Preface

The fiscal year 2004 (FY2004) was the 4th year since the National Institute of Radiological Sciences (NIRS) was reformed as an Independent Administrative Institution (IAI) in April 2001. Our activities that have followed the five-year mid-term plan have progressed smoothly. The achievement of our aims is in sight by the end of FY 2005.

We celebrated the 10 year anniversary since the initiation of the clinical trials of heavy ion cancer therapy in 1994. Successful results with high rates of local control of various cancers were reported both in memorial meetings and publications for both specialists and the general public. The largest number of patients (396) was treated in FY 2004, 72% of which (286) were treated as "highly advanced medical procedure for solid cancer". This has provided us with income additional to that from government budgets. We are pleased to announce that carbon-beam cancer therapy has come into the new phase in the first year of "the 3rd ten-year strategic plan against cancer (2004-2013)" issued jointly by MEXT (Ministry of Education, Culture, Sports, Science and Technology) and MHLW (Ministry of Health, Labor and Welfare). This plan aims at "significant decrease of morbidity and mortality of cancer." We are sure that carbon-beam radiotherapy will greatly contribute to decrease cancer mortality.

In FY 2004 a research project in NIRS on the development of a compact-size carbon beam accelerator to be applied in the medical community was accelerated by a markedly increased budget. We are aiming at completion of the present project by the end of FY 2005.

We began to utilize the newly built research building for low dose radiation effects experiments in FY 2004. The neutron irradiation facility in the new building is to be used after a delay in the schedule. The facilities, when they are fully operated, will facilitate important research projects on biological effects of low dose radiation.

Extra funding was obtained in FY 2004 for the establishment of an appropriate system of medical preparedness for nuclear emergencies including accidents, disasters, and deliberate human actions. The cooperation of multiple institutes and hospitals networking with each other is of increasing importance, for which NIRS plays a central role.

International organizations such as UNSCEAR, ICRP and IAEA have been working on radiological protection of the environment or non-human biota. The importance of this concept has been attracting interests of radiation ecologists and regulators. This emerging field encourages radiation ecologists to promote research in cooperation with radiation biologists and establish a new regulatory framework in cooperation with regulators.

In FY 2004, we started to make a research strategy for the next five year mid-term plan which starts from April 2006. In addition, a general review of IAI was performed by the initiative of administrative reform promotion group of the Japanese government. NIRS was included in the group of IAI which were reviewed one year ahead in FY 2004. The framework for the next five-year plan was made by the end of 2004. We have started to make our detailed plan within this framework.

On the basis of foreseeable successful outcomes by the end of FY 2005, NIRS will continue and enhance its research activities and management in the next 5-year plan. Decision was made to start a molecular imaging research project in FY 2005, which would facilitate a new domain of science by fusing medical imagiology with molecular biology.

I cordially ask for the support and cooperation and welcome critiques of those who are interested in NIRS and its activities.

Yasuhito Sasaki

Yasuhito Sasaki, M.D., Ph.D.
President

1. Outline of Research Activities in 2004

The fiscal year 2004 was the 4th year after the administration system of the Institute was changed from direct-government operation to independent agency system named the Independent Administrative Institute (IAI). In this fiscal year, the NIRS performed all its research activities very smoothly, in part, because all stuff were now familiar with the new systems which were implemented for the IAI. Although some problems occurred, for instance, shortage of funding, reconstruction of laboratory facilities, and construction of a new building, we have overcome these difficulties. Five project research programs and twenty basic research programs were continued in accordance with the Mid-tem Plan of NIRS, and some other research programs were continued or newly started with supports of funding agencies including the Ministry of Education, Culture, Sports, Science and Technology, the Ministry of Economy, Trade and Industry, and the Ministry of Environment.

Judging from the number and quality of the presentations at scientific meetings and the research papers and reports, it can be concluded that the researchers were active and much progress was achieved this year. The number of original papers published by the NIRS members reached 270 papers, and many of them were published in international journals with good reputations. Proceedings at international or domestic scientific meetings included more than 180 papers from us and more than 1200 oral presentations.

The clinical study of cancer therapy with the Heavy Ion Medical Accelerator (HIMAC) saw much progress and was ranked as "S (very advanced program)" by the IAI Evaluation Committee of the Ministry of Education, Culture, Sports, Science and Technology. In this program, approximately 2000 patients were treated and the results were comparable with or much better than conventional therapy. Regarding this study, 57 original papers and many proceeding have been published since 2001, contributing to the promotion and spread of this extremely effective cancer therapy. The development study of four dimensional computer tomography (4D-CT) and high sensitivity/resolution positron emission tomography (PET) reached the stage in which prototype models were constructed and their performance was evaluated. The research project group on the health effects of low dose radiation, and space radiation protection group also had many accomplishments this year. In the former, animal experiments on the induction of cancer by 10MeV neutrons were completed, and the experiments with lower energy neutrons are now being planned. The research project on radiation genomics has determined many radiation-response genes, and effort continues for establishing so-called tailor made radiotherapy.

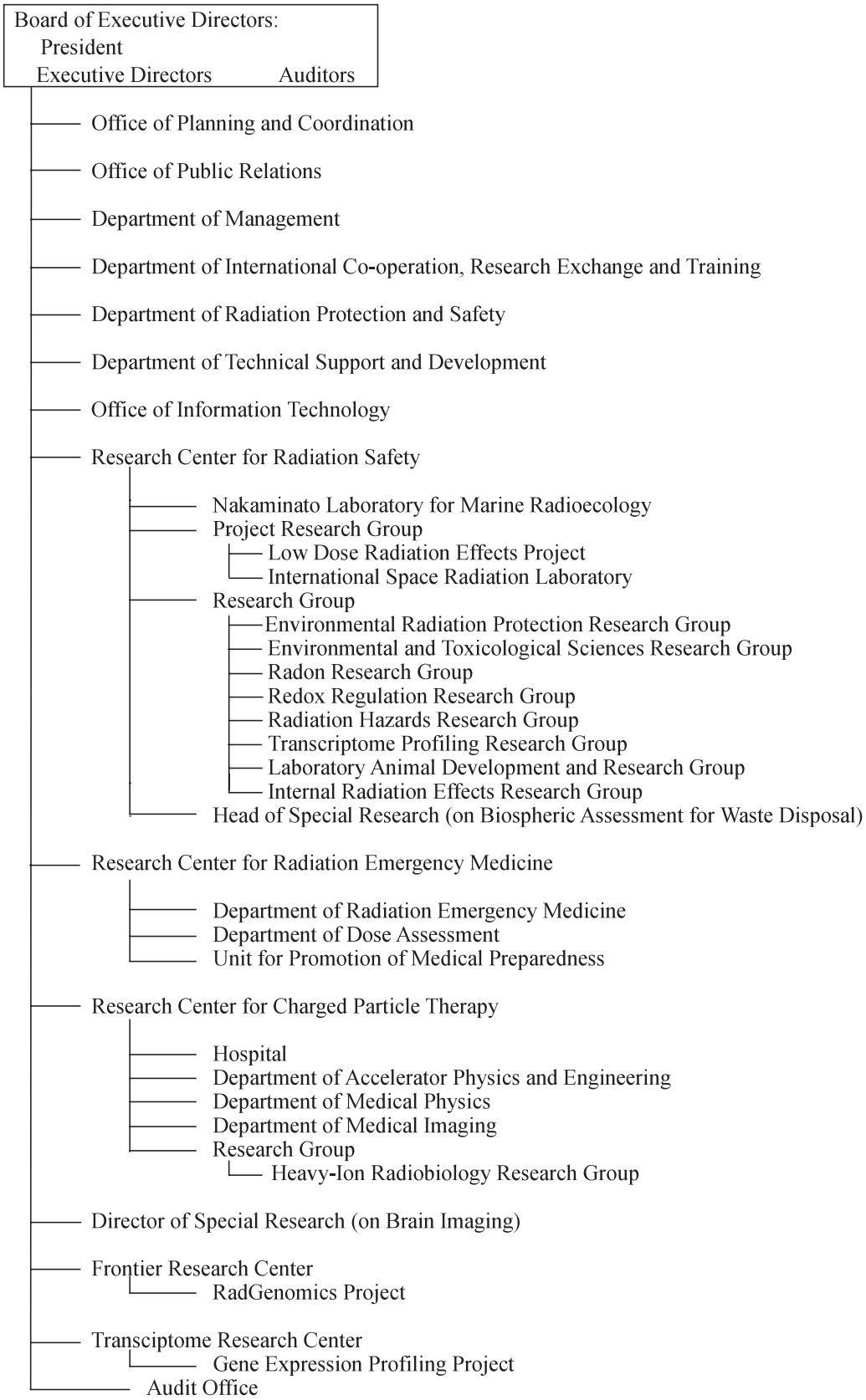
Regarding personnel, the executive director, Dr. Ozawa retired, and Dr. Miki moved to the Ministry of Education, Culture, Sports, Science and Technology. Seven stuff members also retired, 9 moved to other institutions, 4 group leaders and team leaders went to universities as professors or associate professors, and 25 new people were hired this year.

We look forward to reporting on the successful completion of the present mid-term plan and smooth start of the new plan in next year's Annual Report. While we exploit existing opportunities and meet current challenges, we will continue to prepare for future developments.

