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NATIONAL INSTITUTE OF RADIOLOGICAL SCIENCES

ANNUAL REPORT

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Preface

The National Institute of Radiological Sciences (NIRS) was founded in 1957 to promote comprehensive research in science and technology related to radiation and human health. This Annual Report summarizes our research activities and major advances performed during the fiscal year 2008 (April 2008 to March 2009).

NIRS continued research activities according to the second mid-term plan (2006 to 2010). This year, we started the International Open Laboratory in order to promote cutting-edge research in basic radiation sciences. We selected three research units, Particle Therapy Model, Molecular Particle Radiation Biology, and Space Radiation, for this purpose, and invited top scientists worldwide to lead the research activities through a global collaboration.

The charged particle therapy for cancer treatment continues to be the major topic in the clinical research. The patients treated with this modern technology exceeded 4,500 cases over the past 15 years. In addition to the excellent clinical outcome in patients with radio-resistant or non-operative tumors, it is now possible to treat the early stage of common cancers in a shorter treatment period than conventional radiotherapy. We started to construct a new building for the advanced treatment with spot-scanning. Important progress was made in the molecular imaging research program in collaboration with other institutions. Molecular imaging is now being actively applied in neuroscience and oncology, demonstrating the significant value of this technique in early diagnosis as well as in understanding the molecular and biological mechanism of the diseases.

The activities in radiation protection and preparation for possible accidents need to be strengthened in collaboration with national regulatory agencies and international organizations, such as UNSCEAR, ICRP, IAEA and WHO. In order to establish an efficient system to prepare for emergency radiation accidents, we started an international framework to work with Asian countries in collaboration with IAEA, WHO and the Nuclear Safety Commission of Japan.

It is our desire that NIRS continues to make significant contributions to society. We sincerely ask your support to accomplish our mission and we acknowledge with deep appreciate your critiques and constructive comments about our activities.

Yoshiharu Yonekura, M.D., Ph.D.

President

1. Outline of Research Activities

Hirohiko Tsujii, M.D., Ph. D.,
Executive Director for Research

(Outline of Research Activities)

You will see in the following pages that all the research activities at NIRS were performed successfully in the third year of the second Mid-term Plan. I would like to finish with heartfelt thanks for cooperation and advice given to us during FY 2008.

The National Institute of Radiological Sciences (NIRS) was reformed as an Independent Administrative Institution in April 2001, when the first Mid-term Plan was started. This Plan was successfully completed in March 2006. This fiscal year (April 2008- March 2009) is the third year of the second Mid-term Plan. The NIRS research directly supported by the Japanese Government consists of five fields; heavy charged particle therapy, molecular imaging, radiation protection, and radiation emergency medicine. The research activities of these fields have been carried out by four research centers and one fundamental technology center and are presented in detail in this report.

Judging from the achievements in FY 2008, including publications, presentations at scientific meetings, and collaborations with other institutes/groups, etc., it can be concluded that our research activities had been vigorous with much progress and successful achievements obtained. The number of original papers published reached 315, and many of them were published in international journals with good reputations. Furthermore, we had more than 152 proceedings presented at international or domestic scientific meetings, 553 oral presentations, and 60 patent applications. Collaborative studies and exchanges of researchers were also very active: 109 collaborative studies were carried out, 1502 researchers worked as visiting staff, and 366 students were accepted as trainees. This year we started the NIRS International Open Laboratory for the purpose of creating and maintaining favorable environments in which young scientists can engage in advanced research at an international level with the support of Distinguished Visiting Scientists in strategically important fields such as radiology, biology, physics, chemistry, and engineering, thus contributing to the Institution as a whole.

Using the Heavy Ion Medical Accelerator (HIMAC), cancer therapy has been conducted at the Research Center for Charged Particle Therapy. In FY 2008 a total of 684 patients (753 lesions) were treated. The total number of patients treated has reached 4,504 since 1994. The development of new types of irradiation techniques, such as the spot-scanning method for treatment of moving targets progressed successfully. We supported construction of the new charged particle facility at Gunma University, where treatment of the first patients will begin in March 2010. Basic biological studies were also conducted to obtain biological evidence useful for development of effective protocols for carbon ion radiotherapy. Other research achievements included development of novel irradiation techniques, improvement of therapeutic and diagnostic procedures, research on radiation effects for improvement of radiation therapy, etc.

In the Molecular Imaging Research Center consisting of four groups, understanding of the mechanism of brain function and cancer pathology progressed and uses of this knowledge in clinical applications were carried out, mainly by positron emission tomography (PET). The achievements included PET studies on mesothelioma and hypoxic tumors as well as PET imaging of cancer neovascularization using 64Cu-labeled RGD peptide. In a molecular neuro-imaging study, remarkable progress on PET imaging and potential efficacy for treatment of Alzheimer's disease was made. Development of advanced measuring techniques including the OpenPET continued with much progress as well as development of a new depth-of-interaction (DOI) PET detector.

The researches on radiation protection and emergency medicine, an important mission of our institute since its establishment, have been carried out in two centers. These centers also played a role as a national hub for collaboration with international organizations including the International Atomic Energy Agency (IAEA), International Commission on Radiation Protection, United Nations Scientific Committee on Atomic Radiation, World Health Organization, and so on.

The Research Center for Radiation Protection was established to provide a scientific basis for radiation protection and safety. The research done here has focused on the health effects of low dose radiation, levels of natural radiation, and radiation effects on environment (non-human biota). Toward this goal, radiation exposures from various sources were measured, dose-effect relationships for various endpoints were examined, and the mechanisms underlying the effects were investigated. The Research Center disseminated the outcome to promote public understanding of radiation effects and encourage the enactment of more reasonable regulations concerning the use of radiation. The scope of these activities is not limited to Japan. The Research Center has been designated by the IAEA as "Collaborating Centre for Biological Effects of Low Dose Radiation".

The NIRS has been positioned as a national center for radiation emergency medical preparedness in the nuclear disaster prevention system established by the Japanese Government. The Research Center for Radiation Emergency Medicine is assumed to perform the role of a specialized radiation emergency hospital and provide advanced radiation emergency medicine. In this scheme, the Center conducted various studies and investigations, continuously organized the radiation emergency medicine system on standby in Japan as well as maintained the facilities and devices for emergencies. It also carried out activities to maintain and enhance or strengthen the emergency preparedness system required to fulfill its role as the

tertiary radiation emergency hospital by establishing three nation-wide network councils for medicine, chromosome analysis as bio-dosimetry, and physical dosimetry.

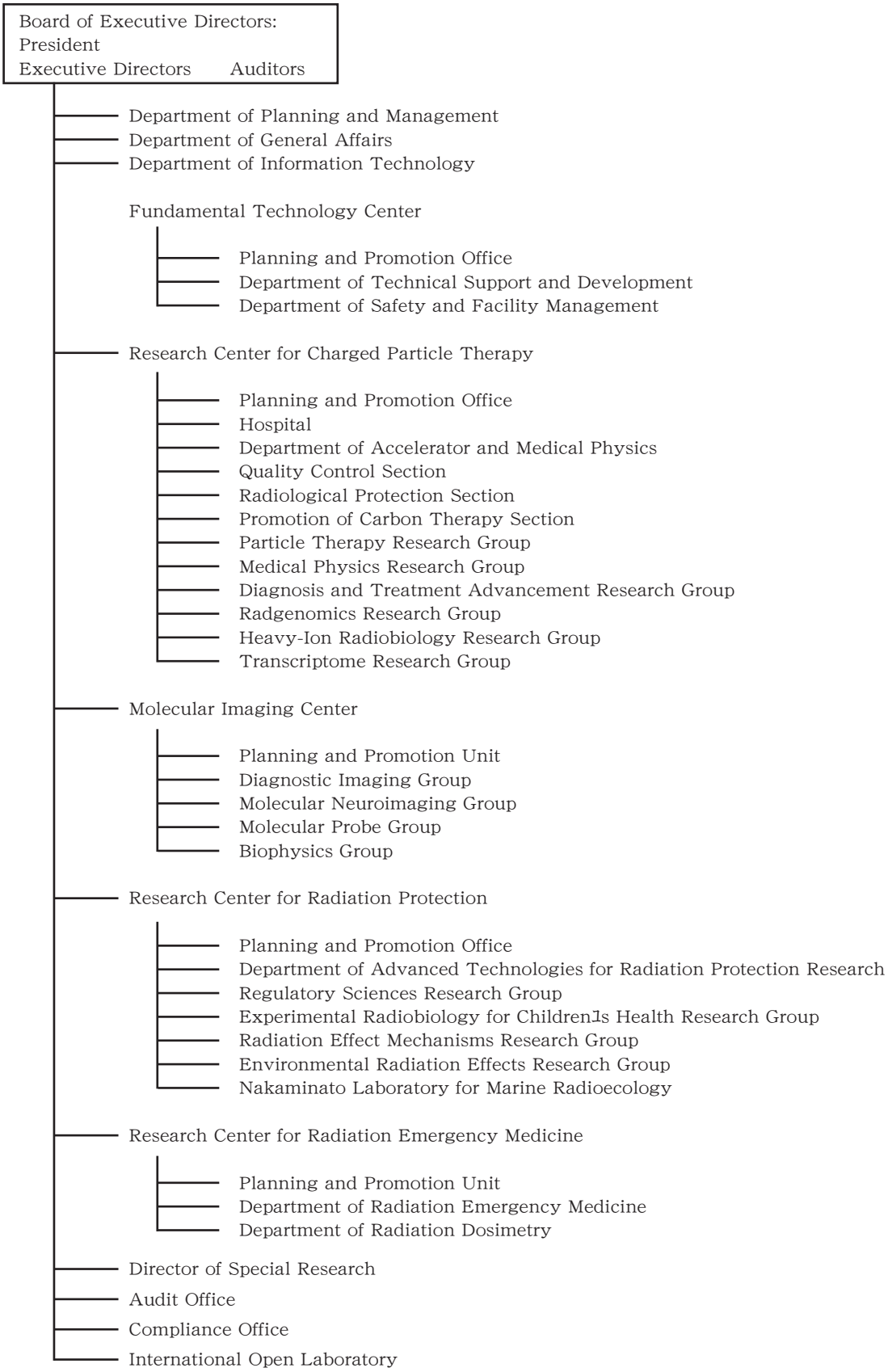
The Fundamental Technology Center was established to support various studies of NIRS with advanced fundamental technology. It also carried out some developmental researches including on a single particle irradiation system to cells, a neutron irradiation device for animal experiments, and a radiation measurement apparatus for cosmic rays.

Some other research programs were also continued or newly started with the support of funding agencies including the Ministry of Education, Culture, Sports, Science and Technology (MEXT), the Ministry of Economy, Trade and Industry, the Ministry of Environment, and so on.

You will see in the following pages that all the research activities at NIRS were performed successfully in the third year of the second Mid-term Plan. I would like to finish with heartfelt thanks for cooperation and advice given to us during FY 2008.

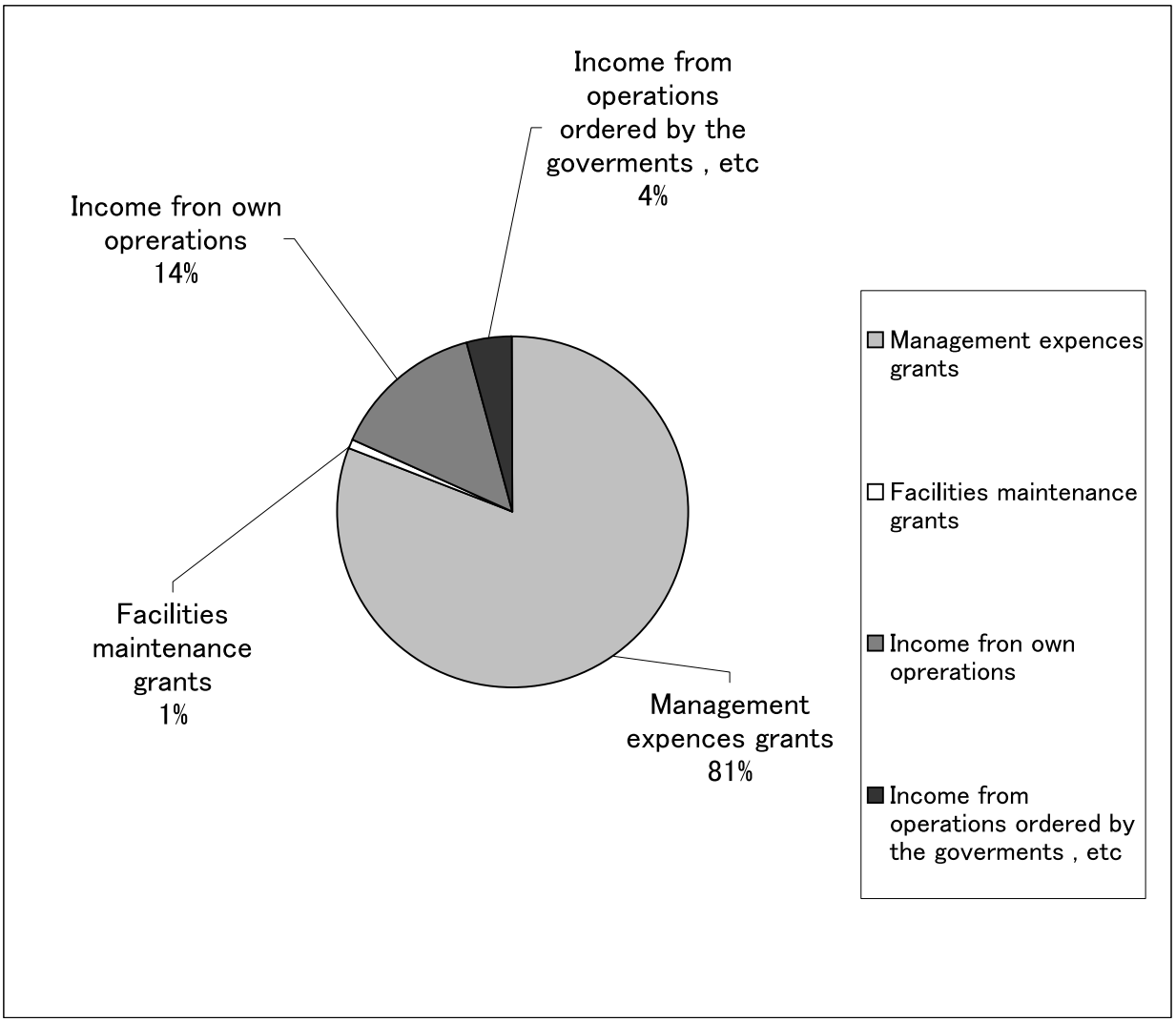
2. Organization Chart and Budget

(1) Organization



(2) Budget (2008～2009.3)

Total	15,339 million yen	%
Management expences grants	12,407 million yen	81%
Facilities maintenance grants	100 million yen	1%
Income fron own oprerations	2,201 million yen	14%
Income from operations ordered by the goverments , etc	631 million yen	4%



3. Research Center for Charged Particle Therapy

Tadashi Kamada, MD, Ph.D.
Director, Research Center for Charged Particle Therapy

(Outline of Research Career)

Dr. Kamada received a Ph.D. from Hokkaido University in 1996 for his study on radiotherapy of bile duct cancer. He has had 29 years of experience in clinical research on radiation oncology, including 14 years experience in carbon ion radiotherapy at NIRS. Since 2006, he has been group leader of the diagnosis and treatment advancement research group for standardization and improvement of therapeutic and diagnostic techniques. He has been a the Director of the Research Center for Charged Particle Therapy, NIRS since 2008.

Objectives

The Research Center for Charged Particle Therapy (hereafter, abbreviated as "the Center") was established in 1993 when the NIRS completed construction of the HIMAC. Since then it has been carrying out clinical, biological and physics research using heavy ions generated from the HIMAC. After accumulating clinical experiences with carbon ion radiotherapy in various types of malignant tumors, in 2003 the Center was successful in obtaining approval from the Ministry of Health, Welfare and Labor for "Highly Advanced Medical Technology".

Carbon ion therapy has in the meantime achieved for itself a solid place in general practice of cancer treatment. The HIMAC has also served more than 500 researchers as a multi-user utilization facility for medical, biological and physics research.

In 2006, when the second mid-term plan of the NIRS was initiated, the Center was reorganized to conduct life science research on ionizing radiation, focusing on carbon ion radiotherapy. This would eventually contribute to the improvement of the quality of life of human beings. Research plans for FY 2008 included: clinical study on carbon ion radiotherapy for locally advanced tumors; development and improvement of radiotherapeutic techniques; design study and R&D for a new extension of the treatment rooms for the HIMAC; research on diagnostic imaging; QA/QC for radiotherapy and radiation protection; radiobiological experiments for improvement of radiotherapy; exploration of variability of radiation sensitivity by investigating SNIPs ; and research on HiCEP.

Overview

The Center is organized as six research groups for two major topics (A and B) and one invited research project (C). Research progress for each topic is summarized below.

A. Research on the use of heavy ion beams for cancer radiotherapy

①Development of advanced cancer radiotherapy with charged particles

This research subject has been pursued by the Particle Therapy Research Group (GL: H. Tsuji) using three teams: Clinical Trial Research Team, Clinical Database Research Team, and Radiation Effect Research Team. The Clinical Trial Research Team has continuously increased the number of patients treated each year; in FY 2008, 684 patients, the maximum number ever, underwent carbon ion radiotherapy (C-ion RT). So far, a total of 4504 patients have been enrolled in clinical trials of C-ion RT and prostate, lung, head and neck, bone and soft tissue, and liver tumors were the leading five tumor types in the trials. The outcomes of the clinical trials revealed that the C-ion RT provided definite local control and offered a survival advantage without unacceptable morbidity in a variety of tumors that were hard to cure with other modalities. In addition, it was possible to implement hypofractionated radiotherapy by using carbon ion beams, with application of larger doses per fraction and a reduction of overall treatment times as compared to conventional photon radiotherapy. In particular, clinical trials of ultra-short course C-ion RT for lung cancer (single fraction) and liver cancer (two fractions) have been successfully achieved. Additionally, advancement of hypofractionation has also been made in other tumor entities. For instance, the fraction number in the treatment of prostate cancer could successfully decrease from 20 to 16, with even lower incidence of late toxicity and comparable outcomes in tumor control.

