RIKEN Center for Molecular Imaging Science

CMIS

In the past,
Humankind gained knowledge of the constituent parts of life
Through observation with their own eyes.

In the modernized world,
The eyes of science are revealing
The miraculous harmonies woven through interaction
Among these parts in your life.

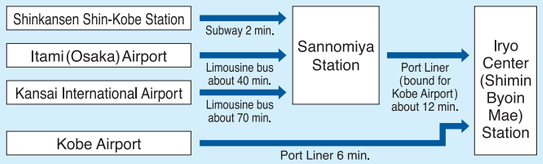
As humankind explores the vast panorama
That gives rise to life,
What mysteries will be revealed?

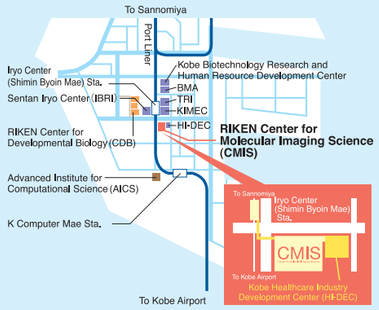
Molecular imaging technology realizes a new era of “live science”

Molecular imaging drives innovations in medical care and accelerates the drug discovery process by monitoring the molecules that function in living organisms. It is also set to create a new wave of life science for the post-genome era.

Access

CMIS is a 1-minute walk from Iryo Center (Shimin Byoin Mae) Station via the footbridge (reception desk situated on 2nd floor).





http://www.cmis.riken.jp

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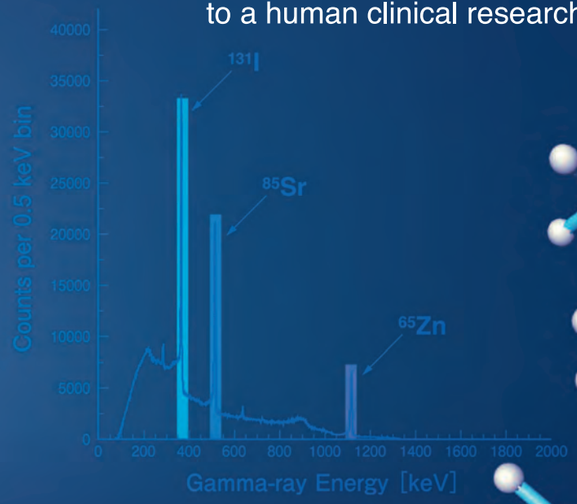
March 2012

RIKEN Center for Molecular Imaging Science

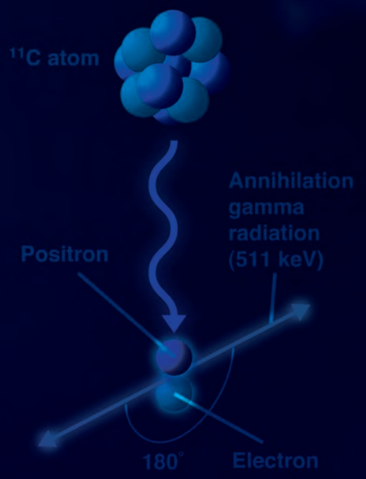
From life science to live science

Understanding biological phenomena: From molecules and cells to organs and organisms
Shifting biomedical study from an animal research phase to a human clinical research phase



Application to medical, clinical and health sciences

From research findings to innovative drug discovery processes
Preventing disease by depicting the complicated biological system and unveiling pre-disease states



Developing fusion and novel molecular imaging technologies

New approaches transcending conventional medical imaging methods
Technical innovations to comprehend spatio-temporal changes in biological activity

We aim to develop novel medical technologies by integrating approaches from many disciplines.

Yasuyoshi WATANABE

Director
RIKEN
Center for Molecular Imaging Science

Molecular imaging science/technology is recognized as very important one for the present and future medicine and therapies. World-wide consensus in this field accelerated the concentration of research and development in molecular imaging. One example is the application of molecular imaging to drug development/discovery process, that could promote the acquisition of direct evidence in human body with safetiness from early stage of drug development. Introduction of molecular imaging in the process gave us the chance to overcome the species difference between experimental animals and human, which is the major obstacle of rational drug development, since the information derived from molecular imaging studies could be the aids to understand how the species difference affects the pharmacokinetics and metabolism of candid molecules. The best candid compounds/molecules from the results of the animal studies could be tested by the same molecular imaging techniques if this is the case in humans, that leads to highly efficient drug development.