Sentaro Takahashi, Ph.D.
Executive Director

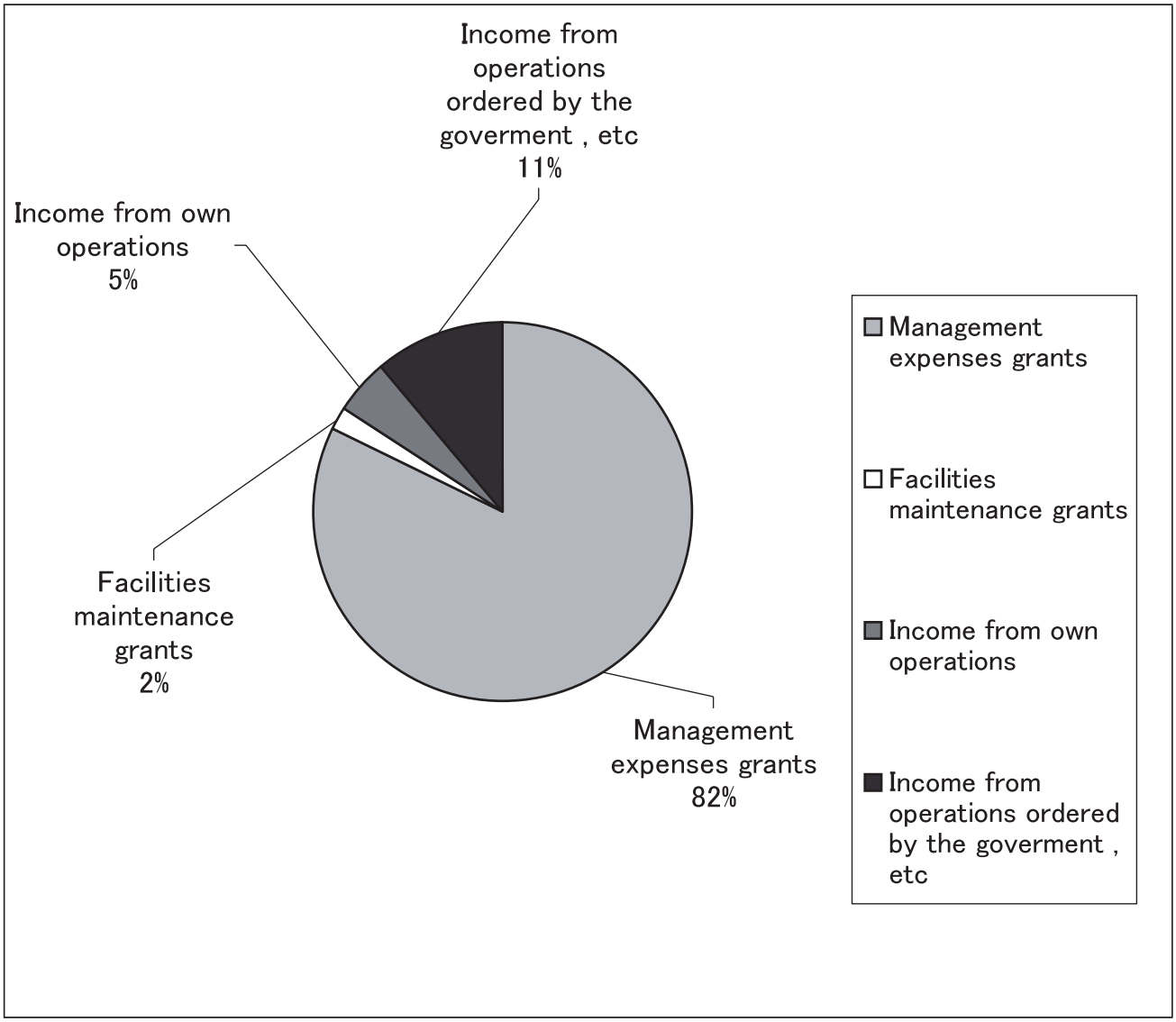
2. Organization Chart and Budget

(1) Organization



(2) Budget(2004.4～2005.3)

Total	16,428 million yen	%
Management expenses grants	13,520 million yen	82%
Facilities maintenance grants	310 million yen	2%
Income from own operations	761 million yen	5%
Income from operations ordered by the goverment , etc	1,837 million yen	11%



3. Research Center for Radiation Safety

Isamu Hayata, Ph.D.
Supervisory Director

Outline of Research Career:

Dr. Hayata worked at Roswell Park Memorial Institute in New York State as a research fellow for three years (1972-1975). He finished the doctoral course and received a D.Sc. from the Faculty of Science, Hokkaido University in 1976 for his cytogenetic study on the genesis of human chronic myelocytic leukemia. He started to work at NIRS in 1976. He was in the Department of Protection, Atomic Energy Commission, Fontenay-aux-Roses, France from 1981 to 1982. His major work areas at NIRS are 1) Cytogenetical studies on the genesis of radiation-induced mouse leukemias, 2) Development of cytogenetical methods and of automated systems to detect the effect of low dose radiation, 3) International collaborative studies on chromosome aberrations induced by natural radiation, 4) Multidisciplinary research and management of work under the Nuclear Cross-over Research Project in collaboration with six other national institutes, 5) Biodosimetry of persons who are accidentally exposed to radiation such as those in the JCO Tokaimura criticality accident, and 6) Networking of a chromosome analysis group on a national basis for emergency.

Objectives:

This Center coordinates various research spheres regarding radiation hazards and safety. Concentrating research resources into research activities for radiation safety, the Center aims at safely utilizing radiation through understanding the basic mechanisms of radiation effects on humans and other living organisms, evaluating the effects of low dose radiation on organisms, and contributing to related scientific fields. Development of advanced technologies, such as development of genetically controlled experimental animals and implementation of advanced measurement technology for ionizing radiation, is also an important objective of the Center. It holds an annual symposium and several workshops during the year inviting overseas researchers as well as Japanese researchers for promoting research work within the Center and for internationally contributing to the advancement of radiation safety. Support for regulatory authorities, governmental committees and international organizations is also provided by the Center. In addition to the research activities, training and education of students and young researchers are actively carried out.

Overview:

The Research Center for Radiation Safety consists of two project research groups, eight fundamental research groups, two research promotion sections, and the Nakaminato Laboratory for Marine Radioecology. The project research groups are PR-1) Low dose radiation effects research and PR-2) Biological and physical protection of man from space radiation. The fundamental research groups are FR-1) Establishment of an environmental radiation protection system against radioactive materials released into the environment (including studies on changes and mechanisms of radioactive substances in the ocean and their environmental pollution assessment at Nakaminato Laboratory), FR-2) Environmental and toxicological science research, FR-3) Studies on environmental radon and its biological effects, FR-4) Research on redox regulation against radiation, FR-5) Basic study of radiation hazards, FR-6) Analysis of gene networks in response to ionizing radiation, FR-7) Development of experimental animals for research on the biological effects of radiation, and FR-8) Studies on experimental carcinogenesis induced by plutonium compounds. Members of the Research Center for Radiation Safety also worked with the Research Center for Radiation Emergency Medicine and Research Center for Charged Particle Therapy.

The Ministry of Education, Culture, Sports, Science and Technology, Ministry of Environment, Agency for Natural Resources and Energy, and several other foundations supported the research of the Center.

There were 93 permanent research persons, 13

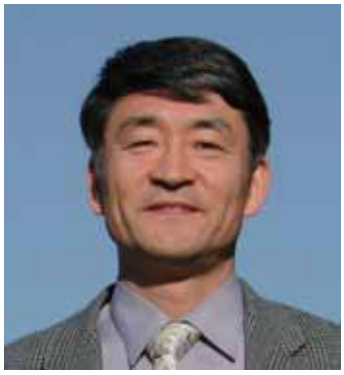
post doctoral fellows, 34 temporary staff members, and 98 part time assistants in this fiscal year. The leader of the International Space Radiation Project, Dr. Fujitaka, and Director of Special Research, Dr. Ogiu, retired on March 31, 2005. The leader of Environmental Radiation Protection Research Group, Dr. Ishigure moved to Nagoya University.

Construction of a new research building for the low dose radiation effects research project was completed and the members of the Project moved into it. The research building for late effects of radiation was renovated and members of plural research groups have now returned to their rooms in the building.

The fifth France-Japan workshop on radiobiology and imaging, JICA training course「Radiation Protection: From sources to effects」and NIRS seminar「Forefront of Radiation Protection」were held in NIRS on June 1-4, on November 9 to December 4, and on September 13, respectively. Staff of the Center participated in 10 meetings of international organizations such as IAEA, NEA (OECD) and ISO, in 59 international scientific conferences, and in 44 research collaboration meetings this fiscal year. There were about 70 overseas researchers who visited the Center and had discussions with researchers.

The number of original papers published in scientific journals in the past year was 178 in addition to many oral and poster presentations. Details of the scientific activities are described in each report shown below.

4. Research Center for Radiation Emergency Medicin



Kenzo Fujimoto, Ph.D.
Supervisory Director

Outline of Research:

Dr. Fujimoto graduated in Science from Kyoto University and obtained a Doctoral Degree in Engineering at the University of Tokyo. He has spent most of his career in studies on natural environmental radiation, especially for terrestrial gamma radiation and indoor radon. After the criticality accident at JCO in Tokai his major involvement shifted to dose estimation for radiation emergencies. He was at the Harvard School of Public Health as a visiting scientist from 1981 to 1982 and in the International Atomic Energy Agency as an environment protection specialist from 1990 to 1994. He also served as a lecturer at the University of Tokyo from 1989 to 1996. He is now Supervisory Director, Research Center for Radiation Emergency Medicine (since 2003), an International Editorial Adviser of the Journal of Radiological Protection and an Advisory Editorial Board Member of Nuclear Technology & Radiation Protection.

Contact Point: kenzofuj@nirs.go.jp

Objectives:

The statutory function of the Research Center for Radiation Emergency Medicine is the establishment of a solid system for dealing with a radiation emergency; the Research Center is assigned as the final stage radiation emergency medicine hospital within the nuclear disaster prevention plan of the Japanese government. In addition to our responsibility for the whole nation as it was before, the primary concern area has now been reduced to be the eastern part of Japan after the assignment of Hiroshima University as the other tertiary radiation emergency medicine hospital to cover the western part of Japan in March 2004.

