Positron Emission Tomography (PET) Facility

The PET Facility at the University of Pittsburgh has been operational since 1992, and is administered as a research division of the Department of Radiology under the direction of N. Scott Mason, Ph.D. The PET Facility is housed in over 12,000 square feet of the ninth floor of the B-wing in Presbyterian-University Hospital, University of Pittsburgh Medical Center (UPMC) Health System. The PET Facility houses a dedicated Siemens Eclipse HP medical cyclotron and three research scanners: a Siemens ECAT EXACT HR+ PET scanner, a Siemens Biograph mCT Flow PET/CT scanner, and a Siemens Biograph mMR PET/MR scanner. These assets are used exclusively to support investigational imaging research studies within the University of Pittsburgh. The entire floor space of the ninth floor, B-wing is dedicated to the PET Facility. This space includes three 500 sq. ft. patient scanning rooms, two scanner control rooms, and inpatient and outpatient preparation rooms. The space also includes a 300 sq. ft. small animal surgery/radiometabolite analysis laboratory. Research investigators and PET Facility staff utilize a 450 sq. ft. data and image processing laboratory. Offices for the PET Facility director, physicists, chemists, computer programmers, research faculty, residents and post-doctoral fellows, nurses, and nuclear medicine technologists are contained within the facility. In addition, there is a small 200 sq. ft. electrical and machine shop. Presently, the PET Facility comprises a dedicated full-time research staff of approximately 30 FTE, including nine full-time Radiology faculty members, four radiochemistry staff, five data analysts, a systems administrators, a data manager, three nuclear medicine technologists, and administrative staff. Located on the University of Pittsburgh Main Campus, the PET Facility benefits from its central location to the major clinical and research activities of the institution. The PET Facility maintains an array of dedicated research scanners and equipment.

Radiochemistry Facilities: The PET Radiochemistry Laboratory produces radionuclides for PET imaging using a dedicated Siemens Eclipse HP medical cyclotron. The Eclipse HP is a negative-ion cyclotron capable of producing a beam of 11 MeV protons, which is designed for the production of positron-emitting radionuclides such as carbon-11 (as $[^{11}C]CO_2$), fluorine-18 (as $[^{18}F]$fluoride and $[^{18}F]$fluorine), nitrogen-13 (as $[^{13}N]$ammonia), and oxygen-15 (as $[^{15}O]$oxygen). The Eclipse HP deep-valley magnet design provides improved beam transmission, reduced levels of internal activation, and higher production yields. A key advantage of the Eclipse HP configuration is the use of a 4-position target carousel as well as the inclusion of a second extraction port equipped with a second 4-position target carousel, which increases the maximum number of mounted targets to a total of eight. The PET Facility's Eclipse HP configuration presently includes seven targets: two $[^{18}F]$fluoride targets, two $[^{11}C]CO_2$ targets, one $[^{18}F]F_2$ target, one $[^{13}N]NH_3$ target, and one $[^{15}O]$oxygen target. One of the eight target positions is free for future expansion in accordance with need.. Increased yields from the $[^{18}F]$fluoride and $[^{11}C]CO_2$ targets (as well as the ability to irradiate two $[^{11}C]CO_2$ targets simultaneously) allows for shorter irradiation cycles and quicker turnaround in production capabilities, which in concert with new automated radiosynthesis equipment has significantly increased the radiopharmaceutical production capacity of PET Facility both in volume and scope. Equipment for the remote synthesis of carbon-11 and fluorine-18 labeled radiopharmaceuticals includes a G.E. Healthcare TRACERLab™ FX MeI gas-phase $[^{11}C]$methyl-iodide system, two TRACERLab™ FX M carbon-11 incorporation platforms, and a FASTlab™ fluorine-18 incorporation platform. The radiochemistry laboratory is equipped with three full-size Capintec-brand hot cells (each fitted remote manipulators) for operator-assisted radiopharmaceutical productions. In addition, there are two large stacked Capintec mini-cells and four smaller Capintec mini-caves for routine automated productions, three radioisotope fume hoods, five organic synthesis fume hoods, three laminar flow hoods, fifteen radio-HPLC systems (including gradient pumps, variable wavelength UV detectors, four photodiode array detectors, a refractive index detector, an electrochemical detector, and about

20 radioactivity detectors), and miscellaneous analytical equipment including a radio-TLC scanner, radio-GC, Varian Saturn GC-MS, two gamma well counters (Packard Cobra model 5003), a liquid scintillation counter, GE Typhoon FLA-7000 phosphor imager, FTIR, and UV/vis spectrometers. Additional analytical equipment and services (e.g., 300 and 500 MHz NMR's, high and low-resolution mass spectrometers, and glass, electrical, and machine shops) are available to PET Facility chemists in the University of Pittsburgh Chemistry Department on an hourly recharge basis.