Molecular imaging is the only noninvasive technique for quantitative monitoring of changes in concentration or distribution of target molecules in living organisms. This technique can be achieved by integrating multi-disciplinary fields including chemistry, physics, molecular biology, pharmaceutical science, medical science, engineering, and computer science. Our center brings together researchers from these diverse areas to work on translational projects through all the steps such as chemical design, elaborate chemical synthesis, development of instruments, animal research, and clinical research. This all-joining collaborative research organization makes our institution very unique in Japan.

The Center for Molecular Imaging Science (CMIS) was founded in October 2008 as the successor to the Molecular Imaging Research Program (MIRP), which was launched in September 2005 at RIKEN. MIRP had also served as a research base for exploring novel drug candidates supported by the Japan's Ministry of Education, Culture, Sports, Science and Technology (MEXT). Furthermore, the "Japan Advanced Molecular Imaging Program (J-AMP)" was initiated by MEXT in April 2010 to extend the research achievements made thus far to gain proof-of-concept in clinical applications on oncology and dementia field. CMIS is expected to play a leading role in this initiative, too.

In order to further promote Japan's molecular imaging research and develop an international collaborative network in this field, we are committed to carrying out research that will establish innovative medical technology, such as drug development and preemptive medicine by higher employment of molecular imaging. We do hope that you find this brochure enlightening in regard to the research conducted at CMIS, and that you could give us your continued support and guidance.

MISSION
Molecular imaging is the way by which we comprehend the whole living organism. We will develop original high technology in this new era of science.

GOAL
We will carry out not only basic research using cell or animal subjects, but also clinical investigation for human applications. Our translational research will lead to innovation in the drug discovery process and elucidation of the molecular mechanisms of a variety of diseases and pre-disease state.

VISION
Molecular imaging research founded in "humanology" will help us to foresee illness and cure it. We hope to help people maintain a state of complete physical and mental well-being.

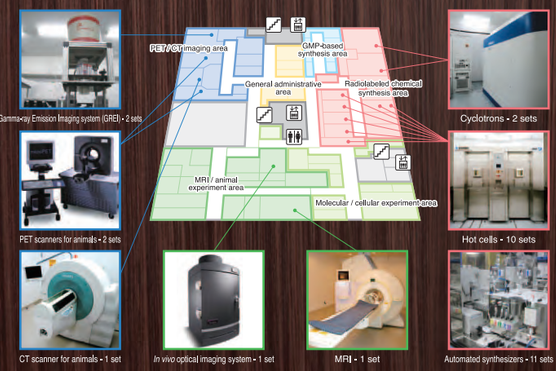
History

2001.12 In the speech just after Nobel prize awarding celemony, Dr Ryoji Noyori, President of RIKEN, proposed the need for molecular imaging science, integrating chemistry, biology and medical science, as a key direction for chemistry in the future.
2004.3 A Promotion Committee for Molecular Imaging Research was formed. The Committee proposed the establishment of both a research base for drug development and a research base for PET diagnosis in Japan.
2004.4 A planning office for the Molecular Imaging Research Program was opened in the RIKEN Frontier Research System.
2005.7 The Ministry of Education, Culture, Sports, Science and Technology (MEXT) launched the Molecular Imaging Research Program (the 1st Phase), and selected RIKEN as a Research Base for Drug Development.
2005.9 The Molecular Imaging Research Program (MIRP), which includes three teams from chemistry, biology and medicine, was inaugurated in the RIKEN Frontier Research System.
2006.4 The Kobe MI R&D Center Building was completed.
2006.10 Research fields of MIRP was placed in KOBE.
2008.10 MIRP was reorganized and inaugurated as the Center for Molecular Imaging Science (CMIS). Research organization was expanded into three teams and three units.
2010.4 RIKEN started the Research Cluster for Innovation, which includes the Program for Drug Discovery and Medical Technology Platforms. To support this, CMIS established new platform units and reorganized into six teams and three units. MEXT launched the Japan-Advanced Molecular Imaging Program (J-AMP) (the 2nd Phase).

Personnel and Facilities

Site area: 6,000 m² Floor area: 8,600 m²
Four-floor building (3rd floor occupied by another research institution)
The number of Staffs: 268 (including Visiting Researchers and Student Trainees) (as of March 2011)

[Main equipment and instruments (lab floor, 1st floor)]



TEAMWORK

CMIS started out with three teams, but now comprises six teams and three units.
We have integrated many different disciplinary fields, and all teams strive as one to develop novel molecular imaging research.
This system enables the processes of drug discovery and establishment of new medical treatments to be accelerated.

