substitution box). Another automated synthesis module for C-11 labeling is

the Bioscan Autoloop. A semi-automated module for carrying out multi-step synthesis has also been set up. The Radiotracer Laboratory has TLC scanners, HPLCs with UV, radioactivity detectors, LC/MS, and counting equipment (ion chambers, pin diode detectors and well counters). There are also facilities for the preparation of sterile radiopharmaceuticals, including pyrogen burning ovens and laminar flow hoods, and for LAL testing of pyrogens, which is performed in-house. Cold chemistry laboratories in the LMP building are equipped for the purpose of developing new synthetic strategies for C-11 and F-18 labeled radiotracers and to synthesize the unlabeled precursors required for radiotracer development and production.

Cyclotron
The PET Center has a new GE PETtrace cyclotron for radioisotope production, with 19 MeV protons and 10 MeV deuterons for production of [11C]cyanide and [11C]methyl iodide (GE Medical Systems unit). This cyclotron has a total of six targets. In addition to the two C-11 targets, it also has a target to produce O-15, a water target (H216O) for the production of N-13 ammonia, a water target (H218O) for the production of [18F]fluoride, and a gas target for the production of [18F]F2.

PET Imaging Suites
The PET Imaging suites have one whole body PET scanner (Siemens HR+ with 32 rings and 63 planes with a resolution of ~ 5 x 5 x 5 mm at center of field of view) and one dedicated brain scanner (Siemens HRRT, 104 rings, 207 slices with resolution of better than 3 x 3 x 3 mm). Adjacent to each scanner room are patient prep and post-scan rooms. The HR+ has a SUN workstation dedicated to image acquisition, reconstruction, and archiving. The HRRT acquires its list-mode data on a high-end PC with 1 TB of disk. The list-mode data files are transferred over the local Gigabit network (behind a hardware firewall) to a dedicated Linux cluster with 58 nodes and 136 processors (3.0-3.2 MHz) and ~ 17.5 TB of disk storage. Images are reconstructed with the MOLAR algorithm (Motion-compensation OSEM List-mode Algorithm for Resolution-recovery Reconstruction). Subject motion information is collected with a Vicra (NDI, Canada), which records head motion at a rate of up to 20 Hz. These are stored in a time-synced file and used by MOLAR to correct head motion.

Computer Facilities
For both the HR+ and HRRT, final images are converted to DICOM format and saved on the 17.5 TB disk farm. The disk farm is backed up to tape nightly. Image processing is performed on one of 4 Linux (Redhat WS4) workstations housed in a data processing room connected to the network with NFS mounts to the 17.5 TB disk array. These systems may be used at their consoles or over the network via X windows. Image data are accessed via the HAVEN image database using scripts and programs employing the commercial programs IDL and MEDx. All data are identified with a code created at the time of the subject's first PET scan. Patient identification can

only be obtained from password restricted access to the HAVEN database. Programs and scripts developed for image processing include PET-MR image registration, region-of-interest placement (on PET or MR), time-activity curve creation, input function creation (see Metabolite lab, below), mathematical modeling routines to create parametric images of flow, metabolism, binding potential, etc. and partial volume correction.

Blood/Metabolite Analysis Lab
An analytical laboratory is adjacent to the PET Imaging suites, with pass-through doors to allow direct passing of samples. This lab includes two Perkin Elmer Wizard gamma counters, scales, centrifuges, blood glucose analyzer and HPLC equipment to analyze plasma samples for unchanged radiotracer, enabling generation of input functions required for kinetic analysis and image quantization. As appropriate, all devices are connected to the network (some via a terminal server) to allow direct reading of the data by IDL programs on the Linux machines.

Hot Lab
Adjacent to the scanner suites is a hot lab for dose preparation and assay. The Capintec CRC-15PET is connected to a terminal server to allow web-based reading of activity in the syringe. These measurements are automatically stored in the HAVEN database and can be displayed in real time via web browsers throughout the facility, with the current activity calculated using the appropriate decay constant.

Office Space
The Yale University PET Center research facility is located at 801 Howard Avenue. Offices for the scientific and professional staff are located in the PET Center and in a newly renovated section of the Laboratory for Medicine and Pediatrics (LMP) at 15 York Street. Construction is underway for an additional research section that will also be housed in the LMP building.

PET Imaging

Section Head: Richard E. Carson, PhD

Our research uses Positron Emission Tomography (PET) as a tool to measure a wide range of *in vivo* physiology in human beings and laboratory animals in a non-invasive manner. We focus on the development and applications of new tracer kinetic modeling methods and algorithms and on research in PET image reconstruction and image quantification. A primary focus of our more biological applications is the measurement of dynamic changes in neurotransmitters.

Tracer Kinetic Modeling
Following administration of a positron-emitting radiopharmaceutical (tracer), PET permits the direct measurement of the four-dimensional radioactivity profile throughout a 3D object over time. Depending on the characteristics of

the tracer, physiological parameters can be estimated, such as blood flow, metabolism, and receptor concentration. These measurements can be made with subjects in different states (e.g., stimulus or drug activation), used to compare patient groups to controls, or to assess the efficacy of drug treatment.

