YALE UNIVERSITY PET INVESTIGATORS GUIDE
July, 2022

Information for Grant Applications

Budget Justification for PET Scan Costs

The Yale PET Center is an internal service provider and rates are set following the NIH guidelines.

For studies with radiosynthesis and PET scans: The full PET study cost includes chemistry personnel, PET technologists, computer support personnel, equipment maintenance contracts (cyclotron, chemistry modules, gas chromatographs, HPLCs, PET scanners, computer cluster, etc.), chemistry supplies (including precursors), sterility and pyrogen tests, PET transmission and/or CT scans, supplies for PET scans such as IV solutions and catheters, daily PET scanner quality control, image reconstruction on a dedicated computer cluster, storage and backup of reconstructed PET data, and processing for fully automated production of binding potential images. Costs for maintaining and overseeing the cGMP compliant PET radiochemistry lab (including pyrogen testing and sterility testing for each production run, weekly viable particulate and monthly total particulate monitoring, annual or bi-annual calibration and certification of all the equipment that is involved in production for human studies) are also included. These include costs for yearly equipment calibrations (HPLCs, gas chromatographs, chemistry modules, hot cell air quality, sterile hoods, pH meters, etc.) that are performed by outside independent firms.

For studies with Arterial line/Metabolites: In this study, arterial blood sampling will be performed with metabolite analysis. The additional charge covers the physician fee for placement of the arterial line, nurse oversight of the line for the duration of the study, additional supplies needed for continuous and discrete arterial blood sampling and laboratory staff and supplies for HPLC and gamma counter analyses as well as data processing.

For studies with PET scans only: The basic PET study cost includes PET technologists, computer support personnel, equipment maintenance contracts (computer cluster, etc.), PET transmission and/or CT scans, supplies for PET scans such as IV solutions and catheters, daily PET scanner quality control, image reconstruction on a dedicated computer cluster, storage and backup of reconstructed PET data, and processing for fully automated production of physiological images.

Clinical Services: A physician and/or nurse is available to handle any urgent medical issues that may arise while a subject is at the Yale University PET Center. For an additional fee, the PET Center offers physician services such as supervision of pharmacologic studies, physical examinations, medical clearance, as well as Physician or Research Assistant services for subject screenings.

The Yale PET Center Resources

The state-of-the-art 16,000 sq. ft. research PET Center was opened at Yale University in July 2005. The PET Center has a GE PETtrace cyclotron, with targetry for producing C-11, F-18, N-13, and O-15 radioisotopes. Chemistry modules are available for the production of a wide variety of radiotracers. The Center has 7 scanners, 3 for clinical imaging (HRRT, mCT-X PET/CT, and Vision PET/CT) and 4 for small animal imaging (3 Focus-220, Inveon PET/CT). Two laboratories for blood and metabolite analyses are available. The Center also has an image analysis laboratory for investigators, with several workstations running image analysis software applications. To date, over 14,000 administrations of PET radiopharmaceuticals as part of quantitative *in vivo* PET studies have been performed with over 150 different radiopharmaceuticals, 62 of which have been used in human studies.

The details for each component of the resources related to this proposal are listed below.

Laboratories:

The laboratory resources within the Yale University PET Center consist of four laboratories: 1. PET radiochemistry laboratory; 2. PET radioligand quality control (QC) laboratory; 3. organic chemistry laboratory; 4. blood and metabolite analysis laboratory.

1. PET radiochemistry laboratory: The radiochemistry laboratory complex at the PET Center, Yale University School of Medicine, is fully equipped for radiotracer synthesis with 6 mini hot cells, 6 full size hot cells from Comecer and a process chemistry cabinet (ProCab) from GE. The ProCab is fitted with several chemistry process modules, including a [^{11}C]CO_2 purification module capable of purifying and delivering [^{11}C]CO_2 at a controlled flow rate for various chemistry applications, a [^{11}C]CO module for conversion of [^{11}C]CO_2 to [^{11}C]CO, a [^{11}C]cyanide module for conversion of [^{11}C]CO_2 to [^{11}C]HCN. Remote-controlled or automated synthesis modules from GE are installed in the various hot cells for either dedicated or diversified synthetic processes. These automated modules include one MicroLab [^{11}C]methyl iodide synthetic device, one FxC module and one FxC-pro module for [^{11}C]methyl iodide and [^{11}C]methyl triflate production, methylation, purification and final product formulation, one FxN module and one FxNpro module for production of F-18 labeled compounds through nucleophilic reaction, one FxE module for making F-18 labeled ligands using electrophilic chemistry, one MX module for FDG production, and two other modules for dedicated production of [^{15}O]water and [^{13}N]ammonia. In addition, there is also one Bioscan AutoLoop for performing loop-based chemistry in the production of C-11 and Advion's microfluidic module for F-18 labeled compounds. Various home-made modules can also be used for the productions of labeled compounds using [^{11}C]CO_2, [^{11}C]CO and [^{11}C]HCN. A total of ten preparative HPLC systems complete the capability to produce and purify radiolabeled ligands. A total of 6 Capintec dose calibrators are installed in the full-size hot cells and on the bench for measurement of radioactivity. A microwave oven from Resonance Instrument can be used in radiolabeling with [^{18}F]fluoride. Various other equipment/instruments includes a drying oven, a glove box for preparation of moisture-free and oxygen-free reagents and solutions, refrigerators/freezers for sample storage, pH meters, vacuum pumps, vortex, sonicators, filtration equipment, water purification system, and others.