■ Organization chart

Center for Molecular Imaging Science

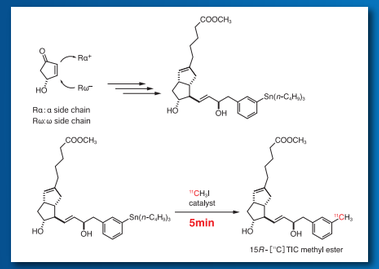
Director, Yasuyoshi Watanabe
Deputy Director, Masaaki Suzuki
Coordinator, Tsuneo Yano

Advisory Council

Molecular Imaging Medicinal Chemistry Laboratory	Team Leader, Masaaki Suzuki
Molecular Imaging Labeling Chemistry Laboratory	Team Leader, Hisashi Doi
Functional Probe Research Laboratory	Team Leader, Hirotaka Onoe
Molecular Probe Dynamics Laboratory	Team Leader, Yasuyoshi Watanabe
Cellular Function Imaging Laboratory	Team Leader, Yosky Kataoka
Multiple Molecular Imaging Research Laboratory	Team Leader, Shuichi Enomoto
Molecular Imaging Integration Unit	Unit Leader, Kazuhiro Takahashi
Drug Discovery Chemistry Platform Unit	Unit Leader, Yoshinobu Hashizume
Drug Discovery Imaging Platform Unit	Unit Leader, Yasuyoshi Watanabe

To clinical research

● Novel PET probe synthesis using the rapid *C*-methylation method



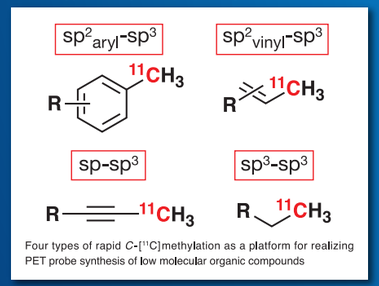
Molecular Imaging Medicinal Chemistry Laboratory

Our laboratory aims to develop new chemical reactions required for the synthesis of novel PET probes and to establish new chemical methodologies in molecular science for exploration of novel drug candidates. In concrete terms, this involves the development of new rapid chemical reactions associated with short-lived positron emitting radionuclides as well as the design and efficient synthesis of metabolically stable, molecular probes specifically targeting for important biological phenomena and diseases.

Creating Molecules


Team Leader Masaaki Suzuki, Ph.D.

● Four types of rapid *C*-[^{11}C]methylation



Four types of rapid *C*-[^{11}C]methylation as a platform for realizing PET probe synthesis of low molecular organic compounds

Molecular Imaging Labeling Chemistry Laboratory

Our laboratory is, in cooperation with the Molecular Imaging Medicinal Chemistry Laboratory, working to develop PET probe syntheses for drug candidates and novel chemical labeling reactions. As one of our main projects, we are striving toward introducing ^{11}C into carbon frameworks of bioactive organic compounds by developing rapid *C*-[^{11}C]methylation reactions based on carbon-carbon bond formation, focusing on the methyl group as the minimum carbon substituent.

Brightening Molecules


Team Leader Hisashi Doi, Ph.D.

● Multipurpose automatic synthesizer module (cassette-type)

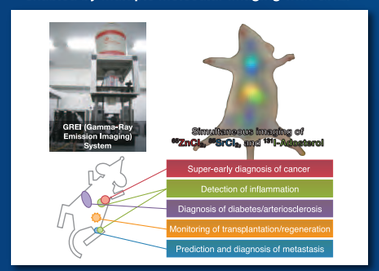
Molecular Imaging Integration Unit

Our unit supports research and development of integrated techniques for spreading the use of molecular imaging by PET. As a first step we have developed a new cassette-type multipurpose automatic synthesizer module which enables anyone to produce the desired labeling probe simply by changing the cassette. We also support the translational research by using our GMP area and transportation of our techniques to other research institutes.

Spreading Molecules


Unit Leader Kazuhiro Takahashi, Ph.D.

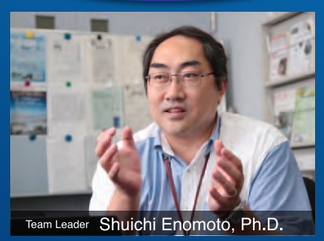
● Multi-factor analysis for advanced medical diagnosis enabled by multiple molecular imaging with GREI



Multiple Molecular Imaging Research Laboratory

Our team is working to develop a new gamma-ray imaging system called GREI. We believe that the simultaneous multiple molecular images produced by GREI will be an effective tool for clinically crucial early diagnosis of intractable diseases such as cancer and metabolic diseases, and for evaluations of transplants and regenerative treatments. Currently, we are working to improve a GREI system and discover new multiple molecular imaging probes for clinical application.