Developments in the technology of the beam delivery system, a new multi-leaf collimator (MLC) and a new method for manufacturing range compensators have also been carried out for the sake of improving treatment efficiency. The range compensator fabricated by a new method was actually used in the treatment of prostate cancer patients this year. The Clinical Database Research Team has achieved improvement of the coordination among several database systems (Hospital Information System, Therapy Plan Database, Therapy Schedule Management System, two PACSs and the Radiology Information System for Radiation Therapy). The developed information systems conforming to the functions, Integrating the Healthcare Enterprise (IHE)-Enterprise User Authentication (EUA) and Patient Synchronized Applications (PSA), made it easy to operate multiple systems in one clinical unit. As a result, the developed system contributed to the improvement of efficiency of patient registration and a resultant increase in the number of patients. In addition, the functions for analyzing the data of the database system were improved and basic analysis, such as the Kaplan-Meier estimate of patient survival, became much easier than before. The Radiation Effect Research Team has aggressively performed experiments and analysis as well. The radiosensitivity analysis based on the TCP model was applied to the analysis of late toxicity on the genitourinary (GU) system in prostate cancer. The results revealed that the α/β value of the GU was substantially larger than that for photons in literature but the BED calculated with the α/β value for the carbon ion beam was consistent with that for photons. The skin reaction of mice was investigated by fractionated irradiation experiments with carbon beams. As a result, it was found that the effect of single fraction irradiation differs uniquely from those by multiple fractionations: the efficacy tends to be small for single fractions. Lineal energy information measured by the tissue-equivalent proportional counter in the therapeutic irradiation field was obtained to estimate biological effectiveness of the beam. The effect of the

field size in the small field treatment and the difference in the biological dose distribution due to the shape of the ridge filter were investigated in FY 2008. It was found the detected effect and difference did not have any serious influence on the current clinical application of carbon ion beams.

②Development of a novel irradiation system for charged particle therapy

This research subject has been pursued by the Medical Physics Research Group (GL: K. Noda) using four teams: Accelerator Development Research Team, Irradiation System Research Team, Therapy System Research Team, and Compact Heavy Ion Therapy System Research Team.

Based on more than ten years of experience with HIMAC, the group has proposed a new treatment facility moving toward adaptive cancer therapy with heavy ions, which makes the one-day treatment of lung cancer possible. In the new treatment facility, it should be possible to accurately treat a fixed target, a moving target with breathing and/or a target near a critical organ.

For these purposes, a 3D-scanning method with a pencil beam is employed in the new treatment facility. A phase-controlled rescanning (PCR) method has been proposed, especially for treating a moving target. In the PCR method, the fast 3D raster-scanning is one of the essential key technologies needed to irradiate a tumor within a tolerable time even scanning several times in each slice. For the fast 3D scanning, we have developed the following technologies: 1) a new treatment planning; 2) an extended flattop operation of the synchrotron; and 3) a fast-scanning magnet system. In order to verify this method, we have designed and constructed a test irradiation port with which we carried out an experiment on the fast 3D raster-scanning. From preliminary findings, we verified that the irradiation time was significantly reduced compared with conventional spot scanning. In the new treatment facility, a rotating gantry with the PCR method will also be employed in order to reduce the treatment burden on the patient and to increase the treatment accuracy for tumors near a critical organ when the multi-field optimization method is used. After the beam-optics design, a mechanical design was carried out. As a result, the weight of the gantry is held to 350 tons, which is about half that of the HIT gantry. Furthermore, for the multi-field optimization, inverse-planning has been studied. We verified that the method can reduce the dose in the OAR significantly while keeping it in the target . Including the studies mentioned above, for the new treatment facility, since April 2006, we designed a fixed beam delivery system, a rotating gantry system, a treatment management system, a patient-positioning system and a treatment planning system. The new treatment facility is connected with the existing HIMAC accelerator complex and the heavy ion beams are delivered to three treatment rooms. Two of them are equipped with both horizontal and vertical fixed beam delivery systems, and the other has the rotating gantry. Construction of the building for the new treatment facility was started in February 2009.

③Standardization and improvement of therapeutic and diagnostic techniques

This topic covers a wide range of research which has been carried out by the Diagnosis and Treatment Advancement Research Group (GL: T. Kamada) with four teams: Image Diagnosis Research Team, Image Processing Research Team, Quality Control Research Team, and Radiological Protection Research Team.

The Image Diagnosis Research Team studied two PET tracers, ^{62}Cu-ATSM and C-11-methionine (MET), for oncologic imaging. This fiscal year, tumor hypoxic imaging using ^{62}Cu-ATSM was continued and primary brain tumor imaging using C-11-MET was also investigated. The team assessed whether Cu-62-ATSM imaging of tumor hypoxia is associated with C-11-MET imaging of amino acid metabolism in 18 patients with cervical cancer, and found that tracers showed different distribution patterns in same patient. For brain tumor imaging using C-11-MET, we found that its accumulation was well correlated to the histopathologic grade of glioma.

In FY 2008, the Image Processing Research Team analyzed intrafractional organ movement during respiration using 4D CT (256MSCT) in patients with lung carcinoma. Interfractional volumetric cine imaging of the lung using 4D CT showed continuous movement of the tumor in the sagittal section satisfactorily. The 256MSCT significantly improved the observation of tumor displacement and overcame some of the limitations of present CT methods in lung cancer treatment.

The Quality Control Research Team carried out studies with regard to dosimetry for the therapeutic hadron beam. The team conducted a nation-wide proton dosimetry intercomparison that involved new proton facilities in Japan. The intercomparison results showed facilities had good agreement within 0.4% and dose uniformity was established among them.

The Radiological Protection Research Team measured organ doses of patients in CT screening using an adult anthropomorphic phantom and TLDs under CT scan conditions routinely used at two hospitals. The estimated equivalent doses of thyroid, lung, esophagus, breast, liver and stomach were between 0.8 and 2.6mGy. Based on evaluation of image quality for the CT images as well as estimated doses, adequate CT scan conditions were suggested considering the optimization of radiation protection in CT screenings

for lung cancer.

B. Research on radiation effects for improvement of radiation therapy

①RadGenomics research concerning radiation sensitivity

This research subject has been pursued by the RadGenomics Research Group (GL: T. Imai) using three teams: Genetic Information Team, Molecular Radio-oncology Team, and Molecular Biostatistics Team.

Normal tissue reactions of cancer patients vary considerably after radiotherapy. A number of observations have indicated that certain genetic factors play important roles in this variability. The aim of the RadGenomics Research Group is to explore the genetic characteristics for both the patient and the bearing tumor, by which the potentially most effective radiotherapy can be delivered. From a molecular biological standpoint, this would open the way to the development of an individual-oriented radiotherapy. This research group has focused on searching genetic predictive markers for clinical radiosensitivity of normal tissues and tumors. The clinical radiosensitivity of normal tissue is likely to be a complex trait that is dependent on the cumulative effect of many minor genetic determinants. We have searched for polymorphisms associated with the radiosensitivity of normal tissue in cancer patients who have undergone radiotherapy. Between October 2001 and March 2009, 2,653 patients were recruited for our project, including 773 breast cancer patients and 855 prostate cancer patients. The candidate genes for SNP typing in this project were selected from our previous comprehensive gene expression analyses data using human cultured cell lines and mouse strains. A total of 190 genes were chosen and 1,300 SNPs have been typed using a matrix-assisted laser desorption/ionization time-of-flight mass spectrometry system.

In FY 2008, we indentified multiple SNPs associated with risk of urinary morbidity after carbon ion radiation therapy in prostate cancer patients. The data suggest that patients with late urinary morbidity after carbon ion radiotherapy can be stratified according to the total number of risk genotypes they harbor.

To obtain haplotype information for individuals, we developed a new analysis method for amplification of long DNA fragments. A limited amount of cellular DNA was released from intact cells into a mildly heated alkaline agarose solution and mixed. The solution was then gently aliquoted and allowed to solidify while maintaining the integrity of the diluted DNA. Exogenously provided Phi29 DNA polymerase was used to perform consistent genomic amplification with random hexameric oligonucleotides within the agarose gels. Simple heat melting of the gel allowed recovery of the amplified materials in a solution of the polymerase chain reaction (PCR)-ready form. The haplotypes of seven SNPs spanning 240 kb of the DNA surrounding the human ATM gene region on chromosome 11 were determined for 10 individuals. Our technique will facilitate determination of individual haplotypes and enhance predictive power for individual radiation sensitivity.

Recently, radiotherapy has been applied to many more patients as one of the best clinical modalities. To layer several kinds of treatments, it is necessary to know the effectiveness of radiotherapy even during it. While the pre-treatment status of cancer is generally correlated with outcome, little is known about micro-environmental changes caused by anti-cancer treatment and how they may affect outcome. We attempted to find a gene that was both induced by irradiation and associated with radioresistance in tumors. We analyzed the gene expression profiles of two murine carcinomas, NR-S1, which is highly radioresistant, and SCCVII, which is radiosensitive, after irradiation with gamma rays or carbon ions. Four genes, Efna1 (Ephrin-A1), Sprr1a, Srgap3 and Xrra1, were selected as candidate genes associated with all kinds of radiotherapy-induced radioresistance. We focused on Efna1, which encodes a ligand for the Eph receptor tyrosine kinase that is known to be involved in the vascular endothelial growth factor (VEGF) pathway. Ephrin-A1 was detected in the cytoplasm of NR-S1 tumor cells after irradiation, but not in SCCVII tumor cells. Irradiation of NRS1 tumor cells also led to significant increases in microvascular density and up-regulation of VEGF expression. Our results suggest that radiotherapy-induced changes in gene expression related to angiogenesis might also modulate micro-environments and influence responsiveness of tumors.

②Biological research concerning the improvement of radiation therapy

This research subject has been followed by the Heavy Ion Radiobiology Research Group (GL: R. Okayasu) with four teams: Biophysics Team, Experimental Therapy Team, Cellular and Molecular Biology Team, and Radiation Modifier Team.

The Biophysics Research Team proposed an experimental fitting function of the LET-RBE relationship to estimate RBE for unknown ion beams at a defined LET. was Experimental LET-RBE spectra of cell survival for different ion beams were fitted by the LQ-model to obtain parameters for the function . The spectra were analyzed with the function, and clear splits of the spectra were found among various ion species. Those parameters can be defined as functions of atomic numbers of ion beams. This method is applicable to estimate overall RBEs in the therapeutic beams because each beam must consist of different ions having different RBEs when passing through a patient body or other absorbing materials in order to adjust the

beam range in the body.

RBE values for 20 % tumor induction in mice by carbon ions at LET of 15, 45, 75 keV/_m are 0.6, 1.0 and 1.4 respectively. To determine variations in the sensitivity of tumors having mixed populations with different sensitivities, the Experimental Radiotherapy Research Team has carried out experiments on mice with tumor cells with resistant and sensitive populations. When more than 10 % of the cells were resistant, the overall sensitivity was very similar to that when 100 % of the cells were resistant. To investigate the relationship between LET and skin reaction, the team performed fractionated irradiation on the normal mouse foot. The α/β ratios were 28 and 39 Gy^{-1} for LET values of 58 and 14 keV/μm, respectively, and 38 Gy^{-1} for γ rays. There seemed to be no significant differences in the α/β ratios for different LETs.

The Cellular Molecular Biology Research Team used the comprehensive gene expression technique (HiCEP) with irradiated human cell lines to demonstrate some characteristic molecular signatures for different types of ionizing radiation (IR) at therapeutic doses. A group of early responsive IR-induced genes (ATF3, BTG2, TP53INP1) in human cells were found to remain active for a longer period with carbon ions than with X-rays. In addition, we successfully detected some common genes which were down-regulated by various types of IR. We also demonstrated that cells irradiated with X-rays and heavy ion particles showed different radiosensitivities depending on the DNA repair characteristics of the cells; in particular, homologous recombination (HRR) defective cells showed an extremely high sensitivity to high LET heavy ion irradiation.

To develop a better free radical scavenger, the Radiation Modifier Research Team performed a kinetic study on the free radical scavenging reaction of vitamin E precursors. The electron-donating groups on the benzene ring of p-hydroquinones significantly enhanced the scavenging activity, based on the second-order rate constants determined by the stopped-flow technique. From the study of in vivo radiation-protectors and -mitigators, it was found that several compounds effective against low LET radiation-induced injury were also effective to protect against bone marrow death or to mitigate the number of bone marrow deaths in mice induced by carbon ion irradiation. A new data acquisition method for CW-ESR spectral-spatial imaging was proposed. Details of reactions between a nitroxyl probe and glutathione were investigated, and the depth-dependent free radical generation by carbon ion irradiation in gelatin sample containing the nitroxyl probe and glutathione was detected using ESR and MRI methods.

③Transcriptome Research for Radiobiology

This subject has been followed by the Transcriptome Research Group (GL: Abe) which consists of three teams: Stem Cell Research Team, Gene Expression Profiling Team, and Model Organism Research Team.

To fully understand genetic information residing in the entire genome is the next major goal in life science and also an important issue for radiobiology. However, the actual number of transcripts expressed from the whole genome is quite large and still unknown, more than 40,000 per cell or more than 150,000 per individual. Thus far, no way has been available to detect such large numbers of transcripts. The transcriptome Research Group has developed a new method for gene expression profiling called High-Coverage gene Expression Profiling (HiCEP). HiCEP enables detection of 30,000 ≲ 40,000 transcripts per cell, allows observation of expression differences of as little as 1.2 times , and allows detection of unknown, very slightly expressed genes . Because this method does not require any sequence information in advance, it can be used for all species, rather than only for the usual laboratory animals. This is another great advantage of this method.

So far, we have successfully observed changes in gene expression of two-fold or less with good reproducibility after irradiation, identified novel rhythmic expressed transcripts in the suprachiasmatic nucleus, which is a minute nucleus in the brain and governs the biological clock, and identified many genes including unknown ones whose expression was deregulated only in gene knockout mouse. All of these would be difficult for conventional methods to detect and analyze.

Issues to be addressed for further successful implementations of HiCEP included the development of: 1) techniques for the mass processing of samples (Fig.3-1); 2) analytical techniques for small amounts of samples; 3) a kit that enables anyone to perform the HiCEP reaction; 4) a rapid peak isolation system after the analysis ; and 5) a mass information processing system. Our current progress on each issue is summarized as follows. 1) An auto-machine named HiCEPer was developed that can carry out the HiCEP reaction for 96 samples simultaneously. 2) Reaction using only 100 cells became possible and we are attempting to develop a reaction system using only 10 cells. 3) A kit using 1 microgram total RNA is now available. 4) A new technology using a microchip was developed and we are constructing a test machine in which the microchip technology was included. 5) Several useful software codes have been developed for HiCEP analysis.

Progress in the construction of these systems has been and is being made by the Development of Systems and Technology and Analysis Project of the Japan Science and Technology Agency and NIRS.

These R&D projects are necessary to encourage the dissemination of this new method over various scientific fields including basic sciences, molecular epidemiology and clinical medicine.

C. Research Project with Heavy Ions at NIRS-HIMAC

In FY 2008, 141 proposals were accepted and carried out at HIMAC. The beam time of 5549 hours was supplied to those studies. Ninety-eight papers and 29 proceedings were published, and 299 papers were presented at various meetings. A total of 530 researchers participated, including 44 foreign researchers for 15 international projects.

3.1 Developing Advanced Clinical Therapy with Charged Particles

Hiroshi Tsuji, MD, Ph.D.
Director, Particle Therapy Research Group

(Outline of Research Career)

Dr. Tsuji received a Ph.D. from Tsukuba University in 1996 for his study on proton radiotherapy of hepatocellular carcinoma. He has had 26 years of experience in clinical reseach on radiation oncology, including 14 years experience in carbon ion radiotherapy at NIRS. Since 2008, he has been group leader of the Particle Therapy Research Group for developing advanced clinical therapy with charged particles.

Contact point: h_tsuji@nirs.go.jp

Objectives

- Carry out clinical studies to develop therapeutic techniques for diseases that are difficult to treat with other therapies (such as pancreatic cancer) and for which charged particle radiation therapy does not yet have a role.
- Carry out studies on optimizing irradiation methods by disease and by region, using clinical investigations of therapies in which radiation is combined with drugs and operations
- Develop a comprehensive database on treatment, clinical course and other factors. Compare and analyze domestic and foreign data on particle beam therapy.
- Provide annual treatment to 500 patients to maximize and disseminate the therapeutic effects of charged particle technology. This is the target number combining patients taking part in clinical studies and those receiving high-technology treatments, and is based on consideration of the fact that the NIRS is primarily a research and development facility.
- Evaluate the therapeutic effects of treatments developed by NIRS from the viewpoints of quality of life (QOL) and therapeutic costs. Patients1 opinions are collected to gauge their level of satisfaction with the therapy.

Progress of Research

The Particle Therapy Research Group for developing advanced clinical therapy with charged particles consists of the Clinical Trial Research Team, Clinical Database Research Team, and Radiation Effect Research Team. It does research and development on charged particle therapy. Progress of research in each team is summarized below.