The PET Facility radiochemistry laboratory routinely performs high-specific activity ^{11}C radiosynthetic work utilizing [^{11}C]methyl iodide, [^{11}C]methyl triflate and [^{11}C]carbon dioxide. We also routinely utilize nucleophilic [^{18}F]fluoride methodologies for radiochemistry projects. In addition, we have a dedicated radioiodination hood suitable for [^{125}I] and [^{123}I] work and shielded space for [^{99m}Tc], [^{68}Ga] and [^{64}Cu] radiochemistry projects. The facility has four high sensitivity radio-HPLC analytical HPLC systems dedicated to radiometabolite analysis work. In addition, we are able to perform radiometabolite analyses utilizing a variety of other methods including, solid-phase extraction techniques, aqueous/organic extraction methods, and thin-layer chromatography techniques.

An array of 30 different investigational radiopharmaceuticals are approved for human use at the University of Pittsburgh PET Facility:

Agent (target):

[^{15}O]H_2O	(perfusion)
[^{15}O]O_2	(oxygen metabolism)
[^{13}N]Ammonia	(Myocardial blood flow)
[^{18}F]FMISO	(hypoxia)
[^{11}C]3-O-methylglucose	(glucose transport)
[^{11}C]PMP	(acetylcholinesterase substrate)
[^{18}F]FLT	(thymidine kinase substrate)
[^{18}F]ML10	(apoptosis)
[^{11}C]flumazenil	(central benzodiazepine receptor)
[^{11}C]PK-11195	(TSPO, aka peripheral benzodiazepine receptor)
[^{11}C]PBR-28	(TSPO, aka peripheral benzodiazepine receptor)
[^{11}C]DASB	(serotonin transporter)
[*carbonyl*-^{11}C]WAY100635	(serotonin 5-HT1A receptor)
[^{11}C]CUMI-101	(serotonin 5-HT1A receptor agonist)
[^{18}F]altanserin	(serotonin 5-HT2A receptor)
[^{11}C]DTBZ	(VMAT2 vesicular monoamine transporter)
[^{18}F]FDOPA	(AADC substrate)
[^{11}C]CFT	(dopamine transporter)
[^{11}C]FLB457	(dopamine D2/D3 receptor)
[^{11}C]raclopride	(dopamine D2/D3 receptor)
[^{11}C]fallypride	(dopamine D2/D3 receptor)
[^{11}C]NPA	(dopamine D2 receptor agonist)
[^{11}C]ABP 688	(metabotropic glutamate receptor subtype 5)
[^{11}C]NOP-1A	(nociceptin/orphanin FQ peptide receptor)
[^{11}C]PIB	(beta-amyloid)
[^{18}F]flutemetamol	(beta-amyloid)
[^{18}F]AV1451	(tau)
[18F]MK 6240	(tau)
[^{11}C]UCB-J	(SV2A)
[^{11}C]IMA107	(PDE10A)

[^{68}Ga]PRGD2 (integrin $\alpha V\beta 3$)
[^{18}F]SMBT-1 (MAO-B)

In addition, the PET Facility has synthesized over 300 radiolabeled compounds for non-clinical imaging studies in animals.

Computing Resources: The PET Facility operates an extensive state-of-the-art data processing network that supports over 60 active PET imaging research protocols, many of which are dynamic quantitative imaging protocols. The computational power for the research network is supplied by multiple server resources. The central servers are a Linux server Mercury RM224 with 2xE5-2660 14-Core processors and 256 GB RAM, 2 Mercury RM212 with two Gold 5218 2.30 16-core processors and 512 GB RAM. Disk storage includes over 1 petabyte of RAID 5 storage housed in 3 disk arrays, including Overland Neo-80XL for data archiving on LTO-6 media. The PET Facility also maintains a network of over 50 Macintosh and Windows computers, including a Mac OS file-server, Windows 2019 Server, tape backup system, two color laser printers. All computers are directly linked to the internet through a local twisted pair ethernet network. Systems are interfaced to a high-speed (1GB/sec) local area network for data transfer to workstations and for analysis and linkage to the MR Research Center (MRRC) located on an adjacent floor.

A joint computing resource allows for efficient and state-of-the-art data storage, archiving, and retrieval for both the PET Facility and MRRC, and this is being extended to other research imaging groups in Radiology. Data archiving is performed in an automated manner using an Overland NEO 8000 Enterprise Tape Library. The resource also includes an eight node linux CPU cluster providing 16 Intel Xeon E5-2667 2.90GHz Six-Core Processors, 2 TB DDR3-1600 Reg ECC Memory and operating on 6Gb/s Interface Solid State Drives. Another resource is a linux GPU cluster with four Nvidia M2090 GPUs, two Intel Xeon E5-2667 2.90GHz Six-Core Processors, 256GB DDR3-1600 Reg ECC Memory and operating on 6 GB/s Interface Solid State Drives. The MRRC also utilizes a Linux cluster with four 2.0GHz dual-core Opterons. The Linux servers provide over 200TB of online data storage. Members of this resource include PET and MR data analysts who work with imaging faculty and staff, research investigators (scientists, Program/Center grant cores). In addition to established investigators, this resource also supports new and junior investigators, and pilot investigations.

