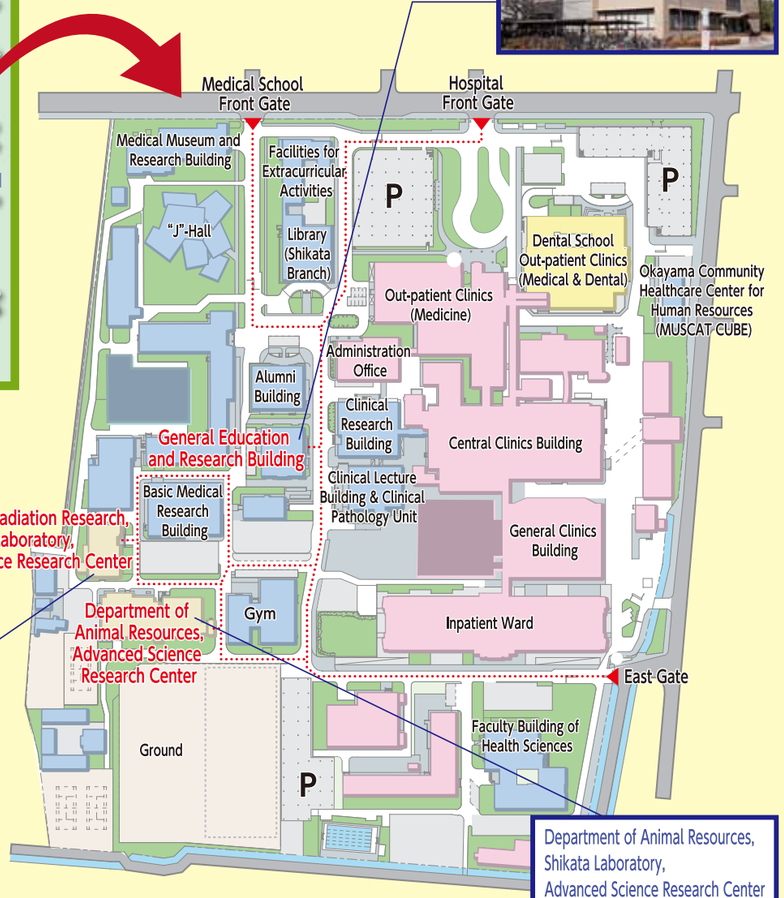
OKAYAMA MEDICAL
INNOVATION CENTER

General Education
and Research Building
1F: Administration for OMIC,
2F: Incubation Facilities

Okayama University Shikata (Medical) Campus



Department of Radiation Research,
Shikata Laboratory,
Advanced Science Research Center
(B1F, 3F, and 5F)

Department of Animal Resources,
Shikata Laboratory,
Advanced Science Research Center

Contact

Collaborative Research Center for OMIC,
Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences

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The MEXT Project for Creation of Research Platforms and Sharing of Advanced Research Infrastructure

The Promotion Project for Collaborative Joint Usage at OMIC Research Facilities for Molecular Imaging Research

OKAYAMA MEDICAL
INNOVATION CENTER

OMIC

Okayama Medical Innovation Center

Providing support for molecular imaging research needs with fully-equipped facilities and supporting systems

- Uncharged non-proprietary usage
- Charged non-proprietary usage
- Charged proprietary usage

Collaborative Research Center for OMIC,
Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences

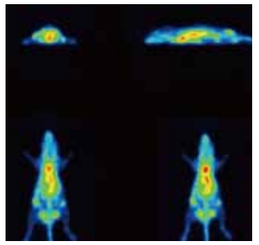
Project for Creation of Research Platforms and Sharing of Advanced Research Infrastructure

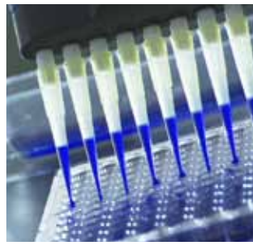
The Project for Creation of Research Platforms and Sharing of Advanced Research Infrastructure promotes the joint usage of advanced research facilities and equipment possessed by universities and independent research institutes for industry, academia, and government organizations. Moreover, establishing the network among related facilities and enhancing the quality of this advanced infrastructure will create research platforms capable of effectively meeting a variety of users' research requirements. As such, the project aims to contribute to "Achieving vital issues through technological innovation," "Strengthening the industrial competitiveness of Japanese corporations," and "Improved return on R&D investment."

Please visit the following Website for details on the MEXT Project for Creation of Research Platforms and Sharing of Advanced Research Infrastructure.