1) Clinical Trial Research Team

From June 1994 to February 2009, a total of 4504 patients were enrolled in clinical trials using carbon ion beams generated by HIMAC. Carbon ion radiotherapy of these patients was carried out by nearly 50 different phase I/II or phase II protocols and highly advanced medical technology. Figure 3-1 lists the number of the patients for each tumor site treated with carbon ion beams.

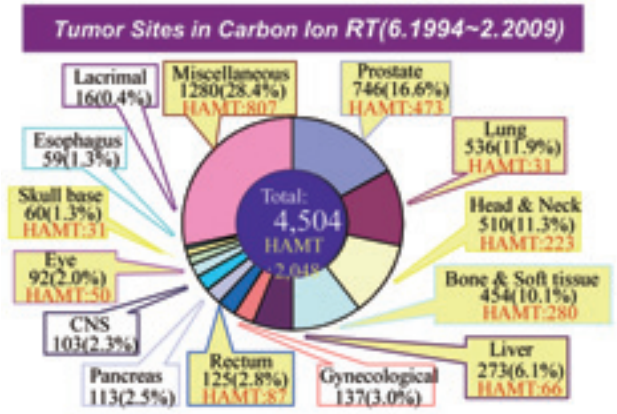


Fig.3-1. The number of patients for each tumor site treated with carbon ion beams.

We treated 684 new patients in FY 2008. Prostate, lung, head and neck, bone and soft tissue, and liver tumors are the leading five tumor types in the trials. A total of 3820 patients who had a follow-up period of 6 months or more were included in this report. The clinical trial revealed that carbon ion radiotherapy provided definite local control and offered a survival advantage without unacceptable morbidity in a variety of tumors that were hard to cure with other modalities. Using carbon ion beams, it was possible to implement hypofractionated radiotherapy, with application of larger doses per fraction and a reduction of overall treatment times as compared to conventional photon radiotherapy. Carbon ion radiotherapy has been approved by the Ministry of Health, Labor and Welfare of Japan as "Highly Advanced Medical Technology (HAMT)" since November 2003. In 2008, nearly 75 % of the patients receiving carbon ion radiotherapy were treated by HAMT.

When irradiating a patient with carbon beams, the patient should be protected from exposure to an unwanted dose. A multi-leaf collimator (MLC) and patient collimators are used to spatially limit the carbon beams for the sake of delivering high localization of the dose to a target. The MLC can easily form an arbitral aperture shape by computer control. However, since each leaf is 6.5 mm thick, it is difficult to make the fine shape which is required for the cases of cancers which are abutting critical organs. It these cases, a patient collimator is used, which is manufactured by boring an aperture in a brass block; this takes a few days and is costly. Furthermore, use of the patient collimator has required radiation therapy technologists set the heavy collimator just above a patient in positioning. Omitting use of the patient collimator reduces the expense and the human burden.

A new MLC has been developed which is equipped with 88 pairs of a 2.5 mm thick leaf with 0.15 mm spacing. This thickness is almost 1/3 of the present thickness of 6.5 mm. We experimentally proved that the leakage dose of the MLC was about 1% of the unshielded dose compared with the 0.6% leakage dose of the present MLC. Of particular interest in the study

was identifying what particles contribute to the leakage dose. Protons were experimentally proven to be the biggest contributor and helium ions, the next biggest. Heavier particles, except for carbon, contribute only slightly to the dose.

Range compensators are also essential in the broad beam method. At present, polyethylene blocks are machined by a numerically controlled device to manufacture the range compensators, a time-consuming process that can take as long as eight hours. Then, cleaning and inspection will take about another hour. We developed a new method for manufacturing range compensators, employing a punch technology. The compensator is assembled by lamination. Each plate is 3 mm thick, the distal end shape is punched out from the plate, and then the shape is inspected automatically. The plates are stacked up at the end stage of the process. The laminated block is manually tightened with bolts. This simple process has greatly shortened the manufacturing time, as punching and stacking take half an hour or less.

2) Clinical Database Research Team

In October 2006, we implemented the Electronic Medical Record (EMR) system and developed a simple input method for each patient's findings which include symptoms, tumor responses, and toxic reactions that should be estimated by the physician during the clinical interview. We improved the coordination among several database systems (Hospital Information System, Therapy Plan Database, Therapy Schedule Management System, two PACSs and Radiology Information System for Radiation Therapy). These systems are connected to each other and data are transmitted to the designated systems.

We also developed information systems that conform to the functions of Integrating the Healthcare Enterprise (IHE)-Enterprise User Authentication (EUA) and Patient Synchronized Applications (PSA). These functions make it easy to operate multiple systems. Two PCs (one for the EMR and one for the PACS viewer) are commonly used for the Hospital Information System in one clinical unit. Many physicians have to enter a user ID and password to log into these systems. The developed functions of the IHE-EUA and PSA ease this troublesome manipulation. We developed middle-ware for the EUA and PSA functions to reduce the implementation load among the EMR, PACS-viewer, report-viewer, radiation scheduling system, and radiation information system. We realized that EUA and PSA functions were essential in a multi-system environment. Our middle-ware resolved the complexities of the application implementation. The established guideline was useful to unify the user interfaces of each application. We found that the EUA and PSA functions are critical for visual integration.

We implemented a system to share medical data between hospitals and medical institutions. This system is based upon the IHE Cross-Enterprise Document Sharing (XDS) which uses SOAP, ebXML RIM and Web Service Description Language (WSDL) and HL7. We prepared the Open Source Software license for the delivery of software. We are now developing the document source, document repository, document registry and document consumer that were defined by the IHE XDS. We had previously developed the application software. We are now modifying them according to the newer IHE version. We think that it is very important to maintain this software and to improve the code periodically. We are working to establish a maintenance framework for the open source software.

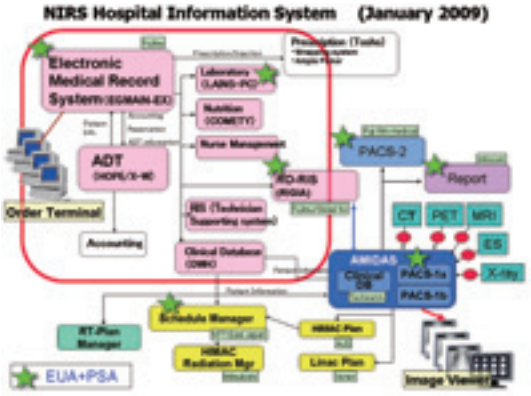
We have a clinical database system which contains information concerning over 4,000 patients who have had heavy particle radiation therapy and over 18,000 patients who have had photon radiation therapy. We improved this database system in its processing speed and ease of operation. By using this system physicians can analyze patients by the heavy particle radiation therapy protocol and generate survival curves in a few seconds. This database can store data concerned with the disease history, staging, radiation schedule, radiation dose/days, adverse effects and follow-up information.

The NIRS Hospital Information System was modified in 2008 and its status in January 2009 is shown in Fig.3-2.

Fig.3-2. Current status of the NIRS Hospital Information System.

3) Radiation Effect Research Team

The radiosensitivity analysis based on the TCP model has been applied for the analysis of toxicity on benign tissue. Late toxicity on the genitourinary (GU) tract observed during treatment of prostate cancer with carbon ions was analyzed with the model. The analysis revealed that the α/β value of the GU was 7.7, which was more than 2 times larger than that for photons (3.0) in the literature. BED calculated with the α/β value for the carbon ion beam was 73.8, which was consistent with that for photons, 74.7. This information



will contribute to the prospective estimation of prescribed dose in different fractionations or to further dose optimization in treatment planning.

Reaction of the skin is one of the most important endpoints to be regarded in radiotherapy; however, its analysis from clinical outcomes is not easy as radiation quality and the dose given to patients significantly differ among individuals. From this viewpoint, skin reaction has been investigated through reaction observations on mice. Through the fractionated irradiation of carbon beams to mouse leg, we found that the effect of single fraction irradiation differs uniquely from those by multiple fractionations: the efficacy tends to be small on single fractions.

Lineal energy information measured by a tissue-equivalent proportional counter in the therapeutic irradiation field is found useful for the sake of estimating biological effectiveness of the beam at the point by processing the information with the Microdosimetric Kinetic Model (MKM). In FY 2008, the method was applied for the verification of actual irradiation fields and the following results have been obtained.

Field effect

In the case of a small irradiation field, the decrease in the absorbed dose at the center of the irradiation field by collimator is almost completely compensated by the increase in radiation quality. The resultant isoeffective dose is regarded as stable.

Port characteristics

Due to the machining precision of ridge filters, therapeutic beam distribution could differ port-by-port. Verification of the port dependency by the MKM revealed a slight difference in radiation quality though that in the absorbed dose was negligible. However, the absolute difference in the isoeffective dose was small and it was confirmed that the therapeutic beam provided in each port can be regarded as identical.

Major publications

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4) T. Nomiya: Carbon ion radiation therapy for primary renal cell carcinoma: Initial clinical experience, *International Journal of Radiation Oncology Biology Physics,* 72[3], 828-833, 2008

5) T. Sugane: Carbon ion radiotherapy for elderly patients 80 years and older with stage I non-small cell lung cancer, *Lung Cancer,* 64[1], 45-50, 2009

6) T. Yanagi: Mucosal malignant melanoma of the head and neck treated by carbon ion radiotherapy, *International Journal of Radiation Oncology Biology Physics,* 74[1], 15-20, 2009

7) M. Wakatsuki, H. Tsuji, H. Ishikawa, T. Yanagi, T. Kamada, T. Nakano, H. Suzuki, K. Akakura, J. Shimazaki, H. Tsujii: Quality of life in men treated with carbon ion therapy for prostate cancer, *International Journal of Radiation Oncology Biology Physics,* 72[4], 1010-1015, 2008

3.2 Research on the Next-generation Irradiation System

Koji Noda, Ph.D.
Director, Medical Physics Research Group

(Outline of Research Career)

Dr. Noda received his B.S. degree from the Department of Nuclear Engineering, Kyushu University in 1979. After completing the M.S. program there in 1981, he worked on development of a PET cyclotron from 1981 to 1989. He also studied accelerator physics from 1985 to 1989 in the Institute for Nuclear Study, University of Tokyo. In 1989, he joined the HIMAC project at NIRS and he was engaged in construction and development of the HIMAC synchrotron. He received his Ph.D. in 1992 from Kyushu University for the study of energy-loss cooling. Currently he is head of the Accelerator Development Section and he holds the additional post of Director of the Medical Physics Research Group.
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Objectives

Based on more than ten years of experience with HIMAC, we have proposed a new treatment facility leading toward adaptive cancer therapy with heavy ions which makes the one-day treatment of lung cancer possible. Further, the new treatment facility should be able to accurately treat a fixed target, a target moving because of breathing, and/or a target near a critical organ. For these purposes, a 3D-scanning method with a pencil beam will be employed in the new treatment facility. A phase-controlled rescanning (PCR) method has been proposed and studied, especially for treating a moving target. A rotating gantry with the PCR method is also employed in order to reduce the burden on the patient, and to increase the treatment accuracy for a tumor near a critical organ through the multi-field optimization method. Therefore, we have designed a fixed beam delivery system, a rotating gantry system, a treatment management system, a patient positioning system and a treatment planning system, and the related R&D work has also been carried out with HIMAC since April 2006. Construction of the building for the new treatment facility was started in February 2009.

Progress of Research

1) Planning of the new treatment facility

The new treatment facility, as shown in Fig. 3-3, is connected to the existing HIMAC accelerator complex and heavy ion beams are delivered to patients through the fixed irradiation port and the rotating gantry. In the treatment hall, placed underground in the facility, there are three treatment rooms to allow treatment of around 1000 patients per year. Two of them are equipped with both horizontal and vertical fixed beam delivery systems, and the other is equipped with the rotating gantry. The 3D raster-scanning method is employed in both the fixed beam delivery and rotating gantry systems. In order to carry out treatment of a moving target as well as a fixed target, the PCR method, which completes the irradiation on one slice during one respiration-gate opening, has been proposed and verified through computer simulation. The scanning speed should be faster than the conventional scanning method in order to complete treatment within a tolerable time, because rescanning naturally takes a longer time. Therefore we have developed fast 3D raster-rescanning with gating.

In cooperation with medical staff in the HIMAC hospital, the treatment hall planning has been carried out. Two treatment-simulation rooms are also prepared for patient positioning as a rehearsal, and for observing any change of the target size and shape during the whole treatment period with X-ray CT. Furthermore, six rooms are devoted to patient preparation before irradiation. The facility building construction began in February 2009.

The specifications of the facility are summarized at Table 3-1.

Table 3-11. Specifications of the new treatment facility

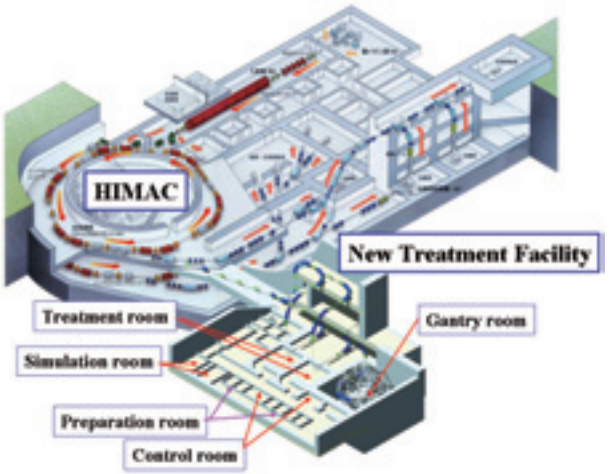
1. Basic parameters
   - Ion species: ^{12}C, ^{16}O (^{11}C, ^{15}O)
   - Delivery beam intensity: 10^7 — 10^9 pps at ^{12}C
   - Treatment room: 2 fixed beam rooms (Hori. & Vert.), 1 rotating gantry room
2. Fixed beam delivery system
   - Energy: 140 — 430 MeV/n
   - Irradiation method: Fixed target: 3D raster-scanning with pencil beam; Moving target: PCR method
   - Scanning speed: H: 100mm/ms, V: 50mm/ms
   - Spot size: 2—4 mm at 1-sigma
   - Lateral field/SOBP/Range size: 22cm×22cm/15cm/>25cm at ^{12}C
   - Irradiation port length: 9m
3. Rotating gantry system
   - Type: Iso-centric rotating gantry
   - Energy: 140 — 400 MeV/n
   - Irradiation method: Same as the fixed beam delivery system
   - Scanning speed: H: 100mm/ms, V: 50 mm/ms
   - Spot size: 2—4mm at 1-sigma
   - Lateral field/SOBP/Range size: 15cm×15cm/15cm/>25cm at ^{12}C
   - Displacement of iso-center: < 1 mm
   - Size and weight: Length: 16.5m, Radius: 7.1m, Weight: 350 tons

Fig.3-3. Schematic view of the HIMAC and the new treatment facility.

2) Related R&D work

a) Development of accelerator technology

In the present operation of the synchrotron, one



cycle, consisting of a beam injection, acceleration and extraction, is made every 3.3 s. Within the cycle, the

beam will be extracted and irradiated onto a patient during approximately 2 s on the flattop of the synchrotron pattern. For moving targets, a respiration-gated irradiation was developed and it will also be used for the raster-scanning irradiation. For the present operation of the synchrotron, an inevitable dead-time exists in the respiration-gated irradiation, because the synchrotron requires a certain time for injection and acceleration, and the cycle of the synchrotron is fixed. This dead-time would make the total irradiation time longer. To overcome this problem, we developed the extended flattop operation. In this scheme, the beam is extracted by using the RF-KO extraction while the respiration gate is opened; this operation will significantly decrease the dead-time of the irradiation. This operation will also be applied to the raster-scanning irradiation in the new facility. The raster-scanning irradiation enables us to irradiate almost 100% of the beam particles on the target. Since the synchrotron ring of the HIMAC can accelerate a few tens of billions of carbon ions within one synchrotron cycle, and the numbers of carbon ions required to treat typical tumor sizes are on the order of 109 particles, most treatments can be completed within a single synchrotron cycle, provided that most of the accelerated particles are actually utilized in the treatment dose. Consequently, having applied the extended flattop operation to the raster-scanning irradiation, the total irradiation time is considerably to be decreased to a few seconds. This operation was successfully tested and implemented in the HIMAC accelerator control.

b) Experiment on fast 3D raster-scanning

We carried out the 3D raster-scanning experiment using the improved spot-scanning system in the secondary beam line. In this experiment, we verified fundamental performances of the dose distribution by the 3D raster-scanning, the PCR method and the treatment planning. As the next step, a test irradiation port was designed and installed (Fig. 3-4) in the HIMAC physics experimental line in order to verify experimentally the fast 3D raster-scanning and the PCR method. This test port has the same configuration as the fixed beam delivery system for the new treatment facility as shown in Table 3-1 and in Fig. 3-3. The scanning experiment has been on-going since December 2008. In the experiment, the extended flattop operation has been routinely utilized. A preliminary result verified that the scanning speed achieved the designed value.

Fig. 3-4. Test port for the fast 3D raster-scanning.

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3.3. Standardization and improvement of therapeutic and diagnostic techniques

Tadashi Kamada, MD, Ph.D.
Director, Diognosis and Treatment Advancement Reseach Group

(Outline of Research Career)

Dr. Kamada received a Ph.D. from Hokkaido University in 1996 for his study on radiotherapy of bile duct cancer. He has had 28 years of experience in clinical reseach on radiation oncology, including 14 years experience in carbon ion radiotherapy at NIRS. Since 2006, he has been group leader of the diagnosis and treatment advancement research group for standardization and improvement of therapeutic and diagnostic techniques. He has been a Director of the Research Center for Charged Particle Therapy, NIRS since 2008.