Our required aims are as follows.

To accept radiation exposed victims who require specialized diagnosis and treatment

To dispatch a radiation emergency medical team to local emergency medical headquarters

To facilitate exchange of information, research activities, and human resources, by constructing networks in cooperation with other organizations who could deal with a radiation emergency

To maintain and reinforce an efficient radiation emergency medicine system under normal conditions

To promote technical development and research on radiation emergency medicine

Other objectives are research on radiation emergency medicine that is carried out as a research project involving scientists not only in this Research Center but also the Research Center for Radiation Safety. Details are given in other pages; only subjects are given here.

1. Pathologic physiology of high-dose exposure
2. Chelating agents for removing radionuclides
3. Development of systems for precise measurement and evaluation in emergencies
4. Mitigation of radiation injuries
5. Emergency response to environmental contamination

Overview

After the nuclear accident at Three Mile Island in 1979, the Central Disaster Prevention Council (CDPC) in the Prime Minister's office reinforced the emergency preparedness for nuclear power station emergency and issued a report "Urgent Disaster Countermeasures to be taken for Nuclear Facilities by Governmental Agencies" in July, 1979. In June 1980, the Nuclear Safety Commission (NSC) came up with a guideline entitled "Off-site Emergency Planning and Preparedness for Nuclear Power Plants." This guideline nominated NIRS as a tertiary radiation emergency hospital that serves as the final stage hospital for receiving heavily exposed or contaminated victims due to nuclear or radiological accidents. From January 2004 the Research Center has served as a liaison institution of WHO/REMPAN.

The Research Center carries out the following activities to maintain and enhance or strengthen the emergency preparedness system required as the tertiary radiation emergency hospital.

1) Network System

The primary goal is strengthening its institutional system to prepare for radiation emergencies by establishing three nation-wide network committees, for medicine, chromosome analysis as bio-dosimetry, and physical dosimetry.

1-1. NIRS Radiation Emergency Medicine Network

Council

This is a group of experts and medical organizations from which NIRS asks for help at the time of a nuclear disaster or a radiological accident. The cooperation involves dispatch of an expert in the specific field in an emergency, arrangement of acceptance of patients at medical facilities affiliated with the expert's organization, and provision of advice. Such collaboration is expected to reinforce the functions of NIRS. NIRS will call the Radiation Emergency Medicine Network Council to solicit cooperation when it is requested by authorities (or when NIRS thinks the necessity arises) to respond to radiation emergencies. We held a meeting in February 2005. An institutional cooperation agreement was signed between Kyorin University and NIRS in March 2005.

1-2. Chromosome Network Council

This council forms a network among specialists having dose evaluation capability based on chromosome analysis . Through this network, NIRS can be prepared for radiation emergencies, and also help maintain and enhance the technical standards of specialists involved by providing support and advice. We held meetings in June 2004 and February 2005.

1-3. Physical Dosimetry Network Council

This council is a network of experts in physical dose evaluation techniques. The network is expected to respond to emergencies through collaboration among experts in prompt and precise dose measurement systems. It is also responsible for accumulating dose evaluation technology, while fostering followers. We held meetings in July 2004 and March 2005.

1-4. Local Medicine Network Council

In Japan, medical systems are currently being constructed in accordance with disaster prevention plans of local governments that have nuclear facilities in their territories. Within the framework of each local nuclear disaster prevention plan, a specific collaboration system with NIRS is required to be set up, specifying the steps to be performed in the prompt transfer of patients from a site to a hospital, including radiation management and prevention at the hospital, and sending patients to other facilities when necessary. We organized meetings with prefectural government officers and medical doctors in primary and secondary radiation emergency hospitals in seven prefectures in fiscal year 2004.

2) Training

The primary goal is conducting educational training in radiation emergency medicine for medical professionals and disaster prevention personnel such as doctors and nurses involved in nuclear disaster medical care, emergency crews, and nuclear establishment employees. KIRAMS/NIRS Seminar on "Radiation Emergency Medical Preparedness" was conducted at NIRS for 24 medical professionals from Korea on 11-13 January 2005. The following training courses were regularly held in fiscal year 2004.

(A) Radiation emergency medicine course

The course was held three times with 20 participants in each course. More than 260 participants were trained so far. Many of them are working actively in primary or secondary medical emergency hospitals.

(B) Emergency rescue training course

The course was held three times with 30 participants in each course.

(C) Training course for the "whole body counter" measurement

3) Emergency Exercises

The primary goal is participating in nuclear disaster prevention training, seminars on medical response and other activities conducted by local governments to disseminate the information to the area. We participated in the nuclear disaster prevention training conducted by Ibaraki prefecture on 30 September 2004 and simulated emergency arrangements for a patient transferred to NIRS by helicopter. On 2 November 2004, the emergency monitoring exercise was conducted in the radiation emergency medicine facility with the participation of our medical staff and monitoring team (Fig.10).

4) Follow-up Studies

In addition to the activities required for the tertiary radiation emergency hospital, the Research Center for Radiation Emergency Medicine also conducts research work in a wide range of areas: medical care, radiation measurement and investigation, health physics, cytogenetics, and psychology. In addition, we study dose evaluation which facilitates decision-making in treatment methods, identification of radionuclides, treatment for high-dose exposure or reduction of high-dose exposure hazards, and rapid evaluation of population exposure. NIRS carries on follow-up clinics for the victims of thermonuclear explosion test on Bikini Atoll, patients with thorotrastosis and the remaining JCO accident victim who has survived.

4-1. Follow-up examination of the victims of Bikini nuclear test

During the nuclear test on Bikini Atoll on 1 March, 1954, 23 crew members (18 to 39 years old at the time) of the Dai-go Fukuryu-maru out of

Yaizu City, Shizuoka Prefecture, were exposed to radiation. This follow-up survey aims to examine the physical states of these patients over a long period of time to study late radiation injuries. The follow-up examinations that have been conducted for 50 years provide precious data. The mode of exposure was composite, and the estimated dose was 1.7 to 6.0 Gy. A physical checkup of still living survivors was conducted at Yaizu City General Hospital this year.

4-2. Follow-up examination of patients with thorotrastosis

Thorotrast is a radioactive contrast medium for angiography. The main constituent is thorium dioxide. A German company started sales in 1930. In Japan, the product was used from 1932 to 1945 for 10,000 to 20,000 patients, the majority of whom were killed in World War II. Thorotrast is deposited in the liver and spleen and causes internal radiation exposure over a long period of time. This follow-up examination estimates the amount of thorium deposited in surviving patients, investigates their clinical symptoms, analyzes the relationship between the deposited amount and malignant carcinogenesis, and elucidates the effects of long-term internal radiation exposure on human bodies.

5) Database

A database including the cases of radiation exposure on Bikini Atoll and cases of thorotrastosis is being constructed. Since radiation accidents are rare, the maximum amount of information must be collected from each accident and accumulated to help medical workers decide strategies to treat patients, and improve and establish therapeutic methods. Today, there are various databases on radiation accidents and their victims, but most are not accessible from other countries. Under the supervision of the World Health Organization (WHO), an international program called REMPAN (Radiation Emergency Medical Preparedness And Response) exchanges information on radiation accidents, including those in the database owned by the US REAC/TS (Radiation Emergency Assistance Center/Training Site). REMPAN has a collaborating center at Ulm University in Germany and manages a SEARCH database of patient information. It aims to construct an international database by registering cases that are attributable to the Chernobyl accident and other radiation accidents. The NIRS registered the Dai-go Fukuryu-maru accident in the SEARCH database. In addition, our center is constructing a database by collecting the medical data of the victims of radiation accidents and exchanging information with countries that have developed radiation accident medicine. In 2004, we obtained 80 data sets for acute exposure patients; 40 from Institute of Biophysics in Russia and 40 from Beijing Institute of Radiation Medicine in China.

6) International Cooperation (Fig.11)

(A) Korea Institute of Radiological and Medical Sciences (KIRAMS) and NIRS signed a Memorandum of Understanding in the fields of radiation emergency medicine and dose estimation in November 2004, and conducted the KIRAMS/NIRS Seminar on "Radiation Emergency Medical Preparedness" at NIRS under this memorandum in January 2005.

(B) Seven professionals from National Defense Medical Center and Atomic Energy Committee (Taiwan) visited us on 4 November 2004 and discussed on radiation emergency medicine with NIRS staff.

(C) Fourteen officers and specialists of emergency from Andes countries (Bolivia, Colombia, Ecuador and Venezuela) in South America visited NIRS on 3 February 2005. We presented our activities in lectures including case studies for radiation accidents and gave a technical tour in the radiation emergency medicine facility.

(D) Dr. M. Benderitter of Institut de Radioprotection et de Surete Nucleaire (IRSN) visited NIRS from France for a week in February 2005. He lectured on medical management of localized radiation exposure at the meeting of the Radiation Emergency Medicine Network Council.

Conducted by Ibaraki Prefecture
(30 September 2004)

Emergency monitoring training
(2 November 2004)

Fig.10. Radiation Emergency Exercise

KIRAMS/NIRS Seminar
(11-13 January 2005)

Visitors from Andes Countries
(3 February 2005)

Visitor from IRSN
(16-22 March 2005)

Fig.11. International Cooperation

5. Research Center for Charged Particle Therapyi

Hirohiko Tsujii, MD.
Supervisory Director

Overview:

The Research Center for Charged Particle Therapy has been carrying out medical practice and research using heavy ion beams generated from the HIMAC (Heavy Ion Medical Accelerator in Chiba) since 1994, as well as medical research on advanced diagnostic imaging techniques such as PET, MRI and CT. After clinical trials of carbon ion therapy had been carried out for various types of malignant tumors, the Center was successful in obtaining approval from the Ministry of Health, Welfare and Labor for its "Highly Advanced Medical Technology" in October 2003. The center offers the state-of-the-art therapy called "Charged Particle Therapy for Solid Tumors". Thus carbon ion therapy has meanwhile achieved for itself a solid place in general practice by accumulating the clinical experiences over a decade.