Research Infrastructure Sharing Universal Navigation Site

"Kyoyo Navi" Search http://kyoyonavi.mext.go.jp/





Okayama Medical Innovation Center (OMIC)

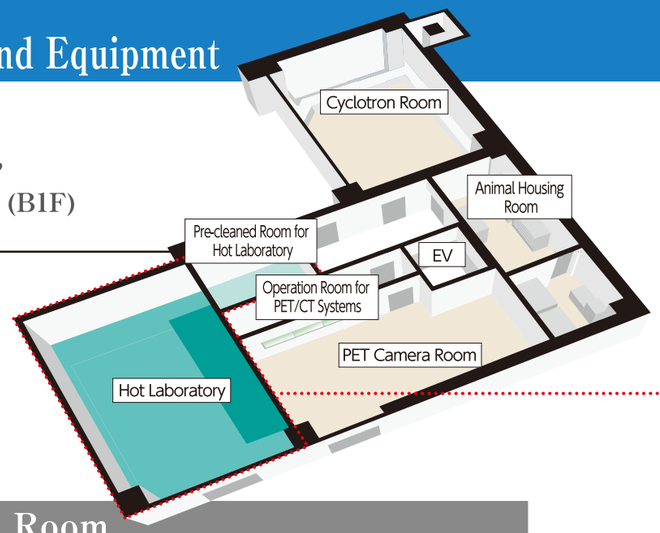
OMIC has fully equipped molecular imaging research facilities established at Okayama University as a joint research center in 2009 by the Japan Science and Technology Agency with the aim of revitalizing regional industries. The center began operating in April 2011 as a collaboration center for industry-academia-government teams dedicated to the research and development of new medicines and medical devices.

OMIC also actively assists educational programs on Molecular Imaging Research at the Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences in official corporation with RIKEN (Kobe), and also contributes in other wide-ranging supporting services such as bio-venture startup assistance.

Introduction to OMIC's Facilities and Equipment

Department of Radiation Research, Advanced Science Research Center (B1F)

All the necessary equipment is provided for any type of imaging studies. At our facility, small to middle-sized animals such as mice, rats, and rabbits are available for the PET imaging experiments. Facilities are also provided for temporarily housing primates.



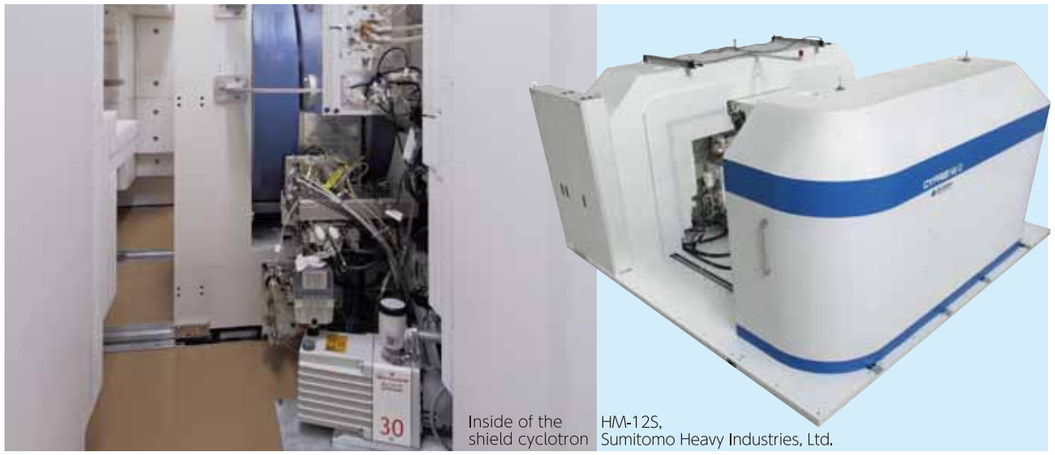
GMP Regulation and its Area

Considering the utility of PET-probes prepared at our facility for clinical researches including exploratory clinical researches in the early stage, OMIC has promoted the introduction of GMP regulation for investigational medicinal products to guarantee the quality and safety since it started servicing in 2011.

The following GMP ares are regulated for investigational medical products.

- Grade A (class 100) in hot cells and a clean bench
- Grade B (class 10,000) in hot laboratory
- Grade C (class 100,000) in pre-cleaned room for hot laboratory

Cyclotron Room



Inside of the shield cyclotron

HM-12S, Sumitomo Heavy Industries, Ltd.