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Objectives

- Development of software to create integrated clinical images, determine early therapeutic effects and analyze prognostic factors using a combination of multiple diagnostic imaging techniques
- Improvement of treatment plans by using integrated images obtained from advanced dynamic imaging devices such as 4-dimensional CT
- Promotion of R&D on indicators of quality standards and methods for quality control and assurance of particle beam and photon beam therapies and of diagnosis using radiation
- Advancement and standardization of therapeutic and diagnostic methods based on investigation of medical radiation exposure in Japan.

Progress of Research

The Diagnosis and Treatment Advancement Research Group for standardization and improvement of therapeutic and diagnostic techniques consists of the Image Diagnosis Research Team, Image Processing Research Team, Quality Control Research Team and Radiological Protection Research Team. The group researched the advancement and standardization of radiation therapy and diagnostic methods. Progress of research in each team is summarized below.

1) Image Diagnosis Research Team

We studied fundamentals of application of new PET tracers for clinical diagnosis. The main targets of our interests were imaging of cell/tissue metabolic indicators leading to treatment effects especially of carbon ion radiotherapy (CIRT).

We continued to assess whether determining Cu-62 labeled diacetyl-bis (N (4)-methylthiosemicarbazone); (Cu-62-ATSM) imaging of tumor hypoxia is associated with C-11-methionine (MET) imaging of amino acid metabolism in cervical cancer. PET/CT was performed in 18 patients with cervical cancer before CIRT for evaluation of both tumor hypoxia using Cu-62-ATSM and amino acid metabolism using MET. Fifteen patients also received both PET studies after CIRT. Data are being surely and steadily accumulated. We also started an assessment using Cu-62-ATSM PET for pancreatic cancer patients.

F-18-FLT PET imaging for head and neck cancers to assess the CIRT effect was continued in cooperation with the Diagnostic Imaging Group of the Molecular Imaging Center.

The role of C-11-MET PET for non-invasive grading between oligodendroglial tumor and other brain tumors was studied. Several investigations have shown that the prognosis of oligodendroglial tumor is dependent on their histological grade. C-11-MET PET imaging is one of the most sensitive techniques for visualizing primary brain tumors. Then we aimed at evaluating the relationship between the uptake of MET and histopathologic grading based especially on oligodendroglial tumor versus other brain tumors. We determined cerebral uptake of MET in 30 patients with histologically proven gliomas (22 male patients and 9 female patients: mean age, 46.9y; range, 14-75y). Grades I, II, III and IV lesions (based on the WHO grading class) numbered 3, 10, 9, and 8 lesions, respectively. There were 3 oligodendroglioma (grade II) and 1 anaplastic oligodendroglioma (grade III) in our cases. Ecat Exact HR+ PET scanner and Biograph DUO PET/CT were used for imaging in this study. A semi-quantitative MET uptake ratio (TNR; Tumor to normal tissue ratio) was correlated with tumor grade. We found there was a significant difference in TNR between grades III and IV lesions, but no significant difference between grades II and III in all the cases. In oligodendroglial tumors, 3 of the grade II lesions tended to show higher TNR than one of the grade III lesions. There was a significant difference in TNR between grade II and III lesions except oligodendroglial tumors from the cases. Oligodendroglioma might represent different metabolic demand for MET uptake from the other gliomas. We concluded that MET PET was sensitive for histopathologic grading of gliomas except oligodedroglial tumors. We must pay much attention to primary staging of oligodendroglial tumors using this tool.

Results were obtained from a study of C-11-MET PET imaging of choroidal melanoma and the time course after CIRT. In this work the team assessed the feasibility of MET-PET as an evaluation method of the therapeutic effect of CIRT. Twenty-four choroidal melanoma patients who were treated with a carbon ion beam underwent at least three MET-PET scans before and after therapy. The uptake was visually and semiquantitatively evaluated on the basis of the tumor-to-brain ratio (TBR). We found accumulation was significantly decreased at 6 months or more after therapy and disappeared in 50% of the patients at 12 months after therapy. The baseline TBR, 1, 6, 12 and 24 months after therapy averaged 1.88 ± 0.65, 1.73 ± 0.52, 1.08 ± 0.42, 0.67 ± 0.27 and 0.65 ± 0.30, respectively. TBR was significantly decreased at 6 months or more after therapy. It was concluded that MET-PET could be an alternative method for evaluating the effect of radiotherapy.

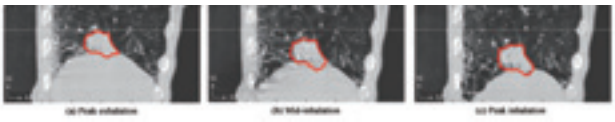
2) Image Processing Research Team

We quantified intrafractional organ motions due to respiration in the thoracic site as a function of time using the 256 multi-slice (MS) CT. Patients were immobilized on the patient bed, as routinely used in treatment. After several minutes rest in a supine

position on the CT bed, all 4D CT acquisitions were performed under free breathing, with patient respiration monitored by the respiratory sensing system. Scan conditions were slice collimation of 256 x 0.5 mm or 128 x 1.0 mm, with 0.5 s in a single rotation and scan time of less than 6 s to obtain one respiratory cycle without patient couch movement. The respiratory cycle was subdivided into 10 phases, with T_0 as peak inhalation and T_{50} as peak exhalation. Gross tumor volume (GTV) was manually contoured on the CT data set at peak exhalation by a certified radiation oncologist. GTV contours at other phases were calculated by deformable registration, following which the oncologist checked the contour curves at each phase. Center of mass (COM) was calculated by using the GTV contours. The GTVs are displayed as a function of time in Fig. 3-5.

Fig. 3-5. Lung sagittal images at (a) peak exhalation, (b) mid-inhalation and (c) peak inhalation. The red lines show the GTV.

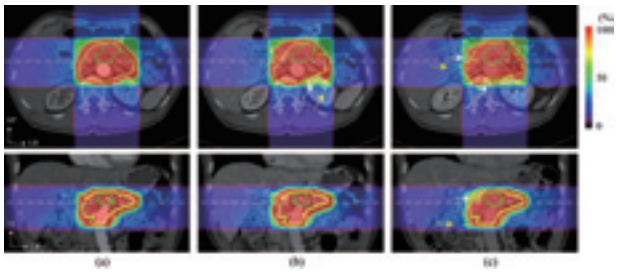
For interfractional analysis, gas in the bowel and stomach could also cause dose variation. However, it is relatively difficult to acquire 4D CT data in the



abdominal region due to the limitation of patient radiation dose. Therefore, triple phase dynamic enhancement CT acquisitions were routinely acquired for diagnostic purposes under inhalation breath-holding using a 16MSCT. After an initial scout topogram and non-enhanced CT scan (native phase) of the abdomen, CT acquisitions were generated in all patients in the helical mode. CT acquisition was started at 35 s (arterial phase), 70 s (venous phase), and 180 s (delayed phase) after injection. The scan interval times of the venous phase and delayed phase from the arterial phase were 35 s and 145 s, respectively. We defined the arterial phase CT data (scan interval time 0 s) as a treatment planning CT and calculated the compensating bolus, which was then applied to the CT data sets at the other two phases.

Figure 3-6 shows carbon ion dose distributions at the scan interval times of 0, 35 and 145 s in axial and coronal sections (patient no.1). Since the bolus was designed to cover the CTV at the planning CT, over 95% of the dose was delivered to the CTV at 0 s. Although anatomical positions at each phase were similar, beam overshoot/undershoot was observed at 35 and 145 s due to extension/shortening of the radiological path length from the anterior and left directions against the planning CT. However, total prescribed dose is not so much a problem even though it causes dose variation due to gas bowel movement.

Fig. 3-6. Carbon ion beam distributions in axial and coronal sections (patient no. 1). Times of (a) 0 s (planning CT), (b) 35 s and (c) 145 s. Beam overshoot (yellow arrows) and undershoot (white arrows) were observed at the scan interval times of 35 and 145 s. Green and yellow lines show GTV and CTV contours, respectively. Red, pink, light blue and blue lines show 95%, 80%, 50% and 30% of doses, respectively.



We evaluated intrafractional organ motion and dose valiation due to interfractional change. Our approached as described here needs to have uncertainties for each treatment planning process quantified in order to provide solutions for increased treatment accuracy. We are convinced, however, that our approach to moving targets in charged particle therapy will be a decisive factor in overcoming these problems and in improving treatment.

3) Quality Control Research Team

Due to frequent radiotherapy accidents, the importance of quality control in radiotherapy has been increasingly recognized. The Quality Control Research Team tries to meet the expectations for safe and reliable radiotherapy through dosimetric research. NIRS has been the Secondary Standard Dosimetry Laboratory (SSDL) for radiotherapy in Japan. The NIRS standard ionization chambers have been calibrated in terms of ^{60}Co exposure by the National Metrology Institute of Japan (NMIJ). More than 700 therapy-level dosimeters from hospitals were calibrated with the NIRS ^{60}Co standard exposure field in the last fiscal year. The team has prepared the standard field of absorbed dose to water and tried to establish measurement traceability in terms of absorbed dose to water in collaboration with NMIJ. The code of practice for therapeutic dosimetry is being revised.

After the establishment of the nation-wide dosimetry audit system using glass dosimeters last year, the team carried out dosimetry intercomparison between this system and the IAEA audit system which is using TLDs (thermoluminescence dosimeters). The results showed a good agreement within 1% for the average dose. This audit system was also applied to the dosimetry intercomparison with Asian countries within the framework of the Forum for Nuclear Cooperation in

Asia (FNCA). China, Korea, Indonesia and Viet Nam had participated in the intercomparison by 2008. The audit detected cases of overexposure with approximately 6% of the dosimeters and recommended the MU value be calibrated correctly.

The Quality Control Research Team has also carried out the studies with regard to dosimetry for therapeutic hadron beam.

The team conducted a nation-wide proton dosimetry intercomparison which involved new proton facilities in Japan. The results showed a good agreement within 0.4% and established there was dose uniformity among the domestic proton facilities.

The team developed a graphite calorimeter for absolute absorbed dose measurements. The graphite calorimeter was applied to the determination of w-value of air for the therapeutic carbon beam. The w-value was evaluated as 35.72 J/C ± 1.5%, which is 3.5% larger than that recommended by the IAEA code of practice for heavy ion beams.

From the viewpoint of microdosimetry, tissue-equivalent proportional counters (TEPCs) were used to study the estimation of clinical dose at HIMAC. The RBE values for carbon beams were calculated by the microdosimetric kinetic model (MKM) and spectra measured with the TEPCs. The field size dependence of the clinical dose was obtained from TEPC measurements.

These research activities are expected to influence other radiotherapy facilities in Japan as well as NIRS itself. We also intend to contribute to the field of radiotherapy internationally in cooperation with organizations such as the IAEA, WHO and the International Organization for Standardization (ISO).

4) Radiological Protection Research Team

a) Dose estimation and protection against medical radiation

Recently, more X-ray CT screenings for early detection of lung cancer have been done because of the usefulness of their image information and relatively lower doses. Most persons undergoing CT screenings are healthy, so the optimization of CT scan conditions is very important. We have measured organ doses of patients participating in the CT screening using an adult anthropomorphic phantom and TLDs under CT scan conditions routinely used at two hospitals. The estimated equivalent doses of thyroid, lung, esophagus, breast, liver and stomach were between 0.8 and 2.6mGy. Based on evaluation of image quality for the CT images as well as estimated doses, adequate CT scan conditions were suggested that consider the optimization of radiation protection in CT screenings for lung cancer.

In addition to the exposures to patients, the occupational exposures of medical radiation workers in brachytherapies were also estimated. TLDs were attached on the clothing and exposed skin surfaces of a physician who performed 125I brachytherapy for prostate cancer treatments, and surface doses during the therapies were directly measured. The results showed that the left hand and arm were higher dose positions of the body, which were nearer to the ^{125}I seeds and the X-ray beam in fluoroscopy. The doses could be reduced to less than 100 μSv when the physician used lead gloves for the protection of the hands. They could also be decreased due to increased consciousness of the physician regarding the exposures and when the physician became more experienced.

To consider radiation safety in proton radiotherapy and CIRT, their secondary neutron doses were measured in five domestic therapy institutes by using neutron rem-counters and water phantoms. Then the results were compared among institutes. The measured doses varied and differences between proton beams and carbon ion beams were observed. The neutron ambient dose equivalents in CIRT were lower than those of proton radiotherapy. To specify the positions producing neutrons, Monte Carlo simulations were made and concrete methods to reduce the exposures of patients to secondary neutrons were studied based on the calculated data. The validations of simulated data by actual measurements are in progress.

b) Survey of medical exposure

A nation-wide survey concerned with X-ray examinations was done by sending questionnaires to about 1,500 hospitals and clinics. The sampled facilities were chosen after categorizing medical facilities into 5 groups depending on their bed numbers. The facilities were requested to supply data on exposure conditions and frequencies in both diagnoses and fluoroscopy in X-ray examinations. The reply data have been analyzed to estimate the total annual frequency and population dose of X-ray examinations by gender and age group. The data on X-ray CT examinations in the survey performed last fiscal year have also been analyzed.

Major publications

1) S. Mori, M. Kumagai, H. Asakura, S. Kandatsu, M. Baba, M. Endo: Magnitude of residual internal anatomy motion on heavy charged particle dose distribution in respiratory gated lung therapy, *International Journal of Radiation Oncology Biology Physics,* 71, 587-594, 2008

2) M. Kumagai, R. Hara, S. Mori, T. Yanagi, H. Asakura, R. Kishimoto, H. Katou, S. Yamada, S. Kandatsu, T. Kamada: Impact of intrafractional bowel gas movement on carbon ion beam dose distribution in pancreatic radiotherapy, *International Journal of Radiation Oncology Biology Physics,* 73, 1276-1281, 2008

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3 .4. RadGenomics Project for Radiotherapy

Takashi Imai, Ph.D.
Director, RadGenomics Research Group

(Outline of Research Career)

Dr. Imai received a Ph.D. from the University of Tsukuba in 1986. Following completion of 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, Institute of Physical and Chemical Research (RIKEN). From 1988 to 1989, he worked in 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. He moved to NIRS in 1994. From 2001 to 2006, he worked as the project leader of the RadGenomics Project. Since 2006 he has been the director of the RadGenomics Research Group.
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Objectives

Normal tissue reactions of cancer patients vary considerably after radiotherapy. A number of observations have indicated that certain genetic factors play important roles in this variability. The aim of the RadGenomics Research Group is to explore the genetic characteristics of both the patient and the bearing tumor, by which the potentially most effective radiotherapy can be delivered. From the molecular-biological standpoint, this will open the way to the development of an individual-oriented radiotherapy. The project will also contribute to future research on the molecular mechanisms of radiation sensitivity in humans.

Progress of Research

1) Patients

Between October 2001 and March 2009, 2,653 patients were registered including 773 breast cancer patients, 345 cervical cancer patients, 855 prostate cancer patients, and 271 head and neck cancer patients. Normal tissue reactions until the third 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) Influence of multiple genetic polymorphisms on genitourinary morbidity after carbon ion radiotherapy for prostate cancer

Objective: To investigate the genetic risk of late urinary morbidity after carbon ion radiotherapy in prostate cancer patients.

Methods and Materials: A total of 197 prostate cancer patients who had undergone carbon ion radiotherapy were evaluated for urinary morbidity. The distribution of patients with dysuria was as follows: Grade 0, 165; Grade 1, 28; and Grade 2, 4 patients. The patients were divided (2:1) consecutively into the training and test sets and then categorized into control (Grade 0) and case (Grade 1 or greater) groups. First, 450 single nucleotide polymorphisms (SNPs) in 118 candidate genes were genotyped in the training set. The associations between the SNP genotypes and urinary morbidity were assessed using Fisher's exact test. Then, various combinations of the markers were tested for their ability to maximize the area under the receiver operating characteristics (AUC-ROC) curve analysis results. Finally, the test set was validated for the selected markers.

Results: When the SNP markers in the SART1, ID3, EPDR1, PAH, and XRCC6 genes in the training set were subjected to AUC-ROC curve analysis, the AUC-ROC curve reached a maximum of 0.86. The AUC-ROC curve of these markers in the test set was 0.77. The SNPs in these five genes were defined as "risk genotypes." Approximately 90% of patients in the case group (Grade 1 or greater) had three or more risk genotypes.

Conclusion: Our results have shown that patients with late urinary morbidity after carbon ion radiotherapy can be stratified according to the total number of risk genotypes they harbor.

3) In-gel multiple displacement amplification of long DNA fragments diluted to the single molecule level

Objective: The isolation and multiple genotyping of long individual DNA fragments are needed to obtain haplotype information for diploid organisms.

Methods and Materials: A limited amount of cellular DNA was carefully released from intact cells into a mildly heated alkaline agarose solution and mixed thoroughly. The solution was then gently aliquoted and allowed to solidify while maintaining the integrity of the diluted DNA. Exogenously provided Phi29 DNA polymerase was used to perform consistent genomic amplification with random hexameric oligonucleotides within the agarose gels. Simple heat melting of the gel allowed recovery of the amplified materials in a solution of the polymerase chain reaction (PCR)-ready form.

Results: The haplotypes of seven SNPs spanning 240 kb of the DNA surrounding the human ATM gene region on chromosome 11 were determined for 10 individuals.

Conclusion: The newly developed igMDA technique described herein, used in combination with the previously established visible multiple SNP typing array, allows convenient experimental haplotype determination with ordinary laboratory instruments. Currently, this method can be used to determine effectively the haplotypes of loci that contain multiple markers, and it allows precise mapping of genes for low numbers of samples such as for individual patients.

4) Visible genotype sensor array

Objective: To develop a visible sensor array system for simultaneous multiple SNP genotyping using a new plastic base with specific surface chemistry.