This year, as in previous years, a number of committees were organized to evaluate the eligibility of each patient to be treated with carbon ion therapy and to scientifically and ethically review the treatment results. The Multi-user utilization of the HIMAC has been successfully implemented for medical, biological and physics research. The biggest event of this year, the 10th Anniversary of the HIMAC was celebrated in July 2004.

Progress of Research:

1) Medical Practice and Research on Carbon Ion Therapy

The Center Hospital is unique in its position as a medical practice/research hospital even on a national scale, specialized in radiation therapy and diagnosis. It is equipped with a range of state-of-the-art diagnostic imaging equipment including CT, MRI, PET-CT, US and endoscopies on a scale and level well above those of a general hospital. The hospital has been also designated as Japan's Third Medical Facility functioning as a core medical place to provide emergency services for accidental radiation exposures. It has been actively engaged in establishing and maintaining a service outfit in readiness for radiation exposure accidents, jointly with the Research Center for Radiation Emergency Medicine. To fulfill the above role, the hospital has both outpatient and inpatient wards as well as a full complement of pharmacies and clinical laboratories to well above normal standards.

An extensive amount of medical information has been obtained from the clinical trials on carbon ion radiotherapy including diagnostic images and medical records. In an effort to achieve higher levels of sophistication, these clinical data has been systematically classified and standardized to establish data access methods based on a unified system of data management. This year, medical records and diagnostic images stored in the data-servers were first put into practice as an on-line service for evaluation of staging diagnosis and quantitative and objective assessment of the efficacy and side effects after treatment.

2) Clinical Results of Carbon Ion Therapy

As of February 2005, the number of patients registered was in excess of 2,000. Experiences to date indicate that carbon beam therapy is advantageous, ①by histology, to adenocarcinoma, adenoid cystic carcinoma and sarcoma (malignant melanoma and bone/soft-tissue sarcoma); ②by tumor origin, to skull base, head and neck, lung, liver, prostate, bone/soft tissue, and pelvis; ③by location, to tumors located in the vicinity of critical organs such as the eye, spinal chord, digestive tract with irregular shape. Tumors that infiltrate or originate in the digestive tract, however, appeared difficult to control with carbon ions alone.

The patient load continues to rise incessantly year after year, due not only to the way in which the irradiation techniques have been established but also as a result of the significant reduction in the number of fractions per patient. There is a rationale to justify the use of short-course RT due to the superior dose localization and the unique biological property of carbon ions. This has been proved in treatment of early stage lung cancer and hepatoma, where the fraction number has been successfully reduced to 1-4 fractions in 1-7 days. Even in prostate cancer and bone/soft tissue tumor, treatment has been performed using 16 to 20 fractions in 4 to 5 weeks with acceptable morbidity, roughly half the number of fractions required in the case of other conventional radiotherapy. This means that the facility can be operated more efficiently, offering treatment for a larger number of patients than is possible with other modalities over the same period of time. Currently, the number of irradiation sessions per patient averages 13 fractions over three weeks in carbon ion therapy.

Papers have been published on original work with lung cancer, liver cancer, head and neck cancer, and bone/soft tissue tumor. In addition, there have also been growing numbers of invitations for special lectures as well as interviews by the media.

3) Development of a Compact Accelerator :

The Department of Accelerator Physics and Engineering is in charge of regular operations, maintenance, and management of the HIMAC, which has been used for carbon ion therapy in the daytime and for biological and physics research at night. Research has been focused on the basic principle and technology of heavy ion accelerators and on the development of methodologies and devices for cancer therapy. During this fiscal year, major activities have been concentrated on R&D of a compact carbon therapy accelerator.

The injector system of the compact accelerator consists of two 10GHz permanent magnet ECR sources, RFQ linac, and IH type drift tube linac. Operation frequencies of both linacs were chosen at the same value of 200 MHz. APF (Alternating Phase Focusing) structure was adopted for both transverse and longitudinal focusing in the IH linac. The APF-IH linac structure has long been studied theoretically and experimentally because of its high energy efficiency and easiness in operation. This type of linac, however, has never been put to practical use since time-consuming model studies are required to fix cavity geometry. The RFQ and APF-IH linacs will be installed at NIRS by the end of 2005, and beam tests will be done using the 10 GHz permanent magnet ECR source. A cobalt based amorphous core was found to have high permeability approximately twice that of a typical magnetic alloy, FINEMET, core. We have developed this type of amorphous core to be used in the RF cavity for a synchrotron. Due to its excellent RF characteristics of high shunt impedance and low quality factor, a cobalt-based amorphous-core loaded RF cavity covers a wide frequency range without any tuning elements to keep its high-energy efficiency. The beam delivery system of this machine should be designed to realize a residual range of 250 mm with the carbon energy of 400 MeV/u and an irradiation-field diameter of 220 mm at maximum with a port length of 5.5 m. For this purpose, a spiral-wobbler method has been proposed.

4) Physical and Biological Aspects of Heavy Charged Particles

The Department of Medical Physics is researching physical aspects of carbon ion therapy and PET scans and is responsible for services supporting them with other departments of the Center. The Department has been supporting clinical trials on heavy ion therapy including the quality assurance (QA) and quality control (QC) services, treatment planning, and fabrication of treatment devices such as compensating filters and patient collimators employed for carbon ion therapy. These have been done in collaboration with the Hospital and the Department of Accelerator Physics and Engineering. This year significant progress has been made in the customization of devices to suit an increased number of patients.

Heavy-ion Radiobiology Research Group has done studies to evaluate the optimum fractionation regimen for carbon ion therapy and to develop methods for identifying the types of tumors suited to carbon ion radiotherapy. In the study on radiation-induced chromosome aberrations in patients who received radiotherapy, no difference was found between carbon ions and x-rays. It was found that in patients with malignant melanoma the anti-tumor effect was enhanced with combined use of Lonidamine, a mitochondria-targeted drug. In the animal study on memory disturbance after irradiation, correlation was found between the degree of disturbance and the brain weight. It was found that beer had a protective effect against radiation and this anti-radiation effect was due to a pseudo-uridine microchemistry.

The Group has also engaged in an inter-facility comparative study by investigating biological effects between the beams used at the HIMAC and GSI.

5) Medical Imaging Research

Medical imaging research has been directed to the promotion of cancer radiotherapy and biological

function imaging with respect to oncology and neurosciences. This year, a preparatory study was aimed at next year's acquisition of a COE grant-in-aid in the field of molecular imaging technology for visualizing biological functions in the body.

As in previous years, a variety of multi-purpose automatic synthesizers and control apparatuses for manufacturing and synthesizing a diverse range of radioactive drugs have been developed, and methods for their use have been tested and proven. Various kinds of molecular probes have been developed for the purpose of imaging hypoxic cells, heart muscles and a particular part of intracerebral activity. In the research activities related to diagnostic machines, the major parts of a 4-D X-ray CT machine and a next-generation PET system were successfully developed.

Regarding the research on MRI (Magnetic Resonance Imaging), the achievements include developing dynamic MRI to demonstrate changes in the pharmacokinetics of Gd-DTPA in experimental tumors after charged particle irradiation, 3-D T1 imaging for quantitative evaluation of articular cartilage degeneration, MRS (magnetic resonance spectroscopy) for diagnosis of temporal lobe epilepsy, and proton MRI method for detecting a small degree of non-uniformity in dialysate flow in a hollow-fiber dialyzer.

6) Medical Exposure Assessment

To determine the "risk of cancer from diagnostic x-rays," estimation of exposure dose has been carried out on Japanese patients subjected to diagnostic examinations. This year, measurements of the exposure dose were performed on patients who had MDCT (Multi-Detector CT) and dental x-ray pictures as well as on patients and operators during IVR (Interventional Radiology).

7) Brain Imaging Project

The research has been focused on mental disorders and functional brain imaging using PET and MRI. In the study of the mechanism of mental disorders, the abnormal neurotransmission in the brain appeared to be related to mental disorders such as schizophrenia and mood disorders. It is known that some drugs for treatment of mental disorders work on the receptor. It was found that the receptor occupancy could be measured by antipsychotics and antidepressants in PET scans. It is essential to develop new promising ligands for PET research. In this regard, we have developed new radioligands for NMDA receptors and peripheral benzodiazepine receptors as an imaging tool of glial cells in the brain.

6. Brain Imaging Project

Tetsuya Suhara, MD
Director of Special Research,
Brain Imaging Project

Outline of Research Career:

Dr. Suhara received the Ph.D. from Jikei University School of Medicine in 1991 for his study of dopamine receptor binding in vivo. He has worked at NIRS since 1989. In 1992-1993 he studied in the PET group of Department of Clinical Neuroscience, Karolinska Hospital, Sweden. He has researched on brain functional imaging for a long period. He has served as visiting professor, Department of Neuropsychiatry of Nippon Medical School since 2004.

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Objectives:

Our research group has been focusing on mental disorders and functional brain imaging using PET (Positron Emission Tomography), fMRI (functional Magnetic Resonance Imaging) and MRI.

1) The mechanism of mental disorders

Abnormal neurotransmissions in the brain were suggested to be related to mental disorders such as schizophrenia and mood disorder. We have been exploring the underlying molecular mechanism by measuring such neurotransmissions as dopamine and serotonin using in vivo PET imaging with a variety of radiotracers such as [^{11}C] SCH 23390, [^{11}C]FLB 457 and [^{11}C]DASB.