PET Data Analysis Resources: The PET Methods and Data Analysis Group, led by Prof. Brian Lopresti, includes three Radiology faculty (Profs. Lopresti, Laymon, and Minhas), 5 full-time staff data analysts, a biostatistician, a data manager, an IT systems administrator, an informatics specialist, and undergraduate students. The PET Methods and Data Analysis Group provides broad support for all PET Facility imaging projects, including manual and automated region of interest determination, inter- and cross-modality image registration, tracer kinetic modeling, parametric image generation, reference-tissue analyses, statistical image analyses, partial volume correction, motion correction, Centiloid scaling, MR volumetrics and cortical thickness determinations, and radiotracer input function determination. Novel image analysis methods are also conceived, developed, validated, published, and disseminated by this group. Preclinical evaluation of radiotracers under development by the PET radiochemistry group is also supported in species ranging from mouse to baboon. PET data analysis activities are supported by the PET Facility's vast computing resources as well as specialized image analysis software that includes 10 PMOD v 4.1 software licenses (PMOD technologies, Zurich, Switzerland) configured with PBAS, PFUS, PKIN, PXMOD, and PNEURO modules. Other commercial and validated public domain software available to the Methods and Data Analysis Group includes FreeSurfer, Matlab, R, SPSS, SAS, SPM, FSL, AFNI, and DTI Studio. Data analysis products, which include raw and processed PET and MR images, intermediate files, input functions, image outcomes, are stored on PET Facility servers and custom-configured relational databases. XNAT, an extensible open-

source imaging informatics platform developed by the Neuroinformatics Research Group (NRG) at Washington University, St. Louis, is supported by the PET Methods and Data Analysis Group, which is currently transitioning all data management activities and some analysis workflows to this platform. The informatics specialist focuses on data tracking, database development, archiving of analysis results, and data quality control reviews, consistent with policies concerning the protection of patient information.

Major Equipment

To support investigational research studies, the PET Facility maintains a dedicated Siemens Eclipse HP medical cyclotron and three human research scanners: a Siemens ECAT EXACT HR+ PET scanner; a Siemens Biograph mCT Flow PET/CT scanner; and a Siemens Biograph mMR PET/MR scanner. Detailed descriptions of these assets are provided below.

Siemens Eclipse HP Cyclotron: The PET Radiochemistry Laboratory produces radionuclides for PET imaging using a dedicated Siemens Eclipse HP medical cyclotron. The Eclipse HP is a negative-ion cyclotron capable of producing a beam of 11 MeV protons, which is designed for the production of positron-emitting radionuclides such as carbon-11 (as $[^{11}C]CO_2$), fluorine-18 (as $[^{18}F]$fluoride and $[^{18}F]$fluorine), nitrogen-13 (as $[^{13}N]$ammonia), and oxygen-15 (as $[^{15}O]$oxygen). The Eclipse HP deep-valley magnet design provides improved beam transmission, reduced levels of internal activation, and higher production yields. A key advantage of the Eclipse HP configuration is the use of a 4-position target carousel as well as the inclusion of a second extraction port equipped with a second 4-position target carousel, which increases the maximum number of mounted targets to a total of eight. The PET Facility's Eclipse HP configuration presently includes seven targets: two $[^{18}F]$fluoride targets, two $[^{11}C]CO_2$ targets, one $[^{18}F]F_2$ target, one $[^{13}N]NH_3$ target, and one $[^{15}O]$oxygen target. One of the eight target positions is free for future expansion in accordance with need.. Increased yields from the $[^{18}F]$fluoride and $[^{11}C]CO_2$ targets (as well as the ability to irradiate two $[^{11}C]CO_2$ targets simultaneously) allows for shorter irradiation cycles and quicker turnaround in production capabilities.

Siemens ECAT EXACT HR+ PET Scanner: The Siemens ECAT EXACT HR+ scanner PET tomograph is also supported by the PET Facility, which primarily supports ongoing longitudinal studies in aging and dementia. The HR+ scanner is capable of acquiring 63 parallel slices over a 15.2 cm axial field-of-view (FOV). The maximum intrinsic resolution of the HR+ scanner is approximately 4.5 mm FWHM. Additionally, the HR+ scanner features retractable septa, enabling data to be acquired in either 2D or fully-3D modes. Operational in 1995, the HR+ scanner is now considered legacy equipment with limited vendor support. The HR+ system will continue to be supported through 2023 in order to complete data collection as part of serial imaging studies spanning several years, after which time the scanner will be retired.