Methods and Materials: Discrimination of SNP alleles was carried out by an allele-specific extension reaction using immobilized oligonucleotide primers. The 3'-ends of oligonucleotide primers were modified with a locked nucleic acid to enhance their efficiency in allelic discrimination. Biotin-dUTPs included in the reaction

mixture were selectively incorporated into extending primer sequences and were utilized as tags for alkaline phosphatase-mediated precipitation of colored chemical substrates onto the surface of the plastic base.
Results: The visible precipitates allowed immediate inspection of typing results by the naked eye and easy recording by a digital camera equipped on a commercial mobile phone. Up to four individuals were analyzed on a single sensor array and multiple sensor arrays were handled in a single operation. All of the reactions were performed within one hour using conventional laboratory instruments.
Conclusion: This visible genotype sensor array is suitable for "focused genomics" that follows "comprehensive genomics".

5) Aging-dependent large accumulation of muscle-specific point mutations in the transcription/replication control region of human mitochondrial DNA
Objective: The aging-dependent large accumulation of specific point mutations, especially the most frequent mutation T414G, in the cultured human skin fibroblast mtDNA transcription/replication regulatory region raised the question of their occurrence in post-mitotic tissues.
Results: Analysis of biopsied or autopsied human skeletal muscle from variously aged individuals revealed the absence or only minimal presence of those skin fibroblast mutations. By contrast, surprisingly, most of the 26 individuals 53 to 92 years old, without a known history of neuromuscular disease, exhibited at the same region of human mtDNA in muscle an accumulation of two new point mutations, i.e., A189G and T408A, which were absent or marginally present in the muscle of 19 individuals younger than 34 years. These two mutations were not found in the skin fibroblasts from 22 subjects 64 to 101 years of age (T408A), or were present only in three subjects in very low amounts (A189G). Furthermore, in several older individuals exhibiting an accumulation in muscle of one or both of these mutations, they were nearly absent in other post-mitotic tissues, whereas the most frequent fibroblast-specific mutation (T414G) was present in skin autopsy, but not in muscle.
Conclusion: The striking tissue specificity of the aging-dependent mtDNA point mutations and their mapping at critical sites for mtDNA transcription/ replication strongly point to the involvement of a specific mutagenic machinery or a specific advantage for the mtDNA replication/ transmission and to the functional relevance of these mutations during the human aging processes.

6) Expression profiles are different in carbon ion-irradiated normal human fibroblasts and their bystander cells
Objective: Evidence has accumulated that ionizing radiation induces biological effects in non-irradiated bystander cells having received signals from directly irradiated cells; however, energetic heavy ion-induced bystander response is incompletely characterized. Then, microarray analysis of irradiated and bystander fibroblasts in confluent cultures were carried out.
Materials and Methods: Each of 1, 5 and 25 sites was targeted with 10 carbon ions (18.3MeV/u, 103keV/mum) using microbeams. Cultures were exposed to 10% survival dose (D), 0.1D and 0.01D of corresponding broadbeams (108keV/mum). Irrespective of the target numbers (1, 5 or 25 sites) and the time (2 or 6h post-irradiation), similar expression changes were observed in bystander cells.
Results: Among 874 probes that showed more than 1.5-fold changes in bystander cells, 25% were upregulated and the remainder downregulated. These included genes related to cell communication (PIK3C2A, GNA13, FN1, ANXA1 and IL1RAP), stress response (RAD23B, ATF4 and EIF2AK4) and cell cycle (MYCN, RBBP4 and NEUROG1). Pathway analysis revealed serial bystander activation of G protein/PI-3 kinase pathways. However, genes related to cell cycle or death (CDKN1A, GADD45A, NOTCH1 and BCL2L1) and cell communication (IL1B, TCF7 and ID1) were upregulated in irradiated cells, but not in bystander cells.
Conclusion: The results indicate different expression profiles in irradiated and bystander cells, and imply that intercellular signaling between irradiated and bystander cells activates intracellular signaling, leading to the transcriptional stress response in bystander cells.

7) CD44 and Bak expression in IL-6 or TNF-alpha gene knockout mice after whole lung irradiation
Objective: To understand the molecular mechanisms that underlie radiation pneumonitis, we examined whether knockout of the TNF or the IL-6 gene could give mice an inherent resistance to radiation in the acute phase of alveolar damage after thoracic irradiation.
Methods: The temporal expression of inflammation (CD44) and apoptosis (Bak) markers in lung after thoracic irradiation was measured to determine the degree of alveolar damage.
Results: At 4 weeks post-irradiation (10 Gy), small inflammatory foci were observed in all mice, but there were no obvious histological differences between control (C57BL/6JSlc), TNF-alpha knockout (TNF KO), and IL-6 knockout (IL-6 KO) mice. However, immunohistochemical analysis of CD44 and Bak expression over a time course of 2 weeks highlighted significant differences between the three groups. C57BL/6JSlc and TNF KO mice had increased numbers of both CD44-positive and Bak-positive cells after irradiation, while the IL-6 KO mice showed stable

levels of CD44 and Bak.
Conclusion: The radioresistant status of IL-6 KO mice in the acute phase of alveolar damage after irradiation suggests an important role for IL-6 in radiation pneumonitis.

8) The proangiogenic factor ephrin-a1 is upregulated in radioresistant murine tumor by irradiation
Objective: While the pre-treatment status of cancer is generally correlated with outcome, little is known about microenvironmental changes caused by anti-cancer treatment and how they may affect outcome. We attempted to find a gene that was both induced by irradiation and associated with radioresistance in tumors.
Methods and Materials: Using singlecolor oligo-microarrays, we analyzed the gene expression profiles of two murine squamous cell carcinomas, NR-S1, which is highly radioresistant, and SCCVII, which is radiosensitive, after irradiation with 137-Cs gamma rays or carbon ions. Candidate genes were those differentially regulated between NR-S1 and SCCVII after any kind of irradiation. Four genes, Efna1 (Ephrin-A1), Sprr1a (small proline-rich protein 1A), Srgap3 (SLIT-ROBO Rho GTPase activating protein 3) and Xrra1 [RIKEN 2 days neonate thymus thymic cells (NOD) cDNA clone E430023D08 39], were selected as candidate genes associated with radiotherapy-induced radioresistance. We focused on Efna1, which encodes a ligand for the Eph receptor tyrosine kinase known to be involved in the vascular endothelial growth factor (VEGF) pathway. We used immunohistochemical methods to detect expression of Ephrin-A1, VEGF, and the microvascular marker CD31 in radioresistant NR-S1 tumor cells.
Results: Ephrin-A1 was detected in the cytoplasm of NR-S1 tumor cells after irradiation, but not in SCCVII tumor cells. Irradiation of NRS1 tumor cells also led to significant increases in microvascular density, and up-regulation of VEGF expression.
Conclusion: Our results suggest that radiotherapy-induced changes in gene expression related with angiogenesis might also modulate microenvironment and influence responsiveness of tumors.

9) Dose measurement on both patients and operators during neurointerventional procedures using photoluminescence glass dosimeters.
Objective: Although radiation skin injuries associated with interventional radiology are known tobe a critical issue, there are few reports mentioning direct measurement of the entrance skin dose (ESD). Thus, the purpose of this study was to clarify the regional distributions of ESDs in neurointervention.
Materials and Methods: Using photoluminescence glass dosimeters (PLDs), we measured the ESDs in 32 patients with a median age of 61.5 years. Angiographic parameters, including exposure time, dose-area product (DAP), and the number of digital subtraction angiography (DSA) studies and frames, were recorded. The ESDs of operators were analyzed by the same method.
Results: The maximum ESD of 28 therapeutic procedures was 1.8 +/- 1.3 Gy. Although the averaged ESD on the right temporo-occipital region was higher than that in other regions, disease-specific patterns were not observed. Statistically positive correlations were found between the maximum ESD and exposure time ($r = 0.5283$, $P = .005$), DAP ($r = 0.7917$, $P < .001$), the number of DSA studies ($r = 0.5636$, $P = .002$), and the number of DSA frames ($r = 0.8583$, $P < .001$). As for operators, ESDs to the left upper extremity were significantly higher than those to other regions. However, most of the ESDs were <0.2 mGy. Lead protective garments reduced the exposure doses to approximately one half to one tenth.
Conclusion: The regional ESD can be measured by applying the PLD. This method should contribute to reducing the dose accumulation in patients as well as in operators.

Major publications

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2) Y. Michikawa, K. Sugahara, T. Suga, et al.: In-gel multiple displacement amplification of long DNA fragments diluted to the single molecule level, *Anal. Biochem.*, 383[2]: 151-158, 2008
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4) M. Iwakawa, N. Hamada, K. Imadome, et al.: Expression profiles are different in carbon ion-irradiated normal human fibroblasts and their bystander cells, *Mutat. Res.*, 642[1-2], 57-67, 2008
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3.5.Biological Research Concerning the Improvement of Radiation Therapy

Ryuichi Okayasu Ph.D.
Director, Heavy-ion Radiobiology Research Group

(Outline of Research Activities)

Dr. Okayasu received his Ph.D. in radiation biology from Colorado State University, USA in 1987 and worked as a post-doctoral fellow at Thomas Jefferson University, Philadelphia and MD Anderson Cancer Center, Houston. He next took a position at Columbia University as an associate research scientist before moving to the University of Texas Medical Branch at Galveston in 1995 as an Assistant Professor and then onto Colorado State University. In 2002, he moved back to Japan to become a team leader at the International Space Radiation Laboratory (ISRL), NIRS. In 2005 he was appointed as Director of ISRL. In 2006, he changed his sectionwas transferred to the Research Center for Charged Particle Therapy and became Director of the Heavy Ion Radiobiology Research Group.

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Objectives

There are three mid-term plans for the Heavy Ion Radiobiology Research Group. Plan 1 has one goal: to provide biological experimental data for analyzing clinical data with regard to tumor control ratio and normal tissue responses for various radiation therapy protocols. Plan 2 has two goals: to estimate the risk and benefit ratio between tumor cell killing and normal tissue sparing by theoretical calculations based on patients1 dose distribution as well as experimental data on cell and animal studies; and to propose a more efficient radiation therapy regimen by comparing heavy ion radiotherapy and other radiotherapy protocols such as use of X-rays. Plan 3 has four goals: to explore radiosensitizers and protectors which can be used with heavy ion radiotherapy; to elucidate the mechanism of effective heavy ion treatment for hypoxic tumor cells which show strong resistance to radiation;, to study the indirect (bystander) effects of radiation which occur in non-irradiated cells adjacent to irradiated cells; and to integrate the proposals of Plan 2 to improve radiation therapy and accumulate biological data resources for a new cancer therapy.

These objectives are studied by four teams: 1) Biophysics Team; 2) Experimental Therapy Team; 3) Cellular and Molecular Biology Team; and 4) Radiation Modifier Team. Each team has different objectives, however, cooperation among four teams is sought in order to accomplish the goals of the group.

Progress of Research

Biophysics Team

To estimate relative biological effectiveness (RBE) for unknown ion beams at a defined linear energy transfer (LET), an experimental fitting function of the LET-RBE relationship was proposed. Experimentally obtained LET-RBE spectra of survival curves for V79 cells exposed to ^{3}He-, ^{12}C-, ^{20}Ne, ^{28}Si-, ^{40}Ar, and ^{56}Fe-ion beams with the LET range of 10-500 keV/㎛ were applied for the study; the exposures were done at the HIMAC, the Medical Cyclotron, and the RRC/RIKEN. Cell survival curves were fitted by an equation of the LQ-model to obtain survival parameters (a and b). The RBE spectrum was analyzed as a function of LET for each ion beam using the proposed function with three parameters: Lp, A, and W. The respective parameters indicate a LET that gives the maximum RBE, a related value to maximum RBE, and the width of the peak of RBE. Clear splits of the LET-RBE spectra were found among ion species. It was also found that those parameters can be defined as functions of atomic numbers (or atomic mass numbers) of the accelerated ion beams. The LET that gave the maximum RBE shifted to higher LET region, and the maximum RBE value decreased with increasing atomic number. The width of the peak was constant when the atomic mass number was smaller than 20, but it increased when the mass number was greater than 20. This method is applicable to estimate overall RBE in therapeutic beams. This is because the beam must consist of different ions having different RBEs that are produced by projectile fragmentation of the beam when passing through a patient1s body or absorbing materials when adjusting beam range in the body . The biological endpoint for this study was limited to the cell survival at 10 % for one cell line. It is necessary to analyze different biological endpoints and different cell lines. We are continuing to study the LET-RBE spectra for different cell lines, DNA damage and cell killing by direct or indirect action of radiation, mutation and transformation for different ion beams at various LETs.

Experimental Therapy Team

Our data confirmed that the RBE values by carbon ions at three different LET values 15, 45, 75 keV/μm were 0.6, 1.0 and 1.4 respectively when calculated at 20% tumor formation frequency of irradiated mice. Furthermore, we have as ongoing research study examining the biological effect of the ratio of cells with two distinct radiosensitivities *in vivo*. Towards this end, *in vitro* colony assay data have been applied.

To investigate the relationship between LET and skin reaction, we have performed fractionated mono-peak irradiation on the normal mouse foot. The α/β ratios were 28 and 39 Gy^{-1} for LET values of 58 and 14 keV/μm, respectively, and 38 Gy^{-1} for γ rays. There seems to be no significant difference among the α/β ratios.

In addition, we have found that carbon-ion irradiation can curatively eradicate transplantable human colon cancer, which showed radioresistance to conventional X-rays, and the suppression of tumor-induced angiogenesis and the disruption of cancer stem cells were considered to be crucial molecular mechanisms of heavy ion radiotherapy. The RBE value for carbon ions (relative to X-rays) for *in vivo* tumor control was 3.82.

Cellular and Molecular Biology Team

Biological differences between X-ray and heavy ion particle (e.g., C, Fe, Ne) irradiations were demonstrated using some quantitative assays such as immune staining with phophorylated proteins and chromosome aberrations, focusing on the molecular mechanism for the early stage of DNA damage response at therapeutic level radiation doses. Using several radiosensitive mutant cell lines, we aimed at understanding the role of either homologous recombination or non-homologous end joining on the mechanism under the repair process of DNA double-strand breaks induced by various

heavy-ion particles.

HiCEP, a novel comprehensive gene expression technique developed in NIRS, was applied to normal human fibroblasts which were irradiated with X-rays and carbon ion particles at a dose of 2 Gy. A group of early responsive IR-induced genes (ATF3, BTG2, TP53INP1) remained activated for a longer period in human cells irradiated with carbon ion particles when compared with conventional X-rays. Our team, for the first time, revealed that the expression of ASPM, a microcephaly gene was significantly downregulated by IR in human and murine cells.

Radiation Modifier Team

This team has studied three subjects. Biosynthetic precursors of vitamin E are known to have a substituted *p*-hydroquinone structure. In order to develop better compounds for free radical scavenger, a kinetic study for free radical scavenging reaction of vitamin E precursors and their derivatives was carried out. The second-order rated constants determined by the stopped-flow technique suggested that the electron-donating groups on the benzene ring of *p*-hydroquinones significantly enhance the free radical scavenging activity. Regarding the second subject, radiation-protectors and radiation-mitigators, several compounds that had been found to be effective against low LET radiation-induced injury were found to protect or mitigate bone marrow death of mice induced by carbon ion radiation, too. As the third subject, the distribution of anti-cancer drugs into the brain was visualized using nitroxyl labeled anti-cancer drug and 7T MRI in a collaboration with the Molecular Imaging Center. A new data acquisition method for CW EPR spectral-spatial imaging was proposed. Details of reactions between nitroxyl radical and glutathione were investigated. Depth-dependent free radical generation in gelatin sample caused by irradiating a carbon ion mono beam was detected with a nitroxyl contrast agent using EPR spectroscopic and MRI methods.