2) Psychopharmacological research

Some drugs for treatment of mental disorders work on the receptor or transporter in the brain. Using PET, the receptor occupancy can be measured. We have been investigating the receptor occupancy by antipsychotics and antidepressants.

3) Neuroscience research

We aim to facilitate understanding of the systematic relationship between cortical dopamine functions and the neuronal network responsible for higher cognitive functions by conducting PET scans and by comparing the results between healthy controls and patients with mental disorders, and between humans and animals.

4) Radioligand development

It is essential to develop new ligands for PET research. We have been developing promising radioligands for NMDA receptors and peripheral benzodiazepine receptors as an imaging tool of glial cells in the brain.

5) Software development

We have written software for the compartment analysis of PET data, and for placing the ROI automatically.

Progress of Research:

1) The fMRI and the cortical dopamine D_2 receptor occupancy by antipsychotics

Using pharmacological fMRI, we demonstrated that acute treatments of dopamine D_2 receptor antagonists with occupancy of about 60-70% of central dopamine D_2 receptors attenuated the activation in the amygdale, hippocampus, and anterior cingulate cortex in response to emotional stimuli. Given these regions are relatively rich in D_2 receptors besides striatum, our findings suggest that D_2 receptors play a crucial role in emotional processing.

2) In vivo measurement of peripheral benzodiazepine receptor in schizophrenia

We are performing clinical PET scans using [^{11}C]DAA1106 for 5 patients with schizophrenia. Due to the present small number of subjects, additional studies will be required.

3) Presynaptic dopaminergic activity in patients with schizophrenia

From the perspective of both the characteristics of [^{11}C]PE2I, a novel PET tracer of dopamine transporter which is more exclusively selective to DAT than conventional DAT tracers, and our unique technique for producing a high quality of radiotracer, we can expect to quantify DAT in

extrastriatal regions as well as the striatum. Particularly, researchers have been so far paid little attention to presynaptic dopaminergic function in vivo. So, we are trying to quantify the dopamine transporter (DAT) of the striatum and extra-striatal regions in patients with schizophrenia. We are performing clinical PET scans of 12 healthy volunteers and 3 schizophrenic patients using [^{11}C]PE2I. Due to the present small number of subjects, the studies will need to be continued.

4) Quantitative analysis of [11C]verapamil

[^{11}C]verapamil has been used for the in vivo imaging of P-glycoprotein function in the blood-brain barrier by PET. We have validated a quantification method of [^{11}C]verapamil transfer from plasma to brain with a graphical analysis of integration plot.

5) Relation of dopamine nervous system to mechanism of nicotine dependence

We explored the brain areas involved in nicotine-craving using PET. As a result, we showed that the magnitude of the craving correlated with changes of dopamine D1 receptors in the nucleus accumbens.

6) In vivo measurement of peripheral benzodiazepine receptor in dementia and mild cognitive impairment

We recently developed a novel radioligand for peripheral benzodiazepine receptor (PBR), an imaging tool for glial cells in the brain. We are measuring PBR in patients with dementia of Alzheimer type, mild cognitive dysfunction, and age-matched healthy volunteers using PET with [^{11}C]DAA1106.

Technical establishment of the combinational measurements between PET and microdialysis with conscious monkeys

We established a technique by which we can direct probes towards any regions in the monkey brain such as the cortical and subcortical areas referring to the corresponding CT scan coregistered with MRI. This method allowed us to sample extracellular neurotransmitters such as monoamine and amino acids from anywhere in the brain of awake monkeys during behavioral tasks and /or PET scanning.

Activation study with conscious monkeys- the neural system underlying the abstract operation

We recently investigated monkey brain activation responsible for joystick-controlled remote operation, including the prefrontal cortex, posterior parietal cortex and cerebellum, regardless of the rules governing moves of a joystick and shovel. Those areas may be engaged in the mental manipulation of an internal representation, in which case the brain activity may be parallel during remote operation even with different operational manners.

To address the above hypothesis, we measured regional cerebral blood flow of two monkeys during a dual-dial operation task in which the monkeys were required to control a shovel by manipulating dual dials, using PET with $H_2{}^{15}O$. Compared to unplanned movement of the dials, the prefrontal cortex, higher-ordered motor cortex, posterior parietal cortex and cerebellum were robustly active during the dial operation task, quite similar to the remote operation with a joystick.

The present study suggests that monkeys might be able to organize their abstract sequential operations accordingly, under respective rules, while understanding the nature of causal relationships, implying the existence of a relatively sophisticated representation system in the absence of language.

In vivo evaluation of the long-term changes in the presynaptic dopaminergic function following fetal mesencephalic cell transplantations to unilateral lesioned rats with 6-OHDA

Using PET with [^{11}C]PE2I, a tracer of the dopamine transporter, we evaluated the effect of a fetal mesencephalic transplantation on the expression of dopamine transporter (DAT). The fetal mesencephalic cells were transplanted into the striatum of unilateral 6-OHDA-lesioned rats. Repetitive PET scans with [^{11}C]PE2I were conducted before, and 2 and 4 weeks after the transplantation. Also, tyrosine hydroxylase (TH) immunohistological examinations were done. In the PET study, the binding potential of [^{11}C]PE2I increased 4 weeks after. The histological examination revealed the appearance of TH-positive cells with axons 2 and 4 weeks after the transplantation. Given the distribution of DA transporter only in the axon terminal of DA neurons, these results suggested that [^{11}C]PE2I binding reflected not only survival, but maturity and functioning of the transplanted cells.

Set-up of experimental system with a small monkey, marmoset as another animal model of higher cognitive function and the disorders

We are developing a marmoset's head-fixation device which can endure all types of movements in the awake condition to be used during the training and PET scanning. We are also developing one compatible with ultra-high field MRI use.

7. Frontier Research Center
RadGenomics Project

Hajime Murata, MD, Ph.D.
Supervisory Director

Outline of Research Career:

Dr. Murata obtained his Doctor of Medical Science degree from the Hokkaido University, School of Medicine in 1973. After he worked as a clinical fellow in the Hokkaido University Hospital, he was chosen Head of Division of Nuclear Medicine & Radiology, Tokyo Metropolitan Geriatric Hospital in 1974. From 1983 to 1997, he worked as the Director of the Division of Radiology, Toranomon Hospital. Dr. Murata was invited to NIRS as Director of the Research Center of Charged Particle Therapy in 1997 and served until 2003. Since 2001 he has been concurrently the Supervisory Director of the Frontier Research Center. His research themes have been the patho-physiological analysis of myocardial disorders with nuclear cardiology and a new strategy for cancer treatment by radiotherapy using heavy ion beams.

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Takashi Imai, Ph.D.
Director

Outline of Research Career:

Dr. Imai received a Ph.D. from the University of Tsukuba in 1986. Following a fellowship from the Japan Society for the Promotion of Science for Japanese Junior Scientists at the Institute of Applied Biochemistry, University of Tsukuba, he joined the Tsukuba Life Science center at the Institute of Physical and Chemical Research (RIKEN). From 1988 to 1989, he worked at the Department of Genetics, Washington University Medical School (St. Louis, Missouri, USA) as a visiting research associate. Here Professor Maynard Olson sparked his interest in the human genome project. After joining The Cancer Institute, (Japanese Foundation for Cancer Research) in 1991, Dr. Imai worked on cancer and population genomics. Since 1994 he has been a senior researcher at NIRS. In 2001 he was named project leader of the RadGenomics Project.

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Objectives:

Cancer patients vary considerably in normal tissue reactions after radiotherapy. Several observations have indicated that certain genetic factors play important roles in this variability. It has been hypothesized that the clinical radiosensitivity of normal tissues should be regarded as a so-called complex trait dependent on the cumulative effect of many minor genetic determinants. Thus single nucleotide polymorphisms (SNPs) on certain genes may somehow associate with the severity of normal tissue reactions after radiotherapy. It is important to uncover a molecular basis underlying radiation sensitivity of normal tissues for further investigation of more complex characters of cancer cells. In this study we have searched for polymorphisms that are associated with normal tissue radiation sensitivity of various cancer patients. We believe the results will open a way for achieving individual-oriented radiotherapy with high-therapeutic ratio.

The human genome contains approximately 3 billion base pairs, and the sequence differs at more than 3 million sites among the human population. It has been ascertained that this difference (genetic polymorphism) in base sequences determines human diversity - not only apparent diversity such as appearance and height but also internal diversity including responsiveness to alcohol, pollen allergen, or susceptibility to disease. Individual variance in susceptibility to radiation is believed to be closely associated with genetic variance.

The outcome of this research will allow us to identify any correlations between an individual DNA sequence and their radiation susceptibility (treatment efficiency and adverse effects). If a correlation is found, the DNA sequence in blood cells will enable the prediction of an individual's radiation susceptibility. Therefore, it will be possible to provide information to determine treatment protocols, such as the irradiation method and the avoidance of

adverse effects, leading to personalized radiotherapy. The project will also contribute to future research on the molecular mechanisms of radiation sensitivity in humans.

Progress of Research

1) Patients

The 1,531 patients who were registered between 2001 and 2005 included 676 breast cancer patients, 212 cervical cancer patients, 180 prostate cancer patients, and 240 head and neck cancer patients. Normal tissue reactions until the 3rd month after completion of the treatment were graded according to the National Cancer Institute-Common Toxicity Criteria (NCI/CTC). Late effects on normal tissues were graded according to the Radiation Therapy Oncology Group/ the European Organization for Research and Treatment of Cancer (RTOG/EORTC) scoring system and the Late Effects of Normal Tissues-Subjective, Objective, Management and Analytic (LENT-SOMA) scoring system. Patients were divided into two groups (radiosensitive and radioresistant) according to the grades determined by the above scoring systems.