Coloring by Molecules


Team Leader Shuichi Enomoto, Ph.D.

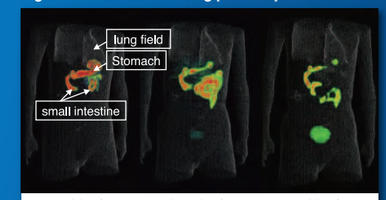
Utilizing Molecules


Team Leader Yasuyoshi Watanabe, M.D., Ph.D.

Molecular Probe Dynamics Laboratory

Our team follows the dynamics of molecular probes developed in CMIS, and recruits the probes to translational research with the clinical research partners. We are also engaged in the labeling of many drug candidate molecules, perform pharmacokinetics and pharmacodynamics (PK/PD) studies, and also could test the drug delivery system (DDS) in animals and humans. Our team also makes efforts to further develop highly elaborate quantitative molecular imaging (MI) methods, fusion MI, and next-generation MI techniques.

● PET-Microdosing study of absorption process from gastrointestinal tract using [^{18}F-FDG]



75-90 min after injection | 35-50 min after injection | 5-20 min after injection
Collaborative Research with Setsunan University, University of Tokyo, & Osaka City University

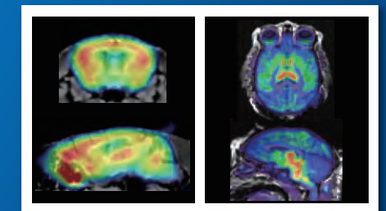
Evaluating Molecules


Team Leader Hirotaka Onoe, Ph.D.

Functional Probe Research Laboratory

For the evaluation of new PET probes for the specific biomarker, we recently have established PET molecular imaging method using not only anesthetized but also unanesthetized animals including the mouse, rat, marmoset, and macaque monkey. Using these systems, we are attempting to develop animal models, including genetically manipulated animals to get the evidence of intrinsic role of imaging biomarkers for their translational/clinical use. In addition, to realize the regenerative therapies using embryonic stem cells and gene transfer technique, we are trying to establish the imaging methodology for regenerative medicine via longitudinal studies using non-human primates.

● PET images of [^{18}F]FDG and [^{11}C]DASB under the unanesthetized condition


Glucose metabolism in the mouse brain | PET imaging of serotonin transporter in the monkey brain

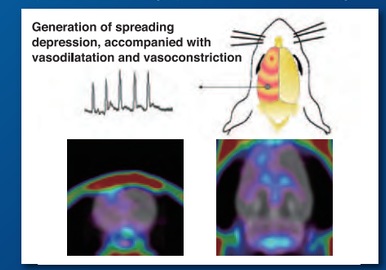
Making Bridges with Molecules


Team Leader Yosky Kataoka, M.D., Ph.D.

Cellular Function Imaging Laboratory

We are investigating the physiological or pathological roles of cells functioning in living tissues by using PET and optical imaging. In order to realize the investigations with linkages between molecules and functions, and the behavior of individual cells and living systems, we conduct multi-modal molecular imaging science integrated with electrophysiology, histochemistry, and behavioral analysis.

● PET imaging of brain immune response (activation of microglia) in an animal model for migraine



Drug Discovery Chemistry Platform unit

Unit Leader Yoshinobu Hashizume, Ph.D.

Our mission is to understand details of biologically-active molecules on their binding activities to the target molecules and the behavior in the living system, by means of an integrated approach combining design, sunthesis, and pharmacological/biochemical characterization.

Drug Discovery Imaging Platform unit

Unit Leader Yasuyoshi Watanabe, M.D., Ph.D.

Under the Program for Drug Discovery and Medical Technology Platforms, this unit conducts molecular imaging studies on efficacy and pharmacokinetics of drug candidate molecules.

Regulatory Science

Coordinator Tsuneo Yano, Ph.D.

We are developing regulatory guidance to facilitate application of the findings of PET medical imaging research to drug discovery and development, and to open pathways for translational research.

The CMIS aims to establish “Humanology”, a real science to realize human benefits. For this purpose, we develop our original inventions and techniques in molecular imaging such as molecular labeling, biofunctional monitoring and next-generation imaging technology.