Major publications

1) K. Manda, M. Ueno, K. Anzai: Cranial irradiation-induced inhibition of neurogenesis in hippocampal dentate gyrus of adult mice: attenuation by melatonin pretreatment, *Journal of Pineal Research,* 46, 71-78, 2009

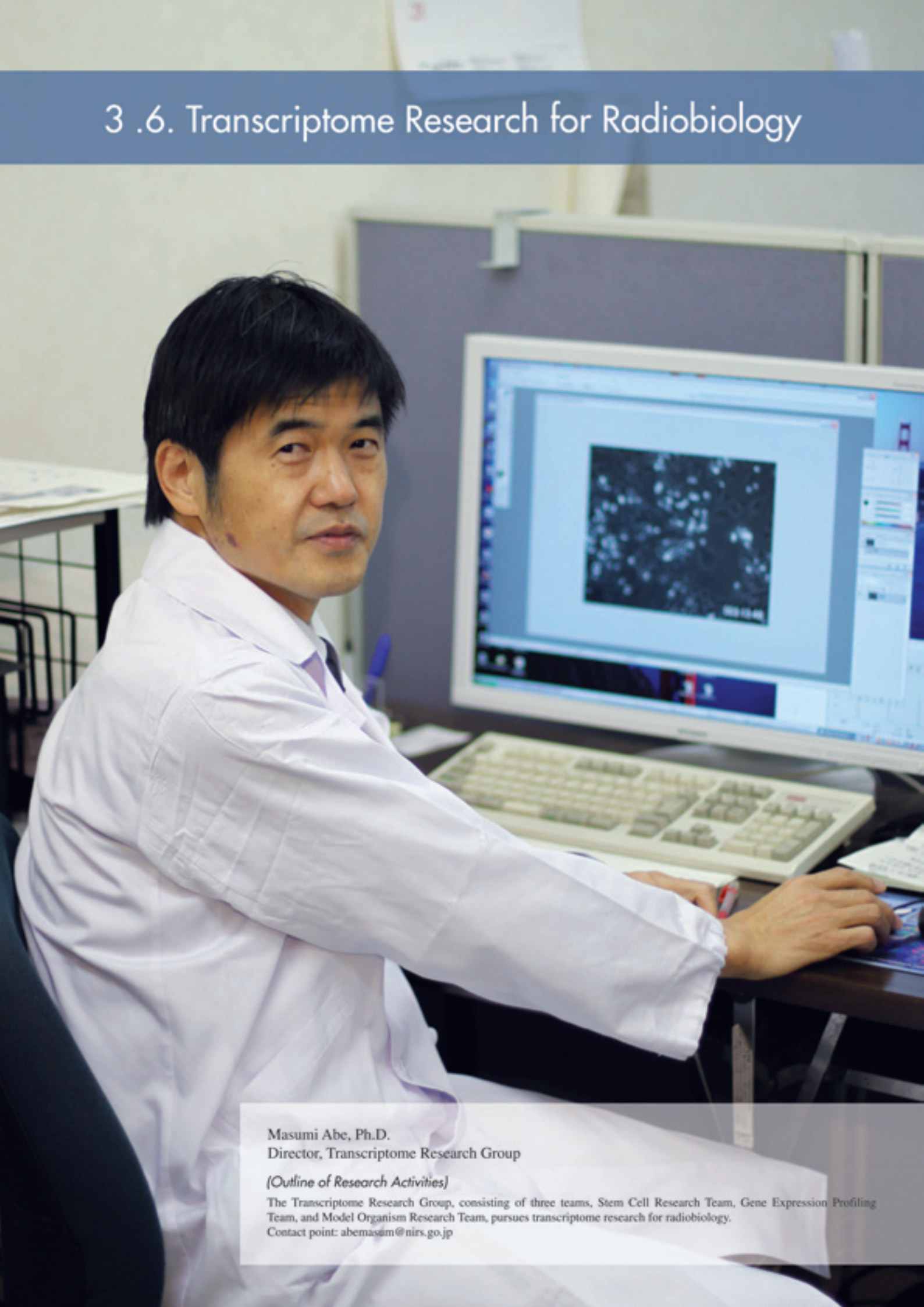
2) K. Matsumoto, K. Anzai, H. Utsumi: Simple data acquisition method for multi-dimensional EPR spectral-spatial imaging using a combination of constant-time and projection-reconstruction modalities, *Journal of Magnetic Resonance,* 197, 161-166, 2009

3) A. Fujimori, W. Bing, K. Suetomi, et al.: Ionizing radiation downregulates ASPM, a gene responsible for microcephaly in humans, *Biochemical and Biophysical Research Communications,* 369, 953-957, 2008

4) C. Tsuruoka, M. Suzuki, P. Hande, Y. Furusawa, K. Anzai, R. Okayasu: The difference in LET and ion species dependence for induction of initially measured and non-rejoined chromatin breaks in normal human fibroblasts, *Radiation Research,* 170, 163-171, 2008

5) R. Hirayama, A. Ito, M. Tomita, et al.: Contributions of Direct and Indirect Actions in Cell Killing by High LET Radiations, *Radiation Research,* 171, 212-218, 2009

3 .6. Transcriptome Research for Radiobiology



Masumi Abe, Ph.D.
Director, Transcriptome Research Group

(Outline of Research Activities)

The Transcriptome Research Group, consisting of three teams, Stem Cell Research Team, Gene Expression Profiling Team, and Model Organism Research Team, pursues transcriptome research for radiobiology.

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Objective

Transcriptome Research Group, consisting of three teams, Stem Cell Research Team, Gene Expression Profiling Team, focuses on and Model Organism Research Team, the effect of radiation at an individual level not at a cellular level only.

Progress of Research

1) Stem Cell Research Team

This team has been focused on germ stem cells. It is known that several genes are expressed both in embryonic stem cells (ESCs) and germ stem cells. However, their function in germ stem cells is still unknown. Our team identified a new gene that expresses in both ESCs and spermatogonial stem cells (SSCs). We generated its knockout mice and found a severe defect in their spermatogenesis, resulting in an accumulation of SSCs in the mice. Further study revealed that the gene plays a role in the differentiation step of SSCs.

Recently the team is also conducting a new project on iPS cells. It has been demonstrated that somatic cells can be converted into pluripotent stem cells by ectopic expression of four genes, Oct3/4, Klf4, Sox2 and cMyc genes, designated as iPS cells. The objective of this program is to understand the molecular mechanism underlying iPS generation. First, we attempted to observe the emergence of iPS cells from somatic cells. To this end, we developed a new investigation system by improving a pre-existing time-lapse system. Consequently, we made the first successful detection of the conversion process of a fibroblast into a stem cell. Quite interestingly such cell lineage conversion occurred within 3 days after the defined gene infection. Furthermore, by means of the HiCEP (High Coverage gene Expression Profiling) method, which has been developed by our 'Gene Expression profiling Team' as mentioned below, we isolated the genes which are closely related in iPS emergence from Day 3 fibroblasts, in which approximately one per 2,000 fibroblasts were converting into stem cells. Currently, we are focusing on their functions.

2) Gene Expression Profiling Team

The HiCEP method that we have developed is an ideal tool for transcriptome analysis, and it is based on a principle different from that for hybridization-based methods. HiCEP technology enables us to achieve comprehensive analysis of transcripts including novel ones.

This year we attempted to improve the HiCEP method to achieve the analysis by using even a small amount of starting materials. At the beginning of HiCEP development, approximately 1 μg of poly (A) RNA was needed for the analysis; however, subsequent improvement has allowed us to perform the analysis with a total RNA amount of 0.1 μg which corresponds to 10,000 mammal cells. This year we successfully developed a new protocol using 200 pg of total RNA, corresponding to 20 of mammalian cells.

Applying this new protocol of the HiCEP method to single cell transcriptome analysis, which contains approximately 10 pg of total RNA, we could observe only about 10,000 transcripts, almost all of which were highly expressed. Now we are attempting to develop an analysis using fewer than 10 cells with high coverage detection.

Using HiCEP technology, we are also beginning a new program for medical applications. The ethical committee of NIRS has authorized our proposal, and we have set up an area and system that will allow us to perform the HiCEP analysis on human materials. The first trial will be started soon.

3) Model Organism Research Team

This team has been primarily supporting other research teams, especially the Stem Cell Research Team. They have generated TG mouse for one gene and KO mice for two genes.

In addition, they are studying spermatogenesis using the spermatogonial stem cell transplantation technology. Functional analysis on iPS cells were also performed by this team.

4 . Molecular Imaging Center

Iwao Kanno, Ph. D.
Director, Molecular Imaging Center

(Outline of Research Activities)

Iwao Kanno started his professional career at Akita Research Institute of Brain and Blood Vessels in 1970, where he was an active researcher for 36 years. In 1997, he developed a custom radionuclide emission tomography system using a handmade rotational dentist chair. In 1979 he developed a hybrid type of emission tomography which combined positron emission tomography (PET) and single photon emission computed tomography (SPECT). His efforts were also directed to developing methodology for quantitative assessment of physiological and biochemical parameters from PET and SPECT images. In 1997, he developed a custom radionuclide emission tomography system using a handmade rotational dentist chair. In 2006, he joined NIRS where he continues his research career.

Objectives

Progress in molecular biology has opened the window to understanding the molecular mechanisms of living healthy and diseased organs. Molecular imaging is a new interdisciplinary field that integrates imaging technology and molecular biology to help visualize molecular behaviors spanning the microscopic to macroscopic scales. PET , magnetic resonance imaging (MRI) and optical imaging will provide clear and comprehensive images demonstrating molecular functions. The Molecular Imaging Center consists of four research groups, Diagnostic Imaging Group, Molecular Neuroimaging Group, Molecular Probe Group and Biophysics Group, and the Research Promotion Unit. The Molecular Imaging Center aims to image molecular functions of living animals in both healthy and diseased conditions. Of several methodologies for imaging molecular functions, the center covers *in vivo* molecular imaging from rodents to humans. It is already a world leader in the development of PET probes and technologies, and it also has invested efforts in other promising technologies such as MRI. Our primary goals are to move towards understanding the mechanism of brain function and cancer pathology and to use this knowledge in clinical applications.

Overview

The Diagnostic Imaging Group continued our clinical PET study with FLT, a marker of cell proliferation, in the evaluation of cancer patients receiving carbon ion radiotherapy in collaboration with the Research Center for Charged Particle Therapy. A multi-center study of PET with ^{62}Cu-ATSM, a marker of tumor hypoxia, is also being conducted. To identify novel targets of mesothelioma, functional screening using siRNA was carried out, which newly identified at least 7 genes having anti-apoptotic function. One of these genes is now being investigated as a target of siRNA-based treatment of malignant mesothelioma. We also found that cellular contents of Mn and Mn-SOD are increased in various mesothelioma cells, suggesting the biological significance of Mn in mesothelioma. We then attempted the visualization of mesothelioma using Mn-MRI, which is giving promising results. Research on the development of an antibody probe for cancer imaging was continued using anti-c-kit and anti-ERC/mesothelin monoclonal antibodies. For the application to PET imaging, a labeling method with ^{64}Cu was optimized and biodistribution of radiolabeled Fab fragments was evaluated. Research on PET imaging of cancer neovascularization using ^{64}Cu-labeled RGD peptide is also ongoing. A novel probe to detect the activated state of EGFR was designed, which showed specific retention in cancer cells with EGFR activation. A rat model of syngeneic and allogeneic liver transplant was established and FDG-PET was proven to be useful not only in the detection of acute allograft rejection but also in the evaluation of immunosuppressive treatment.

The Molecular Neuroimaging Group established PET quantification methods using a dopamine D2 receptor agonistic probe, [^{11}C]MNPA and a peripheral benzodiazepine receptor (PBR) probe, [^{11}C]AC-5216. The inverted U-shaped relation between the prefrontal dopamine D1 receptor and the cognitive function was found in healthy subjects. The functional MRI study showed that the emotion of “envy” was regarded as a psychological pain as suggested by the activated regions. Clinical PET studies with patients demonstrated the increase in the striatal ki of [^{11}C]DOPA in schizophrenics and the widespread accumulation of [^{11}C]DAA1106 in the brain of Alzheimer's disease sufferers. PET protocols calculating the D2 receptor occupancy to evaluate therapeutic effects of antipsychotics have been optimized. An *in vitro* imaging analysis of mice modeling a psychotic state revealed prominent changes in levels of monoamine neuroreceptors and transporters. A PET study of awake rats and monkeys elucidated the localization of metabotropic glutamate receptors involved in the regulation of the striatal dopamine release. Two newly developed ^{18}F radioligands for amyloid plaques and some imaging agents of fibrillar tau were evaluated by *in vivo* imaging tools accompanied with model mice and they are expected to be useful for clinical diagnoses. Utilization of our original materials for PBR delineated that PBR could be upregulated among the gliosis in the brain of Alzheimer's disease model mice and confirmed the correlation between levels of PBR and glial cell line-derived neurotrophic factor in activated astrocytes. Brain regions relating to the addictive cocaine intake in monkeys were identified using $H_2{}^{15}O$ PET, although no changes of dopamine D1 and D2 receptors in extrastriatal regions have been found. Modeling of Parkinson's disease using MPTP-treated marmosets was established and the prominent loss in dopamine transporters by means of [^{11}C]PE2I PET was demonstrated.

The Molecular Probe Group has been developing novel molecular probes for PET and SPECT imaging. We developed a method for assessing multidrug resistance-associated protein 1 (MRP1) function *in vivo* using PET and a newly developed PET probe, 6-halo-7-[^{11}C]methylpurine. When the molecular probe was administrated to Mrp1 knockout mice, the efflux rate of the radioactivity was reduced to approximately 90% compared with wild-type mice. This is the world's first method which allows noninvasive and quantitative assessment for exporter function in the living brain. We also evaluated [^{11}C]DAC as a novel PET ligand and for

imaging of PBR in kainic acid-lesioned rat brain. A small-animal PET study determined that [^{11}C]DAC had high uptake in the lesioned region, where PBR density was increased. The high *in vivo* specific binding of [^{11}C]DAC to PBR is available as a new biomarker for brain injuries, neuroinflammations, and tumors, etc. Moreover [^{11}C]gefitinib was synthesized and used for tumor imaging and evaluation of P-gp/BCRP function. In vivo distribution study on NFSa-bearing mice revealed that [^{11}C]gefitinib specifically accumulated into the tumor. A PET experiment produced a clear tumor image in mice. It was demonstrated that the brain penetration of [^{11}C]gefitinib was related to both P-gp and BCRP. In order to develop a new labeling method, [^{13}N]NH_3, [^{11}C]acetyl chloride and [^{11}C]nitromethane were applied for the synthesis of [^{13}N]urea, [11C]oseltamivir and 2-Amino[2-^{11}C]ethanol. A new synthesis apparatus which supports synthesis of [^{11}C]oseltamivir from a preparation of [^{11}C]acetyl chloride and using the [^{11}C]acetylation reaction and subsequent deprotec-tion reaction, was developed. The apparatus can produce [^{11}C]oseltamivir in sufficient yield and quality for animal PET studies. A rapid and efficient preparative high-performance liquid chromatographic procedure utilizing a hydrophilic interaction chromatography column and a highly volatile organic mobile phase was established to purify short-lived PET probes. Four new PET probes ([^{11}C]Ac5216, [^{18}F]TO-002, [^{11}C]gefitinib and [^{18}F]FAZA) were approved by the Institutional Review Board at NIRS and released for clinical research.

The Biophysics Group consists of four teams. The Magnetic Resonance Molecular Imaging Team investigated: therapeutic drug delivery imaging using a temperature-sensitive liposome; a multimodal nano-probe using quantum-dots; detection of reactive gliosis; immunocyte labeling and tracking; and a multimodal therapeutic contrast agent using nitroxyl radical. The Biosignal Physiology Team investigated: diffusion functional MRI; MR elastography for clinical use; human studies using evidence-based molecular imaging; direct visualization with fluorescent microscopy; and intracortical microcirculation visualized with multi-photon microscopy. The Image Analysis Team developed algorithms and experimental apparatuses to measure and visualize various functionalities of humans and animals using PET, and also developed a system for arterial sampling from mice in which the allowed amount of sampled blood is 1 μL. The Imaging Physics Team proposed an improved OpenPET geometry. The OpenPET mainly has three applications, namely, simultaneous PET/CT, extension of the axial FOV, and in-beam PET, which is a method for *in situ* and non-invasive monitoring of tumor-conforming charged particle therapy. This team also proposed a new depth-of-interaction (DOI) PET detector design, which was named "X'tal cube". Recently, small, light, and thin photodetectors such as avalanche photodiodes (APDs) or multi-pixel photon counters (MPPCs) have become commercially available as alternatives to photomultiplier tubes (PMTs). In this design, therefore, a number of the small photodetectors are coupled to a 3-dimensional scintillation crystal array at any six surfaces.

4.1. Research on Molecular Imaging of Cancer

Tsuneo Saga, Ph.D.
Director, Diagnostic Imaging Group

(Outline of Research Career)

Dr. Saga received a Ph.D. from Kyoto University in 1991 for his investigations on cancer targeting of radiolabeled monoclonal antibodies. He continued his research on antibody targeting at the National Institutes of Health (1991-1993) and at Kyoto University (1995-2006). In addition, for the last 9 years, he has been conducting clinical and basic research covering the wide area of cancer imaging. Since 2006, he has been the leader of the Diagnostic Imaging Group at NIRS; this group works to further advance the basic and clinical research on molecular imaging of cancers.

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Objectives

The Diagnostic Imaging Group is conducting research on functional imaging of cancer by PET and other modalities. By using various cancer-specific probes, the characteristics of an individual cancer such as malignant grade and responsiveness to treatment can be clarified. This information can be used for treatment planning and evaluation of therapeutic effect. Although several PET probes such as FDG and ^{11}C-methionine are available for clinical studies, development of new imaging probes is necessary for more comprehensive evaluation of cancers and to further contribute to the management of cancer patients.

The Clinical Diagnosis Team focuses on clinical research of oncological PET and is aiming to contribute to the management of cancer patients including those considered for carbon ion radiotherapy (CIRT) conducted in the Hospital of the Research Center for Charged Particle Therapy. In addition to FDG and ^{11}C-methionine, we are evaluating newly developed cancer-imaging probes, such as ^{18}F-FLT and ^{62}Cu-ATSM, to determine their clinical usefulness.

The Molecular Diagnosis Team conducts basic molecular imaging research focusing on designing and evaluation of PET probes that capture and depict the changes of biomolecules specifically associated with cancers and other diseases to realize effective non-invasive diagnoses. We also develop novel *in vivo* reporter gene imaging systems to facilitate the establishment of new therapies such as gene therapy and regenerative therapy.

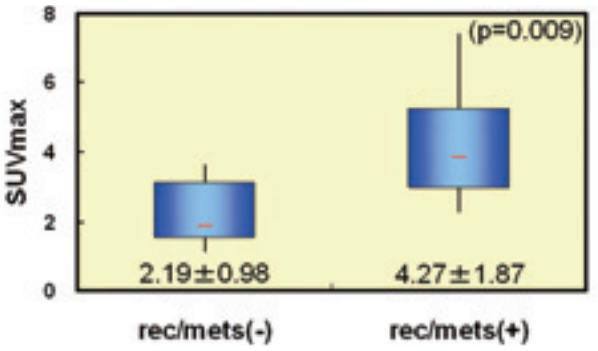
The Biomolecule Team focuses on elucidating genetic/molecular events occurring during carcinogenesis and searching for suitable targets of molecular imaging of cancers. By using functional screening of genes and proteome analysis of the blood and tissue samples, we select the genes and proteins specifically expressed in cancers. Through the exploration of the targets with high specificity, we are aiming for the development of novel molecular imaging methods which can depict the characters of each cancer.