2. Quality control laboratory:

The quality control laboratory, located in a room separated from the main radiochemistry laboratory, is equipped with four Shimadzu analytical HPLC systems including four HPLC pumps, two autosamplers, one photodiode array (PDA) detector, three dual channel UV detectors, four radioactivity detectors and computers running the Class VP HPLC control/data acquisition software. There are one Shimadzu model 2014 gas chromatography (GC) system for residual solvent analysis

that includes autosampler and dual injectors and one Bioscan AR-2000 TLC scanner. In addition, a Varian LC/MS system is in place for quality control and analysis of product and byproducts. A laminar flow hood provides the capability for performing sterile preparations and compounding of radiopharmaceuticals. Also located in this lab are one dose calibrator for measuring radioactivity and equipment for pyrogen testing of radiopharmaceuticals.

3. Organic chemistry laboratory:

Two rooms with a total of 1500 square feet of space in the Laboratory Medicine and Pediatrics (LMP) building are dedicated to organic chemistry and 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. There are a total of six fume hoods for performing chemical reactions. Major instruments include two HPLC systems for analysis of precursors and other synthetic compounds, refrigerators for reagents and samples storage, vacuum pumps, drying ovens, rotary evaporators, melting point apparatus, and others.

4. Blood and metabolite analysis laboratory:

Two laboratories for plasma analysis are adjacent to the PET Imaging suites, with pass-through doors to allow direct passing of samples. These labs include four Perkin Elmer Wizard gamma counters, two balances, four centrifuges, and one blood glucose analyzer. Three HPLC systems are dedicated to the analysis of plasma samples for unchanged radiotracer and radioactive metabolites, enabling generation of input functions required for kinetic analysis and image quantification. Each HPLC system consists of two Shimadzu pumps capable of delivering gradient mobile phase, one control module, one Rheodyne manual injector equipped with a 5 mL sample loop, one Shimadzu variable wavelength UV-vis detector, one Raytest radioactivity detector, and one fraction collector. HPLC system control was provided by the Shimadzu Class-VP software.

As appropriate, devices are connected to the internal computer network (some via a terminal server) to allow direct reading of the data by IDL programs on the Linux machines.

Animal:

Adjacent to the PET facility are three animal housing rooms, with two rooms dedicated to rhesus and cynomolgus monkeys (1350 ft^2), and one to rodents (115 ft^2). There are three dedicated animal procedure rooms. These rooms are used for procedures (intubation, placement of intravenous and intra-arterial lines, PK sampling, port maintenance), and animal training and testing. There is also a fourth swing procedure room space (134 ft^2) that can be converted to animal housing, if needed. There is also a dedicated animal environmental enrichment room. Animal studies share clinical research resources including access to the PET scanners, use of all clinical radiotracers and technical support for input function measurement, protein binding assays, and metabolite assays. In addition, many experimental radiotracers are synthesized exclusively for animal studies.

Three dedicated PET animal imaging areas are adjacent to the PET Center and to our current animal housing area. Three Focus 220 PET scanners can be found in 2 rooms, and a third scanner room contains the Inveon rodent PET/CT scanner. These rooms are adjacent to a hot lab for dose dispensing and blood sample analysis.

Computer:

PET images are converted to DICOM format and saved on a 250 TB disk farm. The disk farm is backed up to tape nightly. Image processing is performed on one of 8 Linux (Redhat WS4) workstations housed in a data processing room connected to the network with NFS mounts to the

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. Human subject 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, above), mathematical modeling routines to create parametric images of flow, metabolism, binding potential, etc. and partial volume correction.

Office:

The scientific and professional staff has offices in the Laboratory for Medicine and Pediatrics (LMP) and in the PET Center.

Others:

Various equipment/instrument in the MR Center and Chemistry Department of Yale University are open to the PET Center personnel. These include the NMR facilities, GC-MS instrument, and other analytical equipment.

Major equipment:

Cyclotron: A GE PETtrace cyclotron for radioisotope production is located in the lower level of the PET Center. The cyclotron uses 16.5 MeV protons and 8.4 MeV deuterons to produce radioisotopes. A total of six targets are mounted in the cyclotron: two C-11 targets, two F-18 targets for production of [^{18}F]fluoride and [^{18}F]fluorine, one O-15 target, and one N-13 target.

PET Scanners: The Yale PET Center has two whole body PET/CT scanners: Siemens Vision with 3 4 mm spatial resolution and ~200 ps timing resolution, as well as simultaneous dual-energy CT capability, and Siemens mCT-X, with 109 PET slices with resolution of ~ 5x5x5 mm resolution, 128-slice CT). In addition, there is one brain-dedicated scanner (Siemens High Resolution Research Tomograph (HRRT), 104 rings, 207 slices with resolution of better than 3 x 3 x 3 mm), three small animal PET scanners (Siemens Focus 220, 48 rings, 95 slices with a resolution of ~ 1.4 x 1.4 x 1.4 mm at center field of view), and one small animal PET/CT (Siemens Inveon, 159 slices, with 0.8 mm slice separation, axial coverage of 127 mm, transaxial field-of-view of 100 mm, resolution < 1.5 mm, peak sensitivity > 9%).). Adjacent to each human scanner room are patient prep rooms. All PET systems acquire list-mode data ad reconstructed on each scanner's reconstruction system. In addition, list-mode data files are transferred over the local Gigabit network (behind a hardware firewall) to a dedicated Linux cluster with 40 nodes and 352 processors (3.0-3.2 MHz). Images are reconstructed with the MOLAR algorithm (Motion-compensation OSEM List-mode Algorithm for Resolution-recovery Reconstruction). For brain studies, 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. Continuous bed motion is available on the mCT and the Vision. Respiratory and cardiac gating are available on the Vision, mCT and Inveon.