Drug discovery

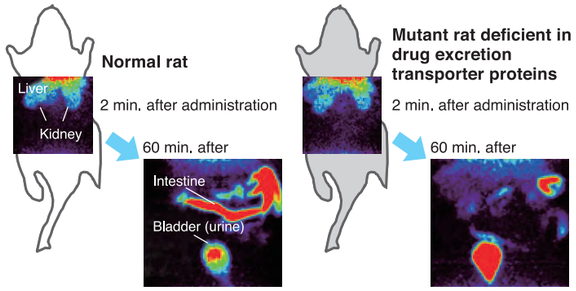
Pharmacokinetics

Raising efficiency through novel drug development processes by use of molecular imaging

Currently, the methodology of drug discovery is founded on the miscellaneous outcomes of life science, so that the number of candidate compounds has been increasing. On the other hand, in light of increasing public demand for the realization of complete cures rather than present symptomatic treatment, and for absolute proof of drug safety, the range of test procedures needed for clinical trials has been on the increase, demanding major investments of time and money. Nevertheless the success rate of drug discovery remains very low. A breakthrough may be possible by utilizing microdosing clinical trials (MD trials: see below) and PET imaging. These two methods enable the evaluation of efficacy of candidate compounds in humans safely during early phase of clinical development. PET imaging can be applied to drug discovery from early screening to the late phase of the clinical development as one of the analysis methods used during MD trials. We can investigate pharmacokinetics in live animals or human bodies at molecular level, and quantitatively evaluate the distribution of drugs to the target tissues/organs, absorption and excretion. In addition, as PET imaging can visualize biochemical and physiological disorders which accompany disease or side effects, more reliable evaluation of efficacy and safety of drugs could be achieved. Thus, the success rate of bringing new drugs to market is expected to become higher. We are now on the edge of a major breakthrough in the drug discovery process.

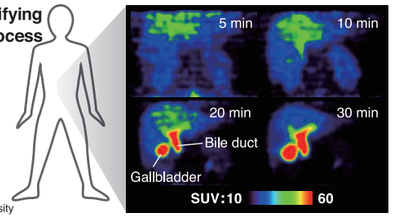
Drug evaluation by Molecular Imaging

● **PET scan revealed the difference in pharmacokinetics between normal rats and drug excretion transporter-deficient rats**



It is observed that in the mutant rat deficient in drug excretion transporter proteins the labeled compounds accumulated in the bladder instead of excreting them into the intestine (in bile).

● **Visualizing and quantifying the drug excretion process in humans (healthy volunteer)**

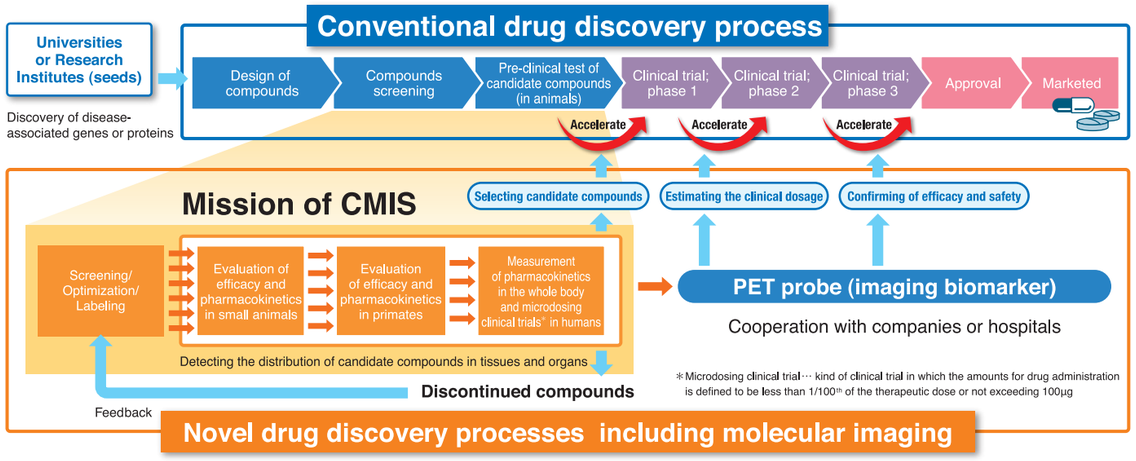


Labeled compounds are detected in bile in the same manner as normal rat.