Progress in Research

1) Clinical studies on cancer imaging using various PET probes

We are conducting clinical PET research using FLT, a marker of cell proliferation, in the evaluation of effectiveness of CIRT. Data from more than 20 lung cancer patients showed that the development of radiation pneumonitis after CIRT modified tumor FLT uptake and made precise post-treatment evaluation difficult. More importantly, patients who developed recurrence/metastasis showed significantly higher pre-CIRT FLT uptake than patients who did not develop recurrence/ metastasis.(Fig. 4-1)

Fig. 4-1 Comparison of pre-CIRT FLT uptake with the development of recurrence/metastasis



We are also conducting PET with ^{62}Cu-ATSM, a marker of tumor hypoxia, for cancer patients receiving CIRT. The uptake pattern of ^{62}Cu-ATSM varied from that of ^{11}C-methionine probably reflecting the difference in distribution of tumor hypoxia and amino acid metabolism within the tumor tissue. Comparison with the treatment response is ongoing.

2) Loss of function screening to identify therapeutic and diagnostic targets in malignant mesothelioma

Malignant mesothelioma is a highly aggressive tumor arising from serosal surfaces of the pleura. To identify therapeutic and/or imaging molecular targets, we conducted a large-scale functional screening of mesothelioma cells using small interfering RNAs (siRNAs) against 8,589 human genes. We determined that knockdown of 39 genes apparently suppressed mesothelioma cell prolifera-tion. At least seven of these 39 genes would be involved in an anti-apoptotic function. One of them was highly expressed in some mesothelioma cell lines, but not in a normal mesothelial cell line. Knockdown of this gene using siRNAs induced apoptosis and suppressed tumor growth not only *in vitro* but also *in vivo*. This gene would be useful for developing effective therapeutic agents of mesothelioma.

4) Development of animal models to facilitate the development of imaging probes and therapies

In the development of cancer imaging probes and therapy strategies, model animals play crucial roles. Other than mouse models, we have developed a fluorescent cancer model in “Medaka” . The GFP (green fluorescent protein) expressing tumor cells were grown at the injection site, and the spatiotemporal changes were visualized under a fluorescence stereoscopic microscope with a cellular level-resolution,

even at a single cell level. Tumor dormancy and metastasis were also observed. Our Medaka model provides a new opportunity to visualize *in vivo* tumor cells "as seen in a culture dish" and is useful for *in vivo* tumor cell biology and facilitates the development of cancer imaging probes and therapeutics.

5) Development of PET/SPECT tumor imaging using antibody probes

For the imaging of c-kit-positive tumors such as gastrointestinal stromal tumor, we labeled anti-c-kit monoclonal antibodies (MAbs) (IgG and Fab) with single-photon (^{125}I/^{111}In) and positron (^{64}Cu) emitters, and assessed their *in vitro* and *in vivo* characteristics. The radiolabeled MAbs showed specific binding to c-kit-expressing cancer cells and ^{111}In-labeled IgG and ^{64}Cu-labeled Fab highly accumulated in xenografted tumors which were clearly visualized by SPECT and PET.

To image epithelioid mesothelioma, radiolabeled MAbs (IgG and Fab) recognizing the mesothelioma related antigen (ERC/mesothelin) was also assessed. The radiolabeled MAbs specifically bound to mesothelioma cells and were internalized after binding. ^{111}In-labeled IgG and ^{64}Cu-labeled Fab accumulated in xenografted tumors which were readily visualized by SPECT and PET.

6) Development of novel reporter gene imaging

In order to develop a novel reporter gene imaging, we are evaluating a ferritin heavy chain (FHC) gene as a reporter. *In vitro* experiments demonstrated that cells transiently expressing FHC gene showed increased cellular uptake of iron resulting in the decreased T2 weighted (T2W) MR signal. When the plasmid designed to express FHC gene together with RFP (red fluorescent protein) was electroporated into mouse subcutaneous tumor, a localized region of lowered T2W signal was observed which coincided with the region of RFP expression. Now we are exploring the possible application of this reporter gene, including a model stably expressing FHC.

7) Search for specific molecular target of mesothelioma imaging and its visualization

During the extensive search for specific molecular targets of mesothelioma imaging, we found that the contents of heavy metals, such as manganese (Mn) and copper (Cu), in various mesothelioma cell lines, are increased compared to normal mesothelial cells indicating the possibility that these heavy metals are involved in mesothelioma formation and/or progression. The Mn content in each cell line was especially well correlated with Mn-SOD expression, suggesting the biological significance of Mn in mesothelioma cells. We then attempted the visualization of mesothelioma using Mn-MRI. MRI imaging of the mesothelioma cells expressing a high level of Mn-SOD gave enhanced MRI images *in vitro* and the *in vivo* MRI imaging of xenografts of the cells are giving promising results as well.

8) Development of neovascularization and tumor imaging by PET

Tumor neovascularization is important not only in the local growth of tumors, but also in tumor invasion and metastasis. Integrin $\alpha_v\beta_3$ is expressed on the surface of endothelial cells of newly formed vessels in tumors and on some tumor cells. Various analogs of RGD peptides bind to integrins and have been used for imaging tumor neovasculature. Among them, RAFT-c(RGD)$_4$ which was developed by Dr. Dumy and contains 4 cyclic RGDs in a single molecule (RGD tetramer) is a very specific and high affinity ligand for integrin $\alpha_v\beta_3$. In collaboration with Dr. Dumy's group, we have synthesized cyclam conjugated RAFT-c(RGD)$_4$, which can be labeled with positron emitting Cu isotopes and used for PET imaging. The labeling with Cu-64 was very efficient and the radiochemical purity was over 90% without purification. The initial small animal PET imaging of integrin $\alpha_v\beta_3$ overexpressing tumor gave clear visualization of the tumor.

9) Development of PET probes for EGFR imaging

EGFR (epidermal growth factor receptor) is often overexpressed and/or mutated in many cancer cells and its abnormal activation is implicated in carcinogenesis and cancer progression. To characterize the cancer and aid treatment planning, we attempted to develop imaging probes to capture the activated state of EGFR. We designed a peptide probe binding to activated EGFR based on the SH2 domain of Grb2, adding TAT for delivery into cells and tissues. *In vitro* experiments confirmed the uptake of the peptide probe into the cells leading to the binding to EGFR. Now we are exploring possible use of the probe *in vivo.*

10) ^{18}F-FDG-PET of acute allograft rejection and therapy efficacy in liver transplantation rat models

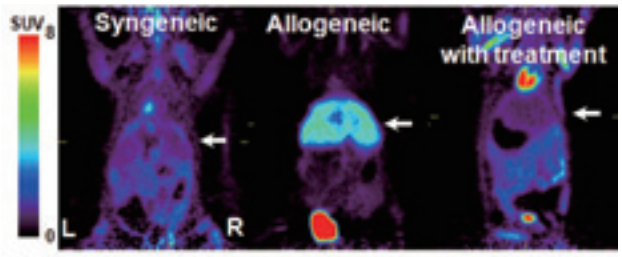
Acute liver allograft rejection remains a major complication after liver transplantation. We developed a semi-quantitative imaging method of detecting acute allograft rejection using ^{18}F-FDG-PET. We established syngeneic and allogeneic liver transplantation models in rats. ^{18}F-FDG uptake significantly increased in liver allografts on day 2 and further increased thereafter. Histopathological study on day 3 exhibited moderate rejection of the allografts. Autoradiography showed that ^{18}F-FDG signals were concentrated in the area where inflammatory cells aggregated around the vessels. Administration of immunosuppressive agents prevented the increase in hepatic ^{18}F-FDG uptake (Fig.

4-2). ^{18}F-FDG-PET imaging would be a valid method for the diagnosis of graft rejection and also for the monitoring of immunosuppressive therapy.

Fig.4-2. Detection of acute rejection and the effect of immunosupression by FDG-PET

11) CIRT efficacy in mouse model of malignant mesothelioma

Since the prognosis of patients with malignant mesothelioma with current multimodality therapy remains poor, it is important to develop a new and



FDG-PET on Day 9

more effective treatment. To assess the efficacy of CIRT for mesothelioma, we evaluated its effect in epithelioid and sarcomatoid mesothelioma mouse models. Both epithelioid and sarcomatoid tumor xenografts irradiated with 15-Gy carbon ion irradiation apparently regressed. We have conducted further experiments at higher doses of carbon ions or X-rays, and are measuring PET tracer uptake in tumors after irradiation to explore the correlation of treatment effect and the uptake of PET tracers.

Major publications

1) M. Koizumi, T. Saga, K. Yoshikawa, et al.: 11C-Methionine -PET for Evaluation of Carbon Ion Radiotherapy in Patients with Pelvic Recurrence of Rectal Cancer. Mol *Imaging Biol* 10, 374-80, 2008

2) S. Hasegawa, M. Koshikawa, I. Takahashi, M. Hachiya, T. Furukawa, M. Akashi, S. Yoshida, T. Saga: Alterations in manganese, copper, and zinc contents, and intracellular status of the metal-containing superoxide dismutase in human mesothelioma cells. *J Trace Elem Med Biol* 22, 248-55, 2008

3) Y. Saito, T. Furukawa, Y. Arano, Y. Fujubayashi, T. Saga: Comparison of semiquantitative fluorescence imaging and PET tracer uptake in mesothelioma models as a monitoring sysytem for growth and therapeutic effects. *Nucl Med Biol* 35, 851-860, 2008

4) A. U Winn, S. Hasegawa, M. Koshikawa, T. Obata, H. Ikehira, T. Furukawa, I. Aoki, T. Saga: Visualization of in vivo electroporation-mediated transgene expression in experimental tumors by optical and magnetic resonance imaging. *Gene Therapy* (in press)

5) A. Tsuji, C. Sogawa, H. Sudou, et al.: 18F-FDG-PET for semiquantitative evaluation of acute allograft rejection and immunosuppression therapy efficacy in liver transplantation rat models. *J Nucl Med* (in press)

4.2. Molecular Neuroimaging Research

Tetsuya Suhara, MD., Ph.D.
Director, Molecular Neuroimaging Group

(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 began working at NIRS in 1989. From 1992-1993, he studied in the PET group of the Department of Clinical Neuroscience, Karolinska Hospital, Sweden. He has researched brain functional imaging for many years. He has served as a visiting professor at the Department of Neuropsychiatry, Nippon Medical School from 2004, and at the Graduate School of Medicine, Yokohama City University from 2006.

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Objectives

1) Clinical Neuroimaging

a) Develop PET quantification methods for the dopamine D2 receptor agonistic probe, [^{11}C]MNPA, and the peripheral benzodiazepine receptor (PBR) probe, [^{11}C]AC-5216.

b) Explore the relation between the regional dopaminergic neurotransmission functions and the higher brain functions in healthy human subjects.

c) Investigate the pathologies of schizophrenia and Alzheimer's disease using PET.

d) Optimize PET measurements of the receptor occupancy to evaluate therapeutic effects of psychotropic drugs.

2) Molecular Neurobiology

a) Conduct an exploratory search for therapeutic means capable of pharmacolo-gically alleviating abnormal phenotypes in rodent models of psychiatric disorders, on the basis of mechanistic links between an aberrant monoaminergic neurotransmission and behavioral alterations.

b) Apply *in-vivo* imaging systems for Alzheimer model mice to: (i) evaluate novel ^{18}F-labeled amyloid-binding agents potentially useful for early detection and therapeutic assessments of the disease; and (ii) develop imaging probes for differentiation of Alzheimer's disease from non-Alzheimer dementias.

c) Clarify roles played by peripheral benzodiazepine receptors (PBRs) and allied functional molecules in glial cells toward the therapeutic regulation of neuropyschiatric disorders.

3) System Neurochemistry

a) Establish experimental environments for transgenic monkeys.

b) Identify the neural mechanism for addiction and the underlying neurochemical mechanism, especially at the neurotrans-mitter level.

c) Carry out trials on a neurophysiological basis for addiction, referring to PET activation results.

d) Carry out PET analysis of Parkinsonian marmosets.

Progress of Research

1) Clinical Neuroimaging

a) The optimal quantification methods and PET scanning protocols were established for [^{11}C]MNPA and [^{11}C]AC-5216 using measured PET data in healthy human subjects.

b) The inverted U-shaped relation between prefrontal dopamine D_1 receptor and the cognitive function (WCST performance) in normal volunteers was found in healthy subjects . With the functional MRI technique, it was revealed that the emotion of "envy" induced neural activation in the anterior cingulate cortex.

c) PET studies with [^{11}C]DOPA demonstrated that patients with schizophrenia showed an increase in dopamine synthesis rates (k*i*) in the striatum. A significant correlation between k*i* in thalamus and the score of severity of symptoms was also observed . The widespread accumulation of [^{11}C]DAA1106 was observed in the brain of patients with Alzheimer's disease, indicating the expression of PBR due to an activation of microglias.

d) The measurement of dopamine D_2 receptor occupancy using PET was optimized for accurate evaluation of the therapeutic effect of antipsychotics .

2) Molecular Neurobiology

a) An exhaustive autoradiographic analysis of mice deficient in calcium/calmodulin-dependent protein kinase II revealed prominent changes in levels of multiple monoamine neuroreceptors and transporters by the reduction of this enzyme. In a positron emission tomographic (PET) study of awake rats and monkeys, crosstalk between dopaminergic and glutamatergic neurotransmissions was visualized and quantified in living brains. These results, in conjunction with electrophysiological data using rat brain slices, also elucidated the localization of metabotropic glutamate receptors involved in the regulation of the striatal dopamine release.

b) Small-animal PET systems showed their utility in characterizing two new 18F radioligands for amyloid plaques developed separately by Tohoku University ([^{18}F]FACT) and a pharmaceutical company. Both tracers were comparable to established ^{11}C-labeled probes in terms of affinities for highly pathological plaque cores, supporting clinical applications of these ligands as diagnostic agents for Alzheimer's disease with advantages over 11C compounds as to the radioactive half-life. We also generated a group of chemicals enabling neuroimaging of fibrillar tau inclusions in Alzheimer's disease as well as related tau-positive neurodegenerative diseases collectively termed tauopathies. Optical and PET scans of tauopathy model mice are being conducted to examine their *in-vivo* capabilities. These agents in combination with

existing technologies to capture plaque lesions would contribute to separation of Alzheimer's disease from non-Alzheimer tauopathies.

c) Our radiochemical and immunohistochemical assays of animals modeling Alzheimer's disease and other diverse neurological conditions demonstrated that PBR could be upregulated in both microglia and astrocytes, reflecting neurotoxic and neuroprotective roles of reactive gliosis, respectively. This indication was further supported by the finding that levels of PBR and glial cell line-derived neurotrophic factor were correlated with each other in astrocytes responding to neuronal injuries. These insights were obtained with the aid of our original materials, including anti-PBR antibodies and a PET ligand for PBR, [^{18}F]FE-DAA1106.

3) System Neurochemistry

a) In collaboration with another neuroscience facility, we established experimental environments to protect against biohazards derived from monkeys with a specific virus-mediated, specific gene expression at the P2A level.

b) We identified the functional system for psychic dependence on cocaine when monkeys were performing an intravenous cocaine-self administration using PET with ^{15}O-labeled water. Also, we compared dopamine D1 and D2 receptors in extra-striatal regions between pre-addicted and post-addicted monkeys. Unfortunately, we could not find any difference between intra-subject comparisons.

c) We are now studying extracellular unit-recording from the ventral striatum of monkeys that self-administered cocaine. The ventral striatum was chosen for study since our PET activation study indicated it was responsible for the psychic dependence on cocaine.

d) We conducted PET with [^{11}C]PE2I to quantify the extent of dopamine degeneration in MPTP-treated Parkinsonian marmosets. MPTP-treated PD marmosets showed significant decrease of DAT compared with DAT of normal subjects, suggesting the prominent loss of DA terminal.

Major publications

1) H. Takahashi, M. Kato, M. Matsuura, D. Mobbs, T. Suhara, Y. Okubo: When your gain is my pain and your pain is my gain: Neural correlates of envy and schadenfreude, *Science,* 323, 937-939, 2008

2) M. Tokunaga, N. Seneca, R.M. Shin, et al.: Neuroimaging and physiological evidence for involvement of glutamatergic transmission in regulation of the striatal dopaminergic system. *J. Neurosci.,* 29, 1887-1896, 2008

3) Takahashi H., Kato M., Takano H., Arakawa R., Okumura M., Ohtsuka T., Kodaka F., Hayashi M., Okubo Y., Ito H., Suhara T. Differential contributions of prefrontal and hippocampal dopamine D1 and D2 receptors in human cognitive functions. *J. Neurosci.,* 28, 12032-12038, 2008

4) F. Yasuno, M. Ota, J. Kosaka, et al.: Increased binding of peripheral benzodiazepine receptor in Alzheimer's disease measured by positron emission tomography with [^{11}C]DAA1106. *Biol. Psychiat.,* 64, 835-841, 2008

5) B. Ji, J. Maeda, M. Sawada, et al.: Imaging of peripheral benzodiazepine receptor expression as biomarkers of detrimental versus beneficial glial responses in mouse models of Alzheimer's and other CNS pathologies, *J. Neurosci.,* 28, 12255-12267, 2008

4.3. Studies on Molecular Probes and Radiopharmaceuticals

Toshimitsu Fukumura, Ph.D.
Deputy Director, Molecular Probe Group

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Objectives

Molecular probes play essentially important roles in the rapidly developing molecular imaging field. The purposes of this research group are 1) developing novel probes assessing in vivo biological and physiological functions (Probe Research Team); 2) developing new labeling methods to expand the possibility of producing a wider variety of probes at high yield and high quality (Radiochemistry Team); 3) developing a new integrated system for the production of safe probes considering the GMP standard, without radiation exposure to personnel by automation (Production System Team); and 4) establishing the production methods and the quality control methods of the developed probes for clinical applications (Radiopharmaceutical Production Team).