2) Polymorphisms in genes related to adverse effects after radiotherapy

This study involves a candidate gene approach with gene selection based on in vitro screening data from human cell lines and animal models. Radiosensitivity was measured in 32 different cultured human cancer cell lines and analyzed for gene expression using microarrays. In addition, *in vivo* gene expression profiles of mouse strains with different radiation sensitivity have been analyzed (See the following topics). The genes were then selected using three criteria: (i) Genes with expression profiles showing statistically significant association with cellular radiation sensitivity; (ii) Genes which are induced or suppressed by irradiation; (iii) Known radiosensitivity-related genes. A total of 108 candidate genes that met at least one of the above criteria have been selected. Information on SNPs for the candidate genes was obtained from the Japanese SNP database (http://snp.ims.u-tokyo.ac.jp/) and the dbSNP database (http://www. ncbi.nlm.nih.gov/SNP/). Typing of the SNPs was carried out using blood white cells and the allele-specific termination of primer extension method using a MALDI-TOF mass spectrometer. Six hundred and forty three SNPs were typed for the 108 candidate genes from 346 individuals consisting of 218 breast cancer patients, 57 ovarian cancer patients and 71 prostate cancer patients. In the study of 284 patients with breast cancers, univariate analysis resulted in 25 SNP markers associated with early reaction of skin after irradiation with p-value<0.05. Different sets of 22 SNP markers were associated with 3 months or 6 months late effects. We constructed "Predictive score" using multi SNP markers selected through our unique statistical method based on selection criteria which maximize AUC-ROC. Fifteen, eighteen, or fourteen SNP markers were identified to predict adverse effects of skin within 3 months, at 3 months, or 6 months, respectively. This study implies that analysis of multiple SNPs on adequately selected candidate genes might be specifically suitable for identification of genetic determinants of radiation sensitivity.

3) Different radiation susceptibility among five strains of mice detected by a skin reaction

Published reports about skin reactions to radiotherapy, especially among breastcancer patients, suggest that there are interindividual differences in the normal tissue response, and genetic factors are thought to be involved in this variation. An analysis of murine strain differences may reveal the mechanism of genetic factors in the extent of normal tissue damage from irradiation for several endpoints. The variation in the radiation susceptibility was observed when the skin of mice from strains A/J, C3H/HeMs, C57BL/6J, C.B.17/Icr-scid and C3H-scid was irradiated with a single dose ranging from 10 to 60 Gy, using Cs-137 gamma rays. The active skin reaction of A/J mice lasted for months. C3H/HeMs mice showed dose-dependent skin damage, and consequently recovered to a state of mild damage within 40 days after local irradiation. The time course of the response in C57BL/6J mice was shorter than in A/J mice. The 2 strains of scid mice exhibited severe damage after irradiation at any dose from 20 to 50 Gy, and did not show any dose dependency. The variation between murine strains in macroscopic and histopathological changes in skin during the progression and resolution of damage caused by irradiation suggests an inter-strain variation in the expression of genes involved in injury, apoptosis, repair, and remodeling.

4) Fractionated irradiation augments inter-strain variation of skin reactions among three strains of mice

The multifraction regimens commonly used in conventional clinical radiotherapy are largely based on radiobiological experiments. However, no experimental reports on skin reactions focusing on inter-strain differences have displayed clinical relevance to the fractionated dose schedule. In this study, mice of inbred strains A/J, C57BL/6J, and C3H/HeMs were used to reveal inter-strain difference after multifractionated irradiation.

Irradiation was performed daily at graded doses of 30-60 Gy total doses, with 10 fractions of 3-6 Gy. Acute skin reactions following irradiation were scored for 50 days after irradiation. Dividing a dose into a number of fractions obviously spared skin damage in the three strains of mice. No mouse exhibited a skin damage score more than 1.5, while single dose irradiation resulted in skin damage scores up to 3. The three different strains, however, showed varying susceptibility to fractionated irradiation within the range under 1.5. C3H/HeMs did not display any skin reaction after irradiation with 40 Gy total dose, while C57BL/6J and A/J demonstrated various skin reactions. Different latent periods of damage were also observed among the strains after irradiation at each dose. Our data suggest that genetic factors cause obvious variations in severity of damage and latent period after fractionated irradiation.

5) Strain dependent differences in a histological study of CD44 and collagen fibers with an expression analysis of inflammatory response-related genes in irradiated murine lung

Using a mouse model, we investigated the mechanisms of heterogeneity in response to ionizing radiation in this research. C57BL/6J and C3H/HeMs mice were irradiated with gamma rays at 10 and 20 Gy. The animals were sacrificed at times corresponding to the latent period, the pneumonic phase, and the start of the fibrotic phase for histological investigation. Small areas of fibrosis initially appeared in C57BL/6J mice at 4 weeks postirradiation with 20 Gy, whereas small inflammatory lesions appeared at 4 and 8 weeks after 20 and 10 Gy, respectively. The alveoli septa were thickened by an infiltration of inflammatory cells, and alveoli were obliterated in lungs from C57BL/6J mice after 20 Gy irradiation. At 24 hours and from 2 to 4 weeks postirradiation, fourfold more CD44 positive cells had accumulated in the lungs of C3H/HeMs than in C57BL/6J mice. Hyaluronan accumulated 12 hours after irradiation, and the rapid resolution was achieved within 2 weeks in the lungs in both strains of mice. C57BL/6J mice lungs accumulated dense collagen at 8 weeks. Quantitative RT-PCR assay was performed for several genes selected by cDNA microarray analysis. The expression of several genes, such as Cap1, Il18, Mmp12, Per3, Ltf, Ifi202a, and Rad51ap1 showed strain-dependent variances. In conclusion, a histological investigation suggested that C3H/HeMs mice were able to induce a more rapid clearance of matrix after irradiation than C57BL/6J mice. The expression analysis showed that several genes are potentially involved in interstrain differences in inflammatory response causing radiation-induced lung fibrosis.

6) Radiosensitivity of peripheral blood lymphocytes obtained from patients with cancers of the breast, head and neck or cervix as determined with a micronucleus assay

The in vitro radiation sensitivities of peripheral blood lymphocytes obtained from 48 normal females and 168 female cancer patients were measured with the cytokinesis-blocking micronucleus assay. Cancer patients group had significantly higher mean baseline micronucleus frequency than normal healthy controls. Breast cancer patients were more radiosensitive than normal individuals. Cervical cancer cases were less radiation sensitive than normal subjects. The relative lack of radiation sensitivity in cervical-cancer cases could be due to modification of the radiosensitivity of patients' immune-responsible cells by human papillomaviruses infection. Normal individuals and cancer patients were classified according to their radiation sensitivity which was evaluated with the radiation-induced micronucleus frequencies. Such a classification will be an important initial step to characterize the radiosensitive, radioresistant, or cancer-prone individuals using specific SNP typing.

Major publications:

1) Y. Matsui, M. Gotou, M. Iwakawa, T. Asano, T. Kanmochi, T. Imai, T. Ochiai: Modified radiosensitivity of pancreatic cancer xenografts by farnesyl protein transferase inhibitor and MEK inhibitor., *Oncol. Rep.,* 10, 1525-1528, 2003
2) Y. Matsui, T. Asano, T. Kanmochi, M. Iwakawa, T. Imai, T. Ochiai: Effects of carbon-ion beams on human pancreatic cancer cell lines that differ in genetic status., *Am. J. Clin. Oncol.,* 27, 24-28, 2004
3) M. Iwakawa, S. Noda, T. Oota, C. Kitazawa, H. Tanaka, A. Tsuji, A. Ishikawa, T. Imai: Strain dependent differences in a histological study of CD44 and collagen fibers with expression analysis of inflammatory response related genes in irradiated murine lung., *J. Radiat. Res.,* 45(3): 423-433, 2004
4) T. Oota, M. Iwakawa, C. Kitazawa, S. Noda, M. Yang, M. Gotou, H. Tanaka, Y. Harada, T. Imai: Fractionated irradiation augments inter-strain variation of skin reactions among three strains of mice., *J. Radiat. Res.,* 45(4): 515-519, 2004
5) S. Ban, C. Konomi, M. Iwakawa, S. Yamada, T. Ohno, H. Tsuji, S. Noda, Y. Matsui, Y. Harada, J. B. Cologne, T. Imai: Radiosensitivity of Peripheral Blood Lymphocytes obtained from Patients with Cancers of the Breast, Head & Neck or Cervix as Determined with a Micronucleus Assay., *J. Radiat. Res.,* 45 (4): 535-541, 2004

8. Transcriptome Research Center Gene Expression Profilng Project

Masumi Abe, Ph.D.
Supervisory Director

Outline of Research Career:

MS Molecular Biology, Hiroshima Univ, 1983. PhD Molecular Biology, Hokkaido Univ Faculty of Science, 1993

Dr Abe first joined the Radiation Effect Research Foundation in Nagasaki, Japan and studied the mechanism of VDJ recombination in immunoglobulin and T-cell receptor genes. His research group found that the SCID mutant mouse
is sensitive to ionizing radiation, enabling them to determine the human gene locus corresponding to the SCID mutation in mice whose aberration in VDJ recombination had been well known. Finally they identified DNA-PKcs as the gene responsible for the SCID mutation by detecting a nonsense mutation in the C-terminal region of the open reading frame. Six years ago, the group began taking a genome-wide approach to research. They developed a new technology for gene expression profiling called HiCEP (High Coverage Gene Expression Profiling) and in Nov 2003 launched the Transcriptome Research Center.

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Objectives:

The Transcriptome Research Center was established on November 1, 2003 to carry out systematic and collaborative research in the field of transcriptome analysis by means of a newly developed technology, HiCEP.

Whole genome sequencing has been completed for several species and now there are transcriptome and proteome projects all over the world. Mutant studies have been the standard approach in this area despite severe

limitations such as lethality and the existence of paralogues.