In collaboration with Osaka City University

Molecular Imaging accelerates the drug development processes

Conventional drug discovery processes using animal subjects often fail to screen candidate compounds that are suitable for human application because of different mechanisms in the metabolic system and drug transport system between human and animal. A number of candid compounds have been thrown away so far; less than 10 percent pass the clinical trials. In the near future, early-phase microdosing clinical trials will be able to narrow down candidate compounds in humans safely. In addition, test evaluation systems will be developed for use across small animals, primates and humans, using imaging biomarkers to enable exact estimation of clinical dose and efficient confirmation of efficacy and safety of the candid compounds. This could raise the success rate of clinical trials up to 30 ~ 50 %.



Core technologies

Molecular labeling, revealing biological function, and next-generation imaging methods

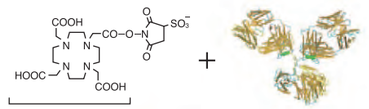
Innovative and integrated technologies and equipments

Labeling techniques for molecular probes are very important in molecular imaging research. CMIS is developing world leading techniques not only to label every small molecule but also to label high molecular-weight compounds such as proteins without inactivating them. We have also established a novel PET system to image rodents and primates under unanesthetized state, whereby we can trace the exact molecular distribution in a whole body under physiological conditions. In addition to such works on PET, CMIS is engaged in various other modalities of molecular imaging research including MRI, CT and optical imaging. An institution based on such collaborative research strategy is very unique in Japan.

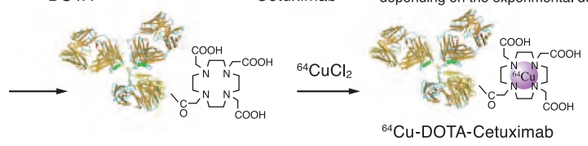
Automated synthesizers

Applying biopharmaceuticals to molecular imaging

● **An antibody becomes a PET probe**

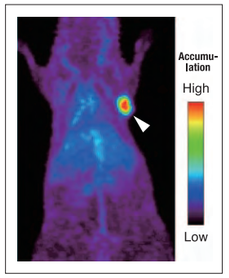


Nucleic acids, glycol-conjugates, peptides, and proteins are considered to be promising candidates for drugs. To explore the molecular dynamics of such biomolecules, we use radioactive metallic isotope ^{68}Ga or ^{64}Cu to label them and make PET probes. ^{64}Cu has a rather long half-life of 12.7 hours, so we can trace the PET probe for three days or more depending on the experimental design.



● **PET imaging of ^{64}Cu-DOTA-Cetuximab**

— Accumulation in tumor 24 hours after administration —



^{64}Cu labeled Cetuximab (^{64}Cu-DOTA-Cetuximab) was administered to mouse with tumor grafted in its shoulder (arrow head). ^{64}Cu-DOTA-Cetuximab signal was observed in tumor regions by PET imaging after 24 hours.

Medical care

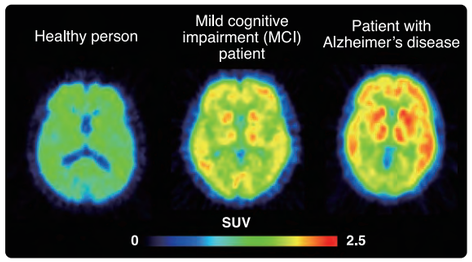
Dementia, cancer, life-style disease, fatigue, pain, and so on

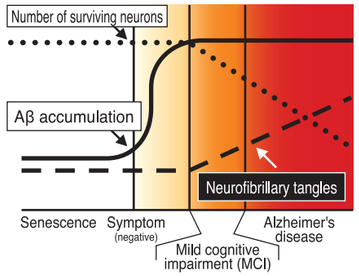
Maintenance of health by exact predictive and preemptive medicine

Ordinarily, most people go to the doctor only when they notice some symptoms. But in the future, it will be necessary to foresee illness, diagnose it and cure it prior to the appearance of subjective symptoms. Molecular imaging technology is expected to realize such a predictive medicine. Predictive medicine will realize more effective treatment not only for conditions such as dementia, cancer, diabetes and arteriosclerosis, but also for the onset of illness such as fatigue, tiredness and pains, which have often eluded objective diagnosis so far. CMIS is seeking to comprehend the expression profile and dynamics of biomolecules related to such diseases in our body by using molecular imaging technology, and challenges technological innovation for predictive medicine, as well as personalized medicine providing customized medical care for each patient.