Cyclotron

Hydrogen atoms are ionized and accelerated in a magnetic field to irradiate a target. The PET-nuclides are generated through nuclide transmutation reactions with protons or deuterons, so-called (p,n), (p,α). A wide variety of nuclides (^{11}C, ^{13}N, ^{15}O, ^{18}F, ^{64}Cu, and ^{89}Zr) can be produced by choosing a suitable target origin.

An automated delivery system swiftly transports ^{11}C, ^{13}N, and ^{18}F to the hot cells (in the hot laboratory), and ^{15}O labeled gas directly to the PET Camera Room. ^{64}Cu and ^{89}Zr are manually transported to the hot laboratory for nuclide purification.
The cyclotron is operated by specialists.


Target

Features

- ○Negative ion cyclotron
- ○Acceleration of 2 particles: proton and deuteron
- ○Acceleration energy: proton = 12 MeV / deuteron = 6 MeV
- ○Max beam current: proton = 100 μA / deuteron = 100 μA
- ○Simultaneous irradiation using 2 ports
- ○Sliding target system (4 target units on one beam port, total of 8 units on both sides)
- ○Self-shielding structure

PET probes usable at OMIC

^{11}C-Choline	tumor, membrane phospholipid synthesis
^{11}C-Methionine	tumor, protein synthesis
^{13}N-NH$_3$	cardiac muscle, blood flow
^{15}O-gas	oxygen metabolism in brain
^{18}F-FDG	tumor, glucose metabolism
^{18}F-FLT	tumor, nucleic acid metabolism
^{64}Cu/^{89}Zr labeling for proteins (such as antibodies) and peptides	

Hot Laboratory

Synthesizing and Labeling System for PET probes

This system is designed with instruments for labeling compounds with radionuclides generated by the cyclotron.

A dedicated "F200 Synthesizer" is installed for short period labeling and high-yield production of ^{18}F-FDG.

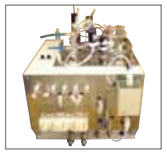
The "CFN Multi-purpose Synthesizer" can label with ^{11}C, ^{18}F, and ^{13}N to create compounds such as ^{11}C-choline, ^{11}C-methionine, ^{18}F-FLT, and ^{13}N-NH$_3$.

Furthermore, the "^{64}Cu Metal-Target Purification System" can separate ^{64}Cu generated by the cyclotron from the target's ^{64}Ni origin with high purity. The purified ^{64}Cu can be applied for labeling with relatively larger molecules such as antibodies and peptides.

Each device is installed inside two shielded hot cells for preventing irradiation during operation.

Inside of the hot cells

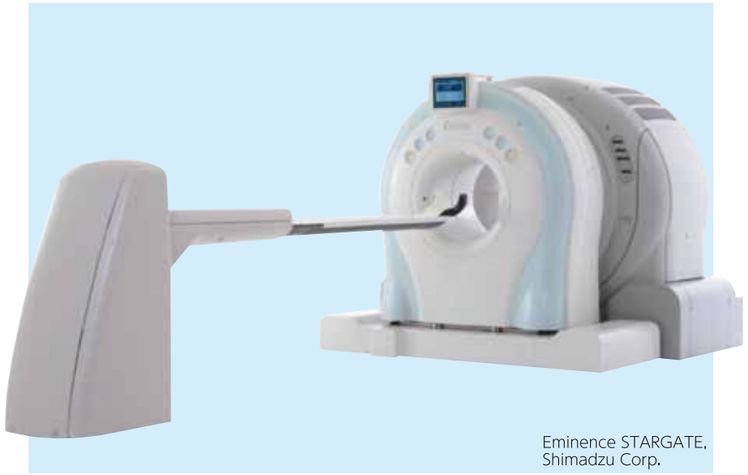

^{18}F-FDG Automated Synthesizer


CFN Multi-purpose Synthesizer


^{64}Cu Metal-Target Purification System

Introduction to OMIC's Facilities and Equipment

PET Camera Room



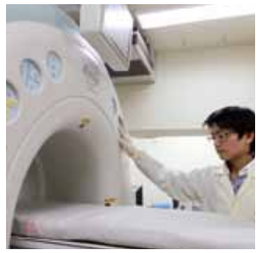
Eminence STARGATE,
Shimadzu Corp.

Clairvivo PET,
Shimadzu Corp.

PET/CT Analysis for Middle-sized Animals

A clinical PET/CT system has been introduced for PET/CT imaging of middle-sized animals. The system is capable of imaging various middle-sized animals, such as rabbits.