Siemens Biograph mCT Flow™ PET/CT Scanner: A Siemens Biograph mCT Flow™ TrueV PET/CT scanner (Siemens Medical Solutions USA, Malvern, PA) installed in the University of Pittsburgh PET Facility in 1Q 2015. The installed Biograph mCT configuration has a 78 cm patient bore and is comprised of a 64-slice helical CT scanner (SOMATOM definition AS 64) and four rings of lutetium oxyorthosilicate (LSO) Hi-REZ PET detector blocks (48 blocks/ring, 4.0 x 4.0 x 20 mm crystal size; 13 x 13 crystals per block). This PET detector configuration acquires 109 transverse image planes (2.027 mm) over a 22.1 cm axial field-of-view with a maximum intrinsic spatial resolution (NEMA NU-2, 2007) of 4.1 mm FWHM (transverse) x 4.7 mm FWHM (axial). The PET subsystem supports incorporation of time-of-flight (TOF) measurement into the reconstruction to yield improvements in randoms corrections and overall image signal-to-noise. The CT subsystem can be operated in diagnostic mode, either alone or in concert with the PET data acquisition, and is equipped with CARE dose reduction technology, gating capabilities, and supports continuous bed motion acquisition. A low-dose mode is supported whereby a non-diagnostic CT scan is acquired to provide scatter and attenuation correction of PET emission data. The effective dose from the low-dose CT scan of the head is < 16 mrem, which is

comparable to the dose a subject receives from transmission imaging with $^{68}Ga/^{68}Ge$ rod sources. PET emission data can be reconstructed using analytic and/or iterative reconstruction algorithms on grid sizes ranging from 128 x 128 up to 400 x 400 voxels.

Siemens Biograph mMR PET/MR scanner: A Siemens Biograph mMR PET/MR scanner is operated by the University of Pittsburgh Department of Radiology, jointly operated by the University of Pittsburgh PET Facility and the Magnetic Resonance Research Center (MRRC), where the system is sited. The mMR allows simultaneous acquisition of whole-body MR and PET images. The mMR scanner design incorporates low-attenuation materials into the MRI coils to minimize attenuation of the PET 511 keV annihilation photons, resulting in outstanding 3T MRI performance and a high-resolution PET scan. The mMR utilizes a 3T niobium–titanium magnet (length: 163 cm; bore: 60 cm), an actively shielded whole-body gradient coil (length: 159 cm; amplitude: 45 mT/m; slew rate: 200 T/m/s), and a radiofrequency body coil (peak power: 35 kW; transmitter bandwidth: 800 kHz). The MR system can acquire a 0.5–50 cm FOV, with a 2D slice thickness of 0.1 - 200 mm, 3D slab thickness from 5 - 500 mm, maximum matrix size of 1,024 elements, and maximum resolution of 9 mm. A PET detector assembly exists between the gradient and radiofrequency coils: 8 rings of 56 detector blocks, 8x8 LSO crystals (4x4x20 mm) per block, coupled to an array of 3x3 APDs for a total of 4,032 channels. The PET system (127 planes; transaxial FOV: 59.4 cm; axial FOV: 25.8 cm) can acquire static multibed and list-mode data in 3D mode.
The mMR system is equipped with a full range of RF coils including head and neck coils, body and spine arrays and a specialty knee coil. The system is equipped with an fMRI paradigm presentation system for functional studies including E-Prime for stimulus presentation, an Avotec MR compatible video projector, Celeritas response gloves, an Avotec eye tracking system and an Avotec audio system with low profile headphones. The system can perform 1H spectroscopy but is not currently capable of multinuclear MR spectroscopy.

Other major equipment sited in the PET Facility that are used for the production of PET radiopharmaceuticals and PET imaging studies include:

- Three full-size Capintec-brand hot cells, each fitted with remote manipulators
- Two large stacked Capintec mini-cells
- Four smaller Capintec mini-caves for routine automated productions
- G.E. Healthcare TRACERLab FX MeI gas-phase [^{11}C]methyl-iodide system
- G.E. Healthcare TRACERLab FX M carbon-11 incorporation platforms (2)
- G.E. Healthcare FASTlab fluorine-18 incorporation platform
- Three radioisotope fume hoods
- Five organic synthesis fume hoods
- Two laminar flow hoods
- Twelve radio-HPLC systems (including gradient pumps, variable wavelength UV detectors, two photodiode array detectors, a refractive index detector, an electrochemical detector, and about 20 radioactivity detectors)
- Radio-TLC scanner, radio-GC, Varian Saturn GC-MS
- Two gamma well counters (Packard Cobra model 5003)
- Liquid scintillation counter
- GE Typhoon 7000 phosphor imager
- FTIR and UV/vis spectrometers