Etiology, patho-physiology and remedy of dementia

● **Images of Aβ (one of the responsible molecules for Alzheimer's disease) accumulation in human brain**





PET imaging of Alzheimer's disease

It is known that amyloidβ(Aβ), an insoluble fibrous protein, is accumulated in the brains of patients with Alzheimer's disease. By using a Aβ binding molecular probe, the presence of Aβ in living brains can be observed without invasion. The progress of PET imaging technology will enable early diagnosis and appropriate determination of therapeutic strategy for Alzheimer's disease. Also, our technology is expected to contribute to the drug discovery process.

collaborative research with Osaka City University

Toward the future of drug discovery and molecular imaging

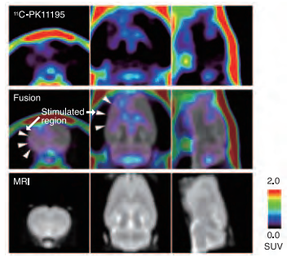
The fruits of CMIS's research contributing to the future of drug discovery are disseminated throughout the world.
We also hold many events to inform people about the field of molecular imaging science.

CMIS interacts and collaborates with domestic and international research institutes to push back the frontiers of knowledge.

Research 1

Monitoring neuroinflammation in migraine by molecular imaging

Migraine is thought to occur by an aseptic inflammation of brain resulting from serum protein leakage during repetitive vasodilatation, which is felt as pain. Microglial cells are known to be activated by inflammatory stimuli in the brain. We synthesized [^{11}C]PK11195, a PET probe exclusively recognizing activated microglial cells and succeeded in capturing the PET image of immune response in the brain of rat model for human migraine (arrowheads in the figure). As activation of microglial cells can be observed for several days after migraine attack, PET scanning of patients who underwent headache will help definitive diagnosis of migraine and evaluation of drug efficacy.

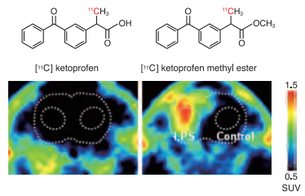


The Journal of Nuclear Medicine (October, 2009)

Research 2

Successful labeling of drugs exhibiting antipyretic/analgesic effects and visualization *in vivo*

Non-steroidal anti-inflammatory drugs (NSAIDs) commonly used as antipyretics and analgesics are also known to possess preventive effect against neurodegenerative diseases such as Alzheimer's disease. We succeeded in the world's first labeling of six kinds of NSAIDs including 2-arylpropionic structure (i.e. ibuprofen), with a radioactive carbon isotope (^{11}C). PET study using these labeled NSAIDs revealed poor transfer into the brain in rats. Replacement of the carboxylic acid (-COOH) group with a methyl ester (-COOCH$_3$) dramatically improved the permeability into the brain. These knowledge and technique are expected to be applied to elucidation of pathological conditions, diagnosis, and drug discovery.



Chemistry-A European Journal (April, 2010)

Research 3

PET molecular imaging analysis of intestinal insulin absorption

Insulin, a drug for diabetes, is not applied by oral administration because of the poor intestinal absorption. Therefore, insulin is usually administered by injection, and it is a burden on patients. We invented a novel technique to label insulin with PET radionuclide and elucidated its pharmacokinetics, in collaboration with Hoshi University. In a world-first, we succeeded in monitoring the facilitated absorption of insulin from the intestine by oral co-administration with cell-penetrating peptides (CPPs). These techniques are likely to be useful for developing various drug delivery systems for convenient and safe medicinal therapy.

This article was published in jounal of controlled release, Vol 146, Kamei N. et al., "Molecular imaging analysis of intestinal insulin absorption boosted by cell-penetrating peptides by using positron emission tomography", 16-22, © Elsevier (2010).

Molecular imaging Summer school

Lecture series on molecular imaging techniques from basis to application including drug discovery and diagnosis.