The ability to overlay PET and CT imaging views facilitates accurate identification of the injured area due to combining PET-based functional imaging with CT-based anatomical imaging.



PET Analysis for Small Animals

Capable of measuring small animals like mice, rats, etc. Localized imaging in other animals is also possible (i.e. marmosets).

High sensitivity and resolution for high-precision are provided for observation of small animals with organs smaller than humans.

Animal Housing Room

Temporal Animal Housing Facilities and Drying Equipment

Outfitted with temporary housing facilities for experiment animals. Multiple experiments and animal drying with special equipment for post-experimental use are also available.

Department of Animal Resources, Shikata Laboratory, Advanced Science Research Center located on the same campus is also available for middle- and long-term housing needs such as for the development of disease-animal models.

Other Equipment and Systems

FX3000
Pre-clinical Imaging System,
Gamma Medica-Ideas, Inc.

SPECT/CT System

Combination of SPECT/CT in a single modality smoothly facilitates analysis with SPECT and CT imaging. Utilization of a CZT with high-energy resolution enables simultaneous collection of signals from different radio-nuclides.

IVIS Spectrum,
Xenogen Corp.

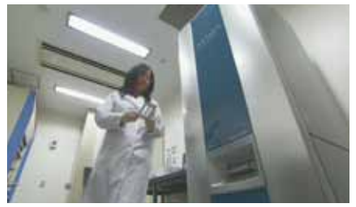
Optical Imaging

Facilitates non-invasive chemiluminescence/fluorescent imaging of small animals.

AXIMA Performance and CHIP-1000,
Shimadzu Corp.

MALDI Imaging

Displays 2-D distribution of intended biological molecules based on their positional information on tissue sections.



Stereo-microscopes, cryotome and other equipment for pathological analyses are also available.

Security management system

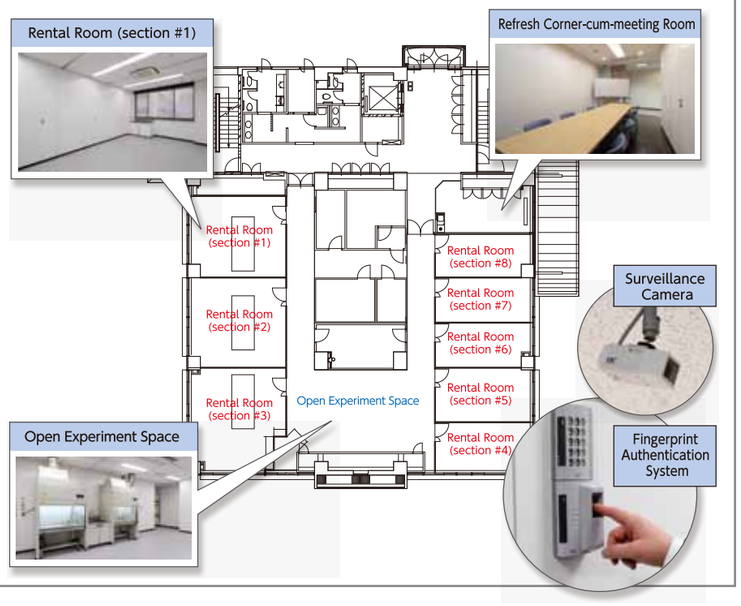
A thorough security management system is provided, including an entry control system and a data management system for the facility.

Incubation Facilities (General Education and Research Building, 2F)

The research center provides incubation facilities for corporations conducting molecular imaging at OMIC.

We have strengthened security with a fingerprint authentication system and surveillance cameras at all major entrances.

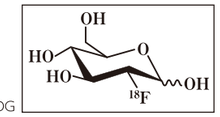
- ●Rental Rooms: 8
- ●Common Space
  - ・Open Experiment Space
  - ・Culture Room
  - ・Sterilization Room
  - ・Cold Room
  - ・Homiothermal Room
  - ・Emergency Shower Room
  - ・Refreshment Corner-cum-meeting Room



A Model Case for PET Imaging Experiments

case 1 Pharmacodynamic Evaluation of Drug Candidate Compounds
【Confirmation of Antitumor Efficacy】

^{18}F-Fluorodeoxyglucose (^{18}F-FDG) is the most common radiotracer used for obtaining information relevant to glucose uptake.
Cells with accelerated glucose metabolism, such as cancer cells, take up large amounts of ^{18}F-FDG, enabling application of this kind of tissue diagnosis and quantitative evaluation.