The goal of PET tracer kinetic modeling is to devise a biologically validated, quantitatively reliable, and logistically practical method for use in human PET studies. Animal studies are typically performed to characterize the tracers, followed by initially complex human studies, typically leading to the development of simplified methods, e.g., using continuous tracer infusion. Mathematical methodology includes linear and non-linear differential equations, statistical estimation theory, methods to avoid the needs for arterial blood measurements (the input function) such as blind deconvolution, plus the development of novel rapid computational algorithms.

PET Physics and Reconstruction

Proper characterization of the PET image data is essential for modeling studies. This requires accurate and carefully characterized corrections for the physics and electronics of coincident event acquisition. Studies of these effects are performed with phantom measurements made on the scanner.

A critical component in the application to real data is the correction for subject motion, particularly as the resolution of modern machines has improved (better than 3-mm in human brain machines). Both hardware and software approaches are employed to address these issues. To produce accurate images with minimum noise, a statistically-based iterative reconstruction algorithm is necessary. Developments in this area include the mathematical aspects of algorithm development, the computer science issues associated with a large cluster-based algorithm, the incorporation of the physics and motion correction, the use of prior information provided from MR images, and the tuning and characterization necessary for practical application for biological studies. The ultimate goal is the combination of the tracer kinetic modeling and image reconstruction to directly process a 4D dataset into parametric images of the physiological parameters of interest.

Neurotransmitter Measurements with PET Tracers

PET neuroreceptor studies have focused on determining changes in receptor concentration as a function of disease or measurement of receptor occupancy by drugs. A more recent approach provides an estimate of changes in synaptic neurotransmitter concentration. This method determines the change in tracer binding levels after administration of behavioral or pharmacological stimuli that affect neurotransmitter levels. With careful experimental design and appropriate mathematical modeling techniques, the change in radiotracer binding can be attributed to changes in the level of synaptic neurotransmitter that competes with the radiotracer for receptor binding. Such changes have been successfully demonstrated in the dopaminergic, muscarinic, and serotonergic systems.

PET Radiochemistry

Section Head: Yu-Shin Ding, PhD

Our research concentrates primarily on the development of new methodologies to synthesize short half-lived radiopharmaceuticals and applying them towards investigation of biochemical transformations and drug mechanisms in primates and humans. We have focused on the investigation of the functional significance of various neurotransmitter systems, such as dopamine, norepinephrine, serotonin, acetylcholine, as well as oncology and cardiology studies. Our researchers have previously developed many unique radiotracers, many involving multi-step sequences; for example, the F-18 (t1/2: 110 min) labeled catecholamines. We devised and carried out the first synthesis of no-carrier-added (NCA) F-18 labeled electron-rich aromatic rings and applied this strategy to the synthesis of NCA F-18 labeled catecholamines, which enabled the first PET studies to be carried out without producing vascular effects. We also employed the deuterium isotope effect in mechanistic studies to understand the behavior of F-18 labeled catecholamines in living systems.

The research on catechol-O-methyltransferase (COMT) proposed in Dr. Ding's FIRST award and DOD breast cancer grant provides links between basic neuroscience and drug research, drug development and oncology. Our recent data that showed relatively higher COMT activities in tumor tissue, as compared to normal tissue from breast cancer patients, support the promise of future PET investigation of this disease.

We have successfully translated several radiotracers from pre-clinical studies in animals to clinical investigations in humans; for example, we developed C-11 labeled methylphenidate (Ritalin, a drug for the treatment of ADHD) and its active enantiomer, [11C]*d-threo*-methylphenidate, as ligands (t1/2 of 11C: 20 min) for the dopamine transporter. This development work allows the first studies of this drug in the human brain leading to a better understanding of the reinforcing abilities of psychostimulant drugs, and also has initiated investigations in drug abuse, alcoholism, obesity, Parkinson's disease and normal aging.

Our recent development of potent and selective radioligands to carry out PET imaging studies of nicotinic acetylcholine receptor (nAChR) and norepinephrine transporter (NET) systems in humans should provide an opportunity to better understand their roles in various CNS disorders, such as substance abuse, depression, ADHD, Parkinson's disease and Alzheimer's disease.

Publications

Yale Publications in PET Imaging

Neumeister A, Carson RE, Henry S, Planeta-Wilson B, Binneman B, Maguire RP, D'Souza C, Krystal JH, Frost JJ. Cerebral metabolic effects of intravenous glycine in healthy human subjects. J Clin PsychoPharm. 26:595-599, 2006.

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Rodriguez M, Barker WC, Thada S, Liow JS, Iano-Fletcher A, Johnson CA, Carson RE. Spatial resolution and noise characteristics of list-mode reconstruction for the HRRT. J Nucl Med. 47:182P, 2006.

Rodriguez M, Liow J-S, Thada S, Sibomana M, Chelikani S, Mulnix T, Johnson CA, Michel C, Barker WC, Carson RE. Count-rate dependent component-based normalization for the HRRT. IEEE Trans Nucl Sci. 54:486-495, 2007.