Hybridization-based technology is usually used for transcriptome analysis, but it has serious problems with coverage, sensitivity and reproducibility. These problems are especially acute in the analysis of low-abundance

transcripts. HiCEP is designed to overcome these limitations. HiCEP is basically a tool for discriminating between a huge number of DNA molecules precisely, and therefore is applicable to several other important analyses such as rapid restriction enzyme mapping of the genome, comprehensive analysis of methylation in the genome for epigenetic studies and comprehensive analysis of transcription regulation elements like ChIP-on-Chip. The objective of the Transcriptome Research Center is the further improvement of HiCEP and its application to a variety of life-science fields. We also want to analyze the relationship between gene expression and function by means of HiCEP and RNAi. We are confident that we can avoid the difficulties of mutant studies.

Overview:

The center contains a projective research and promotion office (including administrative activity) and is supervised by the Supervisory Director, Dr M Abe. There are three research groups led by Ryoko Araki, Toshiyuki Saitoh and Akira Nifuji. The first group focuses on developing and improving HiCEP technology to increase throughput and decrease the required amount of starting material. The group is also working on isolating the genes responsible for re-programming the genome, and preparing gene knockout cell lines and mouse strains which are needed for transcriptome analysis. The second group focuses on developing bioinformatics tools. Because HiCEP produces massive amounts of output, rapid analysis is crucial. This group is developing a web site by which we can release gene expression profiling data and users can register data collected by HiCEP analysis. The third group is developing methods for large-scale functional analysis of genes. All transcriptome analysis methods have the limitation that they can not identify the responsible gene. Further study in combination with transcriptome analysis and massive functional analysis such as RNAi is needed to meet this goal.

The current capabilities of HiCEP are as follows.

1) Novel transcripts including non-coding transcripts are detectable, because no sequence information is required for the analysis.
2) It is applicable to any species, even newly discovered species.
3) Its coverage over whole transcripts is approximately 70%.
4) 1.2-fold differences in gene expression can be discriminated.
5) Its sensitivity is equal to that of the RT-PCR technique.

Progress of Research:

1) A high throughput system

This year we developed a high-throughput version of HiCEP and built a peak database that will largely obviate the need for peak isolation and sequencing in HiCEP. We also developed a version of HiCEP that uses only a small amount of starting material.

The standard HiCEP protocol has excellent sensitivity and the ability to detect even unknown transcripts, but it takes one month to complete. Roughly two weeks are needed for the wet experiment part, including RNA prep, cDNA synthesis, HiCEP-specific processing, selective PCR and capillary electrophoresis, and two weeks for information analysis. To shorten the analysis time, we developed a new machine called HiCEPer that can automatically perform the reaction after RNA preparation. We also developed an RNA preparation system by which we can prepare 48 samples a day. We expect that this machine will improve the throughput of our system by up to 20-fold over the standard protocol performed by a lab worker. Fig.25 shows HiCEPer, which performs liquid handling, programmed temperature shifting using 96 well blocks and DNA handling with magnetic beads. Results of an analysis with HiCEPer are shown in Fig.26, showing its high reproducibility. As a check, we carried out simultaneous reactions over 8, 12, 48 and 96 wells, and got good results equivalent to those obtained by hand. Even using the high throughput protocol, we could detect 1.2-fold expression differences.

There is still room for improvement in the development of HiCEPer. It is not yet reliable enough to leave it unattended; sometimes it fails to complete a step. But we are confident we can correct this problem

Fig.25. One 96-well plate / 3 days is possible for HiCEPer

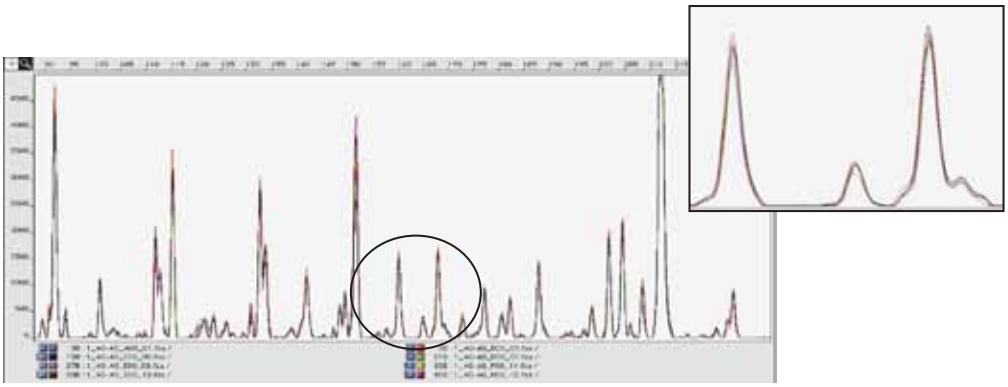

Fig.26.Reproducibility of HiCEP reaction with HiCEPer

Using traditional AFLP, more than 50% of the detected peaks are false positives. Furthermore, a false-positive peak may overlap with a real peak, preventing us from measuring the expression of each transcript precisely or isolating peaks of interest easily. We improved the selective PCR primers in the AFLP procedure and fine tuned the PCR conditions and were able to reduce the false-positive rate to less than 5%, which enables us to assign each peak to a transcript unequivocally. Consequently there is no need for isolation after HiCEP analysis if we have a database that gives the corresponding transcript for each peak. To examine the feasibility of this idea, we built such a peak database for the mouse E14 (embryonic stem) cell line. A pattern of E14 peaks is shown in Fig.27. We confirmed that the peak database could be used for other mouse ES cell lines. Approximately 3,000 peaks were detected in E14. 52% of them were cloned and their sequences determined to assign each peak to a registered transcript or a specific region in the genome. Approximately 2,000 of them turned out to be novel transcripts. The experience of constructing this peak database will help us to prepare peak databases for other cell lineages and species more quickly.

2) Reducing the necessary amount of starting material

Originally 1-2 micrograms of mRNA, equivalent to 50-100 micrograms of total RNA, was needed for HiCEP analysis. For mammals, that is approximately 107 cells. The preparation of such a large amount of RNA is feasible only in extraordinary cases such as when using in vitro cultured cells. Usually only a smaller amount of RNA fraction is available. We improved the HiCEP method to work with only 103-105 cells. To get this improvement, we removed the EtOH precipitation step from the reaction completely and introduced magnetic-bead technology for quantitative handling of nucleic acids. We also tried using RNA amplification. With this we could do gene expression profiling with 10 nanograms of total RNA, but it was labor-intensive and time-consuming, and prone to bias.

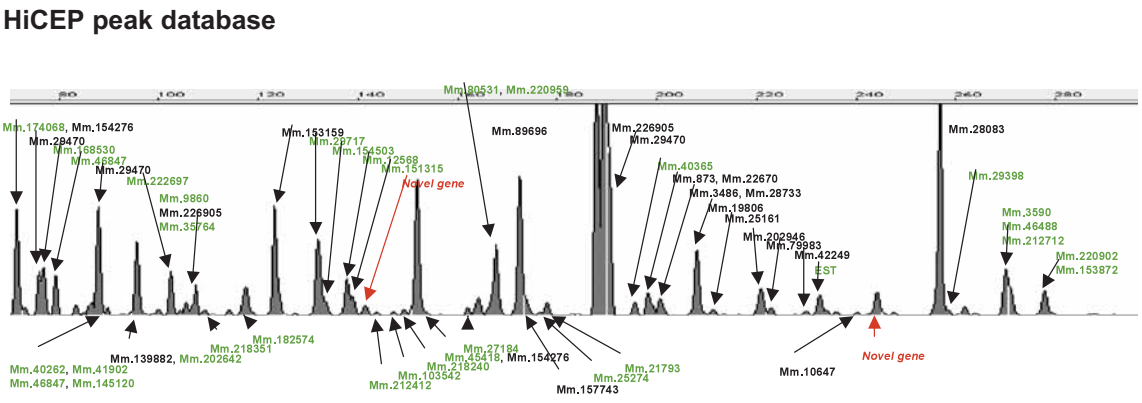

Fig.27.Example of HiCEP peak database using mouse embryonic stem cells, E14.

9. Development of Droplet-PIXE System for Environmental Monitoring Samples

Hitoshi Imaseki, PH.D.
Section head, Division of Technical
Support and Development

Outline of Research Career:

Dr. Imaseki received the Ph.D. from Tohoku University in 2005 on development of the droplet PIXE analyze system. He has been developing accelerator techniques for biological and environmental sciences, and working as the manager of the radiation irradiation facility and shared units in NIRS. Now he is engaged in developing the microbeam cell irradiation system and neutron exposure system based on electrostatic accelerator.

Objectives:

Behaviour of radionuclides in the environment and organisms has been investigated to evaluate the radiation effect on humans using stable isotopes with PIXE (particle induced x-ray emission) analysis at the PASTA (PIXE analysis System and tandem accelerator) facilities in NIRS. Since some of the environmental monitoring samples are in the liquid state, pre-treatment of the samples such as filtration, drying and solidification are necessary prior to the PIXE analysis. During sample preparation, there may be element loss due to sublimation or evaporation that must be corrected for in quantitative analysis. To avoid such problems, we have developed a suitable droplet-PIXE system. It is based on the following points: (i) development of equipment with good stability to supply a droplet of good reproducibility, (ii) optimisation of all equipment that includes a stable beam line (proton, 2.8MeV) and (iii) evaluation of irradiation dose for quantitative analysis. The system will be advantageous to many researchers since it is very simple and saves time during the sample preparation. However, there are some disadvantages in the detection range compared to conventional PIXE. Limits of detection with or without any chemical preparation and its superiority or advantages over other PIXE methods have been investigated by application of the droplet-PIXE system to a few case studies.