^{18}F-FDG

1 Preparation of Mouse Models
The tumor to be targeted by the candidate compound is xenografted into mice.

2 ^{18}F-FDG Generation
^{18}F is generated by the cyclotron and ^{18}F-FDG is synthesized in the dedicated synthesizer.


Cyclotron


^{18}F-FDG Automated Synthesizer

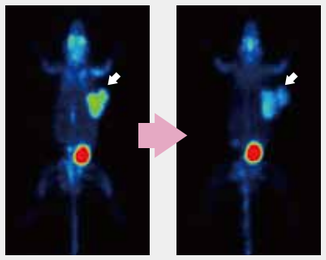
3 ^{18}F-FDG Administration and PET Imaging
The mice are administered with ^{18}F-FDG for uptake by the tumor.

4 Drug Candidate Compound Administration & Animal Management
Mice are divided into two groups, an administration group given the drug candidate compound and a non-administration group, and subsequently raised.

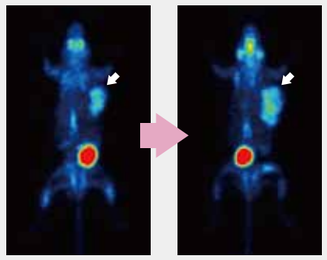
5 ^{18}F-FDG Preparation and PET Imaging
^{18}F-FDG is repeatedly prepared for sequential PET imaging.
Repeated PET imaging in the same specimen allows for quantitative evaluation of tumor growth before and after candidate compound administration and subsequent conformation of antitumor efficacy.

Follow-up observation of tumor

Compound Administration Group



Compound Non-administration Group



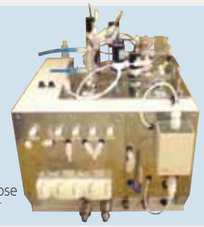

A cryotome can be used to perform histologic experiments after radiation is administered.

case 2 Pharmacokinetic Evaluation of Drug Candidate Compounds
【Confirmation of Excretion Pathway and Speed】

PET is capable of tracking the compounds' kinetic change with short interval imaging.
Along with tracing the pathway taken by the drug to the tissue after introduction into the body, a single animal specimen can be used to determine how fast it accumulates and is excreted from the tissues.

1 Labeling
Different labeling methods are used for individual compounds.
At OMIC, purification conditions are considered and preparations are made for synthesizing with the automated synthesizer.

2 Radionuclide Generation and Compound Labeling
The compound is labeled by the CFN multipurpose synthesizer with a radionuclide generated by the cyclotron. Reactions inside the hot cells are remote-controlled by a computer while being monitored by camera.

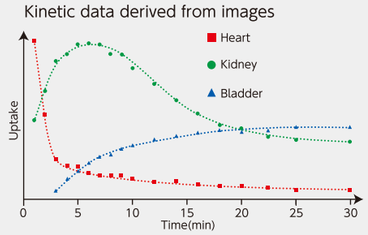

CFN Multi-purpose Synthesizer

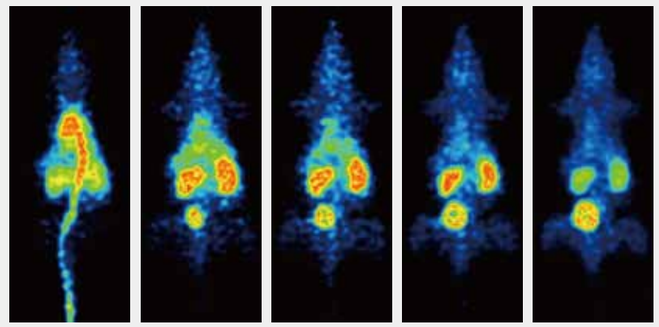
3 Administration of the Labeled Compound and PET Imaging
PET imaging is started before the labeled compound is administered to the mice,
and the compound's kinetics can be tracked from the moment of administration.

4 Image Reconstruction
The imaging data is reconstructed to create 4-D data that includes time information.
The ideal timeframe is set for tracing the kinetics.

5 Dynamic Analysis
The region of interest is set for the reconstructed 3-D image to derive a temporal transition of the radiation for each tissue, enabling temporal tracking of a drug's kinetics.