Symposium

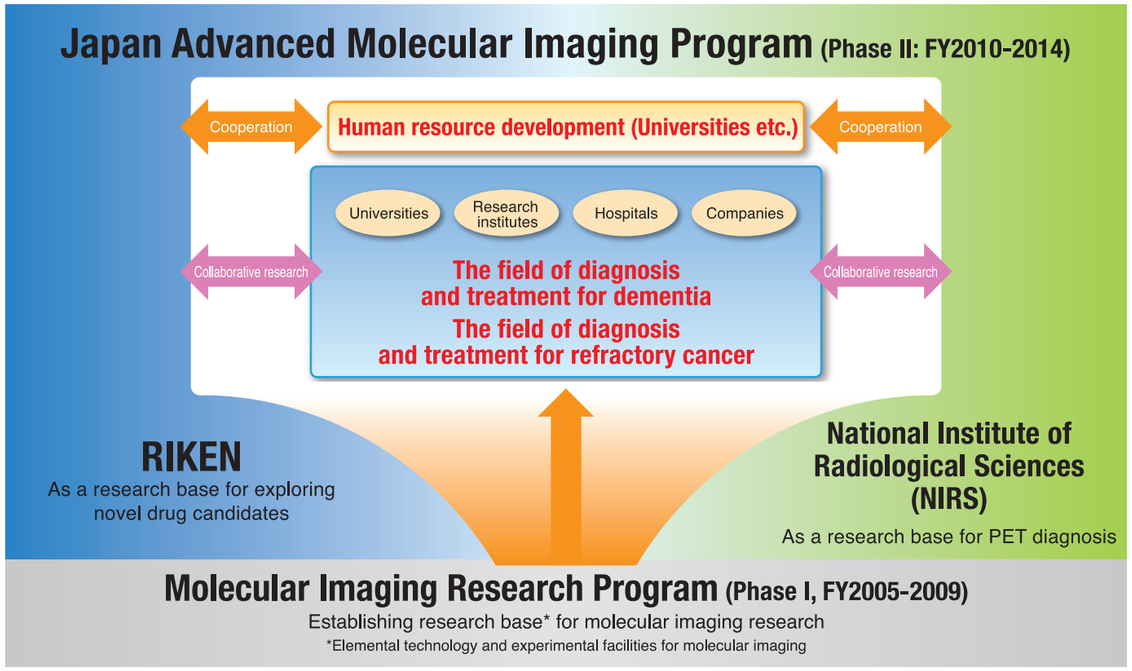
The fruits of research commissioned under the Japan Advanced Molecular Imaging Program (J-AMP) by MEXT will lead to technology transfer and public benefit, enhancing cooperation among industry, government and academia.

Open house

We open our laboratories once a year and inform the general public about our cutting-edge research and its results.

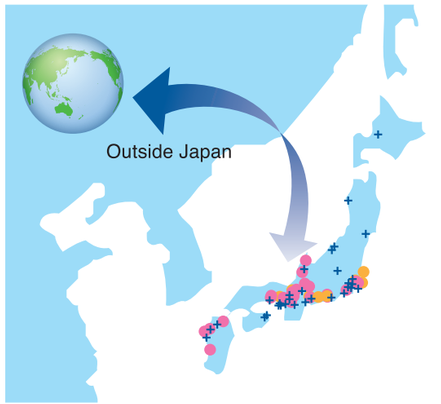
Japan Advanced Molecular Imaging Program (MEXT)

This program aims to put molecular imaging technology to practical use, especially in the treatment of refractory cancer and dementia, for which social needs are high. This is achieved through a cooperative research system consisting of a Research Base (RIKEN and the National Institute of Radiological Sciences), universities, hospitals, and healthcare industries.



Joint research and collaboration with other research institutes, etc.

CMIS formulates a system for international and internal cooperation and personnel exchange through collaborative research with the universities and research institutes below.



Domestic Exchange

Collaborative research…22 companies, 46 universities/research institutes (FY2011)

- Translational research…Osaka City University, Institute of Biomedical Research and Innovation, etc.
- Drug delivery and pharmacokinetics…University of Tokyo, Kyoto University, Pharmaceutical companies, etc.
- NEDO microdose project…University of Tokyo, Setsunan University, Institute of Biomedical Research and Innovation, etc.
- Development of novel molecular probes…Tokyo Medical and Dental University, Osaka University, Gifu University, etc.
- Development of automatic synthesizer…Joint development with companies, etc.

Affiliated graduate programs…Gifu University, Okayama University, Tokushima University and Kobe Gakuin University

Providing synthesized PET probes for clinical research

PET Science Academy, Molecular Imaging Summer school, CMIS seminar, etc.

International Exchange

Europe…… Uppsala University, Karolinska Institute (Sweden), University of Lyon (France) University College London, Imperial College London (United Kingdom), etc.

Asia…… Zhejiang University (China), Daegu haany University, Gachon University of Medicine and Science (Korea)

North America… NIMH, MD Anderson Cancer Center, Brookhaven National Laboratory, Harvard University, Stanford University (USA)

●Joint research (universities, research institutes, etc.) ●Collaborative research (companies) +Personnel exchange