Progress of Research:

The PASTA facilities of NIRS are used for development of the droplet PIXE system. The accelerator is Tandetron (Model4117MC) manufactured by High Voltage Engineering Europa B.V. For PIXE, the facility provides three beam lines, which are a conventional-PIXE line, a micro beam scanning PIXE line and an in-air PIXE line.

The beam line has been optimized by modification of the existing in-air PIXE system for a droplet PIXE measurement including (a) suitable design of beam collimator, (b) suitable layout of the irradiation chamber, and (c) optimized attachment angle of the Si(Li)detector and final geometrical arrangement.

The system is composed of a pumping unit to generate constant size droplets, stable supply of a 2.8 MeV proton beam, and irradiation control for quantitative analysis. The system has several dripping modes to enhance performance compared to the static liquid target method. The features of the system are divided into three categories; (i) precise flow control system that corrects non-linearity of the pumping unit controller, (ii) by monitoring droplet size, image capture has been carried out using a CCD (charge-coupled device) camera, and (iii) a keyboard emulation program that enables utilization of commercial MCA (multi-channel pulse height analyzer) software and integration of a current integrator and beam shutter control and the MCA.

The ion chamber provides real time beam current measurement, and the same radiation dose can be given on each droplet. This is the most important point for the quantitative determination method using external standard. Since the ion chamber must be set between the sample and the beam collimator, the following points are taken into consideration; (i) the ion chamber must be as small as possible. (ii) Since the kapton foil of the collimator is exchanged frequently, the job should be easy and the attachment accuracy should be guaranteed. (iii) It has very good accuracy for repetition measurement

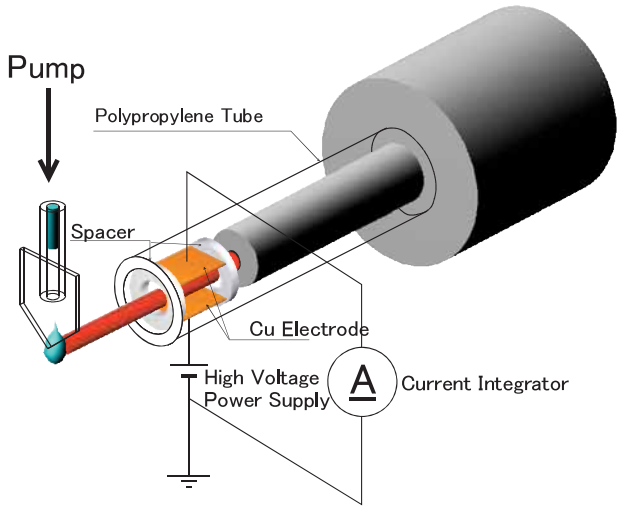

Fig.28. Schematic image of ion chamber for real-time beam current measurement

as a monitor of the amount of irradiation dose. Fig.28 is the concept drawing of the measuring method of irradiation dose using the ion chamber.

Analytical method should have sufficient accuracy not only for qualitative but also for quantitative results. To check this, the reliability has been examined for measured values and the stability. The results are as follows.
(i) Accumulated ionization current of the ion chamber and number of irradiation particles show a proportionality relation. (ii) In quantitative PIXE analysis, it is important to check the difference in X-ray production cross section of each element. (iii) Since fluorescence yield of X-rays emitted from the droplet depends on the size, the size of the droplet should be constant during measurement. The error originating in the beam size is less for a larger size than for a smaller size. (iv) Since penetrating range of an irradiation particle into a sample depends on the specific gravity (density), yield of induced X-rays changes due to density of the sample. Therefore, density of the sample must be considered in the quantitative analysis of the elements. The decreasing rate of the yield corresponds to increase in specific gravity of the sample. (v) When viscosity of a liquid sample becomes high, the yield of induced X-rays decreases. Since a detailed experiment has not been conducted regarding the change between viscosity and the yield of induced x-rays, no conclusion can be specified. (vi)When considering the detection efficiency of elements, the ionization current of the ion chamber and the influence of the density of the sample, quantitative analysis can be achieved. (vii) As some elements may evaporate or sublimate during long time irradiation, determination of the elemental concentration in a liquid sample using this equipment should be carried out within less than one hour. Detection limit of Fe with this system has been estimated to be 1 ppm.
Examples of practical use of the droplet PIXE system are described below.
1. Measurement of a liquid sample of very small quantity with the necessity of being stabilized for a long time: Human Cu, Zn- SOD (superoxide dismutase) has been selected as an example due to its importance in the field of biological materials, and the sample amount available is usually very small. Therefore, the Auto measurement mode has been applied. The quantity used for this measurement was about 90 l (three drops). Peaks of Cu and Zn were observed. A significant peak of Cd could not be identified contrary to the expectation.
2. Measurement of a living body sample where element concentration changes with time: This method measures the liquid while sample is always flowing, and it is expected that the element contained in a liquid changes with time. Flow measurement mode is followed. The drop was changed into the state of flowing at a fixed speed, and during fixed time (fixed in the range with size) measurement. In this paper, we selected healthy rat bile without giving any stress, such as irradiation of X-rays, to find change in the concentration of element with time. However, no change was noticed in the bile.
3. Measurement method recording variation of element concentration with time change: It is expected that the element contained in a liquid changes with time, and it has been proposed, as an example, in this case to obtain the measurement results of the process precisely in the form in which it is carried out at a time rate and also to notice any changes during the procedure. A capsule containing CuSO4 has been applied to this measurement. Water drop was dropped for the measurement of fixed time (at this time, the quantity to drop can also be set arbitrarily), and measurement will be resumed if the water drop of the same standard size is made. This is the Flow (Time) mode, which can have repeated measurement and all the measurement data can be saved in a separate file. Ten water drops were dropped for the measurement within 15 minutes. During this period, data were saved in another file which records the measurement result and time interval with a new file name for every stop. After a period of 20 minutes, the concentration of Cu was observed which indicates that concentration of Cu from the capsule started to dissolve slowly and after 120

minute, it was recorded that CuSO4 has been completely dissolved and released from the capsule. This measurement is completely automated. Fig.29 shows temporal response of element concentration.

The results obtained during development of a droplet PIXE system are summarized as follows.

(i) Detection limit obtained using this method was about 1 ppm (Fe).

(ii) To monitor beam current, the ion chamber was suitable for droplet PIXE analysis equipment.

(iii) Various measuring modes of equipment allowed a user to choose the optimal measuring method. The practicality of droplet PIXE was shown by these results.

This study demonstrated that the droplet PIXE analyzing method is a new technique for liquid analysis. Droplet PIXE system shows advantages over other equipment since work burden on a researcher for chemical pretreatment of a sample can be reduced. Application of droplet PIXE system can be expanded in future and there is expected suitability for other applications.

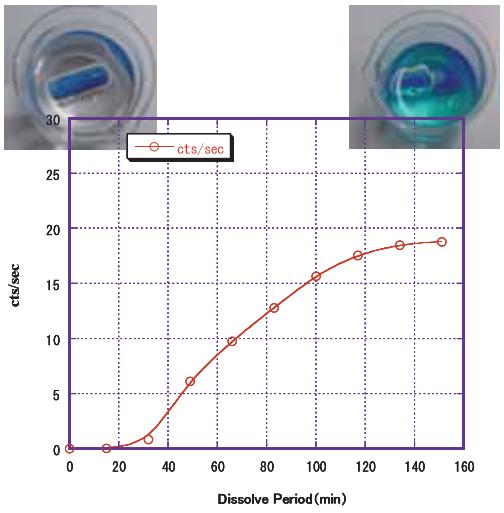

Fig.29. Temporal response of element concentration: pump control mode flow (time).

Major Publications

1) H. Imaseki, et al., "Development of a Droplet-PIXE system for Environmental Monitoring Samples" *International Journal of PIXE,* accepted.

2) H. Imaseki, and M. Yukawa, "Introduction of PIXE analysis system in NIRS," *International Journal of PIXE,* 10, Nos. 3 & 4 77-90 (2000).

10. List of Original Papers

This list includes main publications by the staff members issued during the period from April 1, 2003 to March 31, 2004

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○***Research Center for Rradiation Safety***

Low Dose Radiation Effects Research Project

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(***Department of Medical Physics***)

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Status of March 31, 2005
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Yoshiro Miki, Executive Director

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Senior Researcher
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Shigeo Uchida, Ph.D., Head 1)
Keiko Tagami, Ph.D. 1)
Nobuyoshi Ishii, Ph.D. 1)
Yasuo Nakamaru, Ph.D. 4)
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Yasushi Ohmachi, D.V.M., Ph.D.
Shin Saigusa, Ph.D.3)

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Yoshiya Shimada, Ph.D. Team Leader 1)
Mayumi Nishimura
Tatsuhiko Imaoka, Ph.D.
Shizuko Kakinuma, Ph.D.3)
Yoshikazu Kuwahara, Ph.D. (April 2004-December 2004)4)

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Hiroko Ishii, Ph.D.
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Takashi Nakamura, Ph.D. 2)
Toshisuke Kashiwagi, Ph.D. 2)

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Masashi Takada, Ph.D.
Yukio Uchihori, Ph.D.
Nakahiro Yasuda, Ph.D.
Hisashi Kitamura, M.S. 2)

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Susumu Kinpara, Ph. D.
Michiko Takami, Ph.D. 4)

Cellular and molecular effects in space
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Sergey Druzhinin, Ph.D. 4)
Chizuru Tsuruoka2)
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Shino Homma-Takeda, Ph.D. 1)
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Shinji Yoshinaga, Ph.D.

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Tatsuo Aono, Ph.D.
Jian Zheng, Ph.D.
Takahiro Nakanishi, Ph.D. 4)
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Toshiaki Ishii, Ph.D., Team Leader
Motokazu Nakahara, B.S.
Mitsue Matsuba

Assessments of Radiological Impacts of Releases of Radioactive Substances into the Marine Environment
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