Kinetic data derived from images





A Model Case for PET Imaging Experiment

case 3

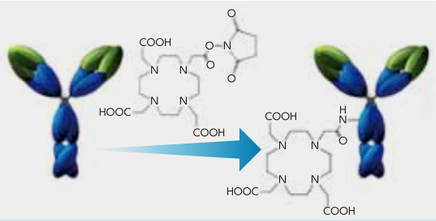
Imaging Using Antibodies

【Radioactive Metal-Nuclide Labeling】

Pathological areas occasionally show disease-specific molecules that are not normally seen in healthy tissue. Using antibody specific to such molecules facilitates highly specific imaging.
Macromolecules like antibody take time to accumulate in tissue, making imaging with metal nuclides featuring relatively long half-life like ^{64}Cu and ^{89}Zr particularly effective.

1 Antibody Preparation

A chelating agent is covalently bound to the antibody prior to labeling the radio-active metal ion.



2 Radionuclide Generation

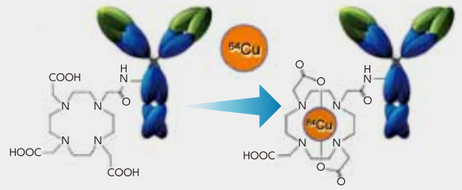
Radio-active metal nuclide is manufactured in the cyclotron and the resulted nuclide is purified using the metal-target purification system.


Metal-Target Purification System


^{64}Cu Extraction

3 Metal Nuclide-Chelating Bond

Radiolabeling of the antibodies is performed by mixing the purified radio-active metal nuclide and the chelating molecule-bound antibody.



4 Purification of Labeled Antibodies

The labeled antibody is purified using a suitable method, such as gel filtration chromatography and the purity of the RI-labeled antibody is evaluated by TLC and HPLC.

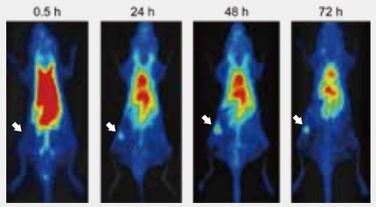

Purification using gel filtration chromatography

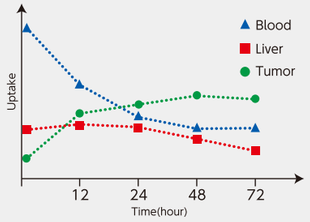

Confirming the radioactive fraction


Identification of molecular species using HPLC

5 Labeled Antibody Administration and PET Imaging

The mice are administered antibody and imaged.
Due to a relatively long half-life of the nuclide, the administered mice can be repeatedly imaged every few hours to track variations in the antibody's successive accumulation.






A stereomicroscope can be used after imaging to dissect small tissue.

Usage Patterns/Usage Flow/Support System

The Collaborative Research Center for OMIC functions as a one-stop consultation desk for all the necessary procedures.
Please don't hesitate to contact us with your enquiry.

Usage Pattern 1

Uncharged non-proprietary usage

Free use of cyclotron and PET

- Up to 2 units of use where each cyclotron operation is 1 unit.
- Publishing of results is a condition (up to 2 years given for publishing).

Usage Pattern 3

Charged proprietary usage

Full cost for use of equipment

- Can use facilities without publishing results.

Usage Pattern 2

Charged non-proprietary usage

Half cost use of cyclotron and PET

- Publishing of results is a condition (up to 2 years given for publishing).

Usage Flow

Usage Consultation	Please contact the Collaborative Research Center for OMIC.
Research Proposal	The research proposal form can be downloaded from the website and submitted at any time.
Adoption	Screened at a monthly proposal adoption & evaluation committee.
Reservation	After approval, the schedule, experiment method etc. are decided and an application for usage is submitted.
Experiment	Research staffs are on hand for everything from usage consultations and equipment operation, to post-experimental image analysis.
Report	As a rule, a results report is to be submitted within 60 days of final usage. (note)

- Joint research (trust) agreement with Okayama University may be required for usage.
- (Note) In the case of "uncharged non-proprietary usage" and "charged non-proprietary usage," the results report will be published on the website and MEXT's Kyoyo Navi (shared navigator) after being evaluated by the proposal adoption and evaluation committee. However, publication may be delayed by up to 2 years for reasons such as patent application.

Support System

Research staffs are ready to assist in everything from prior usage consultations to post-experimental data analysis.

Collaborative Research Center for OMIC
Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences

Director

Vice Director

Technical guidance researchers for joint use facilities (4)
Joint use promotion liaison (1)

- Usage consultations
- Support for planning research projects
- Equipment operation
- Support for animal experiments
- Post-experimental data analysis

Administrators (2)
- Application procedures etc.