The Probe Research Team objectives are to develop novel probes for quantitative assessment of oxidative stress and/or disruption of homeostasis and brain efflux function targeting multidrug resistance-associated protein (MRP). This team is also taking part in the development of a novel tumor imaging probe to assess DNA synthesis in tumor cell proliferation and the development of novel receptor ligands. The Radiochemistry Team objectives are to develop new labeling methods with PET radionuclides, especially, a direct fluorination method for $^{18}F^-$ onto a benzene ring in an unstable compound and to achieve higher specific activity for various kinds of PET probes. The Production System Team and Radiopharma-ceutical Production Team have not only the above objectives but also have missions to support research activities for PET molecular imaging in collaboration with the Planning and Promotion Unit. The research activities performed in FY 2008 are described below.

Progress of Research

1) Probe Research Team

Our primary role is to develop novel molecular probes for the PET and SPECT imaging of molecular targets in humans. The targets are underlying causes of various diseases, such as neurodegenerative disorders and tumors. In particular, we focus on development of probes that allow measurement of oxidative stress or the stress-induced alteration of biological functions, because oxidative stress is considered to be a key feature of the disease process. Such probes would be applicable to investigations of the underlying causes of various diseases and of the mechanisms and efficacies of existing or proposed treatments and therapies.

Multidrug resistance-associated protein 1 (MRP1) protects against toxic compounds and oxidative stress by exporting intracerebral xenobiotics and endogenous metabolites into the blood. The currently available methods for studying brain-to-blood efflux are limited due to either their invasiveness or the ability to provide only a qualitative assessment. To overcoming these limitations, we developed a method for assessing MRP1 function *in vivo* using PET and a newly developed PET probe, 6-halo-7-[^{11}C]methylpurine. This radioprobe is efficiently converted to its glutathione conjugate (MRP1 substrate) in the brain after intravenous administration. When the molecular probe was administrated to Mrp1 knockout mice, the efflux rate of the radioactivity was reduced to approximately 90% compared with wild-type mice. This is the world's first method which allows noninvasive and quantitative assessment for exporter function in the living brain.

In close collaboration with the Biophysics Group, Diagnostic Imaging Group and Osaka Prefecture University Biopolymer Chemistry Group, we developed a new thermo-sensitive pegylated liposome which encapsulates doxorubicin (anti-cancer agent), manganese (MRI imaging agent) and technetium-99m (SPECT imaging agent). Encapsulation of technetium-99m and manganese allows the detection of the concentration and decomposition of liposome in a tumor, respectively.

In addition, we developed a non-radioactive reagent for selective measurement of acetylcho-linesterase (AChE) with Ellman's method, based on our experience regarding development of radioprobes for measurement of AChE in the brain. The AChE selective substrate for use with Ellman's method has been desired for the past half century.

2) Radiochemistry Team

The Radiochemistry Team is looking at two subjects: labeling techniques and novel PET ligands. A practical labeling method of [^{13}N]ligands was developed using no-carrier-added [^{13}N]NH_3 with high specific activity. [^{13}N]Urea and [^{13}N]carbamate were synthesized by reacting precursors (isocyanate, carbamoyl chloride or chloroformate) with [^{13}N]NH_3. The precursors were prepared by treating amine and alcohol with triphosgene *in situ*. These reaction mixtures were not purified and were used directly for [^{13}N]ammonolysis, respectively. Using the one-pot method, [^{13}N]carbamazepin was synthesized for the putative brain imaging.

[^{11}C]Acetyl chloride ([^{11}C]AcCl) as a labeling precursor was used to synthesize [^{11}C]oseltamivir ([^{11}C]Tamiflu) and its active metabolite [^{11}C]Ro 64-0802. A detailed study on the biodistribution and metabolism of the two radioligands was performed on mice and rats. The presence of [^{11}C]oseltamivir and [^{11}C]Ro 64-0802 was determined in the rodent brain after the [^{11}C]oseltamivir injection.

As a third labeling-related study, a nitroaldol reaction between nitro[^{11}C]methane and formaldehyde was investigated. Controlling all the nitroaldol product, nitroethanol, nitrodiol, and nitrotriol, was accomplished by changing bases, additives, and reaction temperature

in 3 min. 2-Amino[2-^{11}C]ethanol was synthesized as an application of the reaction by treatment with EtONa and EtOH followed by nitro-group reduction

The team developed [^{11}C]DAC as a novel PET ligand for imaging of PBR in kainic acid-lesioned rat brain. A small-animal PET study determined that [^{11}C]DAC had high uptake in the lesioned region, where PBR density was increased. The high *in vivo* specific binding of [^{11}C]DAC to PBR is available as a new biomarker for brain injuries, neuroinflam-mations, and tumors etc.

[^{11}C]Gefitinib was synthesized and used for tumor imaging and evaluation of P-gp/BCRP function. *In vivo* distribution study on NFSa-bearing mice revealed that [^{11}C]gefitinib specifically accumulated into the tumor. A PET experiment produced a clear tumor image for mice. It was demonstrated that the brain penetration of [^{11}C]gefitinib was related to both P-gp and BCRP. [^{11}C]Gefitinib is thus a promising PET ligand to evaluate the effect of brain penetration of gefitinib by combined therapy with P-gp or BCRP modulators, and to characterize the penetration of gefitinib into brain tumors.

3) Radiopharmaceutical Production Team

Research by this team is intended to establish routine production/quality assurance methods for new PET molecular probes. This includes the development and validation of satisfactory regular production and quality control methods for safe administration into human subjects as well as the evaluation of the toxicity and radiation dosimetry for clinical applications. Four new PET probes ([^{11}C]Ac5216, [^{18}F]TO-002, [^{11}C]gefitinib and [^{18}F]FAZA) were approved by the Institutional Review Board at NIRS and released for clinical research.

Ultra-fast and sensitive high-performance liquid chromatographic methods were established for the quality control of short-lived PET probes. These methods allowed the chemical mass of the PET probes to be determined with ultra high specific radioactivity (>3.7 TBq/μmol) and ultra high-throughput analyses (<1 min) to be carried out for a wide array of pharmaceuticals (>30 probes).

We have developed a method combining on-line multi microdialysis sampling with ultra-high-performance liquid chromatography for the continuous monitoring of radioactive and endogenous metabolites of PET probes. This method allowed highly sensitive radiometric detection with good time resolution and could be successfully applied to continuous and simultaneous monitoring of radioactive and endogenous dopaminergic metabolites in the striatum and cerebellum dialysates of the same rat after the administration of L-[β-^{11}C]DOPA.

A rapid and efficient preparative high-performance liquid chromatographic procedure utilizing a hydrophilic interaction chromatography column and a highly volatile organic mobile phase was established to purify short-lived PET probes. Several ^{11}C-radio probes could be prepared within one half-life of carbon-11 (20.4 min) with sufficient radiochemical and chemical purity and high levels of radioactivity and specific radioactivity.

The chemical impurity tests of [^{18}F]FDG preparations produced in other PET facilities in Japan are being conducted for 213 samples from 108 PET facilities.

4) Production System Team

The Production System Team has been developing new attachments for a versatile synthesis apparatus. A new synthesis unit which supports synthesis of [^{11}C]oseltamivir from a preparation of [^{11}C]acetyl chloride and using the [^{11}C]acetylation reaction and subsequent deprotection reaction, was developed. The synthesis apparatus can produce [^{11}C]oseltamivir in sufficient yield and quality for animal PET studies.

An irradiation system producing ^{124}I and ^{76}Br has been developed and is being optimized . The system showed high thermal tolerance allowing proton beam irradiations up to 20μA. Such a high beam current yield for ^{124}I is near the theoretical thick target yield.

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4 .4. Research and Development of the Next-generation Technology for Molecular Imaging

Iwao Kanno, Ph.D.
Director, Biophysics Group

(Outline of Research Career)

Iwao Kanno started his professional career at Akita Research Institute of Brain and Blood Vessels in 1970, where he was an active researcher for 36 years. In 1997, he developed a custom radionuclide emission tomography system using a handmade rotational dentist chair. In 1979 he developed a hybrid type of emission tomography which combined positron emission tomography (PET) and single photon emission computed tomography (SPECT). His efforts were also directed to developing methodology for quantitative assessment of physiological and biochemical parameters from PET and SPECT images. In 1997, he developed a custom radionuclide emission tomography system using a handmade rotational dentist chair. In 2006, he joined NIRS where he continues his research career.

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Objectives

The Biophysics Group works to develop methodologies and technologies for watching, detecting, analyzing and understanding the molecular and physiological signals emitted from humans and other living animals. This is done by using the kinetics of radioactive molecular probes, magnetic resonances signals of protons interacting with molecular probes, multi-photon laser microscopy, and engineering physics for detection and imaging of positron annihilations. The group consists of four research teams. The Imaging Physics Team covers software and engineering physics involved in PET instrument systems. The Biosignal Physiology Team combines molecular information and physiological information measured from MRI and microcirculation facilities on hemodynamic signals relating to neurovascular coupling during neuronal activation. The Data Analysis Team aims to extract quantitative parameters from dynamic PET images taken from human subjects and animals after radioactive ligand administrations. The Magnetic Resonance Molecular Imaging Team develops novel methods and applications for detecting the variable signals from high tesla (7T) MRI and multimodal imaging. These four teams collaborate to assess quantitative molecular mechanisms from *in vivo* measurements on humans and other animals. The Biophysics Group is thus supporting research and applications of other groups working on molecular diagnostic imaging and molecular neuropsychiatric imaging at the Molecular Imaging Center.

Progress of Research

1) Magnetic Resonance Molecular Imaging Team

a) Therapeutic drug delivery imaging using temperature-sensitive liposome

We tested doxorubicin-containing liposomal drug delivery imaging *in vivo*. The multimodal and multifunctional liposome was synthesized as a MRI contrast agent, optical imaging agent and anti-cancer drug with tumor targeting capability. We visualized the drug kinetics, accumulation in the tumor, drug release using a thermo-trigger, and the anti-tumor effect in mouse .

b) Multimodal nano-probe using quantum-dots

Multimodal probes were developed from quantum-dot nanoparticles for both MR and optical imaging. Quantum-dots have higher fluorescence properties than conventional organic dyes. The fluorescence properties were protected by using a hydrophobic structure around the nanoparticle core and MRI contrast agents were facilitated by adding a further amphiphilic silica shell structure. We tested for *in vivo* applications.

c) Reactive gliosis

Reactive gliosis is an important neuronal response after stroke or spinal cord injury. Recently, it has been a subject of interest in regenerative medicine. We proved that a manganese MRI contrast agent can provide good image contrast for studying reactive gliosis in a rat stroke model and have published our analysis.

d) Immunocyte labeling and tracking

Non-invasive *in vivo* detection of trans-planted cells is an important technique for regenerative biology and medicine. We developed a new nontoxic method for labeling immunocytes that provides MRI signal enhancement. The labeled immunocytes were intramuscularly administered to a rat ischemic leg and heart model and imaged with the 7T MRI.

e) Multimodal therapeutic contrast agent using nitroxyl radicals

As a novel nonradioactive methodology, the visible anti-cancer drug "SLENU" was developed for *in vivo* noninvasive, real-time imaging of blood-brain barrier (BBB) permeability for conventional drugs, using nitroxyl radicals as spin labels and MRI .

2) Biosignal Physiology Team

a) Diffusion functional MRI

Recently, it has been suggested that diffusion-weighted (DW) fMRI could provide a more direct method of observing neuronal activity. We developed a new MRI sequence where a multiple spin-echo echo-planar-imaging sequence is added after a pulsed gradient spin echo, and we succeeded in extracting the BOLD component from DW fMRI signals. The results suggested to us that the main contribution to heavily diffusion-weighted functional MRI signal is not from the BOLD effect.

b) MR elastography for clinical use

MR elastograpy (MRE) methods deform a sample using an external vibration system. A transverse driver is widely used, which generates shear waves at the object surface. One of the problems is that shear waves rapidly attenuate at a tissue surface and do not propagate into the body. We compared the shear waves generated by transverse and longitudinal drivers. The longitudinal driver was found to induce shear waves deep inside a porcine liver phantom. These results suggested that the longitudinal driver will allow measurement of the shear modulus deep inside the body.

c) Human studies using evidence-based molecular imaging

We performed collaborative studies with active

clinical sites using evidence-based molecular imaging methods such as MR spectroscopy (MRS), DW imaging, susceptibility imaging, and target-specified enhanced MRI. Proton MRS was applied to pediatric radiology in cooperation with the Kanagawa Children's Medical Center, and ^{13}C MRS was used for diagnosis of liver function with the Institute for Adult Diseases. We succeeded in visualizing tumor structures by diffusion tensor imaging in a colloaborative study with the NIRS Hospital. Glycosaminoglycan specific MR contrast enabled us to evaluate dysfunction of cartilages around the knee joints; this was done in a collaborative study with Chiba University and Teikyo Chiba Medical Center.

d) Direct visualization with fluorescent microscopy

For visualization of cortical vasculature, a bolus of Qdot was intravenously injected and the 3-dimensional vascular structure was visualized with in vivo multi-photon excitation fluorescent microscopy. The vein emerging from the parenchyma was identified by tracking the pial venous networks, and its cross-sectional diameter was measured at the focal point. Three-dimensional vascular images were obtained from the cortical surface to a depth of 0.9 mm with a 0.01-mm z-step. The number density and cross-sectional diameter of veins continuing from the pial networks to the parenchyma were measured at a depth of 0.4 mm.

e) Intracortical microcirculation visualized with multi-photon microscopy

The microcirculatory response to anesthesia in brain tissue was determined with multi-photon excitation fluorescence microscopy. The intracortical capillary dimension and red blood cell (RBC) flow were visualized up to a depth of ˜0.6 mm from the cortical surface in rats anesthetized with either isoflurane or _-chloralose. Significant differences in the capillary diameter and mean RBC speed in single capillaries were observed between isoflurane or _-chloralose conditions. The findings indicated that local mechanism for blood flow control may exist at the capillary level to maintain the balance of oxygen supply and demand induced by anesthesia in brain tissue.

3) Image Analysis Team

This team aims to realize algorithms and experimental apparatuses to measure and visualize various functionalities of humans and other animals using PET. For fully quantitative PET molecular imaging, a parametric model analysis based on kinetics of an administered radiopharmaceutical in tissues is conducted. In a practical situation, large noise in the PET data is problematic and, therefore, mathematical image processing techniques should be adopted. We developed and evaluated some new algorithms: omission of arterial blood sampling using an intersectional searching algorithm combined with clustering, a denoising algorithm and partial volume correction using Wavelet transformation, and a bias-free algorithm for neuroreceptor imaging.

Moreover, a quantitative PET scan for mice is important for molecular imaging investigations because of the large variety of genetically modified mice. For the scans, radioactivity in the arterial plasma is required. However, this is difficult to do because of the small size of the mice. The team is investigating surgical methods to insert a small catheter into a mouse artery and a system for arterial sampling. In the arterial blood sampling from mice, the allowed amount of sampled blood is 1 μL and its volume should be measured precisely. We are considering a technique using microfluidic chips to develop a practical μL order blood sampling system. An experimental trial system is being evaluated.

4) Imaging Physics Team

This team proposed an improved OpenPET geometry. The OpenPET geometry is our innovative idea which consists of two detector rings of axial length W each separated by a gap *G*. The OpenPET mainly has three applications; namely, simultaneous PET/CT, extension of the axial FOV, and in-beam PET, which is known as a method for *in situ* and non-invasive monitoring of tumor-conforming charged particle therapy. To obtain an axially continuous field of view (FOV) of $2W+G$, the maximum limit for G must be W. However, two valleys of sensitivity appear on both sides of the gap. Setting a more limited range for the gap as $G<W$, which is desirable for filling in the sensitivity valleys, results in not only a shortened gap, but also a shortened axial FOV. Therefore we proposed an alternative method for improving the uniformity of sensitivity by shifting two detector rings axially closer to each other or further apart at the same velocity. We simulated an OpenPET scanner which measures events simultaneously by shifting the detector rings. The results showed that the right and left peaks of sensitivity approach each other upon shifting of the detector rings, and these valleys of sensitivity are effectively recovered.

This team also proposed a new depth-of-interaction (DOI) PET detector design, which was named “X'tal cube”. Recently, small, light, and thin photodetectors such as avalanche photodiodes (APD) or multi-pixel photon counters (MPPCs) have become commercially available as alternatives to photomultiplier tubes (PMTs). In this design, therefore, a number of the small photodetectors are coupled to a 3-dimensional scintillation crystal array at any six surfaces. For a

preliminary experiment to study the characteristics of the new DOI detector, we constructed a crystal block consisting of six layers of a 6 × 6 crystal array with two types of Gd_2SiO_5 (GSO) crystals. Each crystal size was 2.9 × 2.9 × 3.75 mm^3. To measure how the scintillation photons spread into the whole crystal block and distribute on the surface of the crystal block, the crystal block was coupled to a position sensitive PMT at the bottom surface, where all the crystal block surfaces except for the bottom surface were covered with the reflectors. We irradiated fan-beam gamma rays to the crystal array and studied the scintillation photon distribution by analyzing crystal responses on the 2-dimensional position histogram.

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5 . Research Center for Radiation Protection

Kazuo Sakai, Ph.D.
Director, Research Center for Radiation Protection

(Outline of Research Career)

In 1982, Dr. Sakai received a Ph. D. in biochemistry from the University of Tokyo. He worked as a Research Associate in the Department of Radiation Biophysics, Faculty of Medicine, University of Tokyo (1982-1989), and then was a Lecturer in the Department of Radiation Oncology, Graduate School of Medicine, University of Tokyo (1989-1999). The main subjects of his research were radiation induced DNA damage and its repair, and the mechanism of radiation induced cell death. From 1983 to 1985 he worked as a research fellow in the Genetics Division, Children's Hospital, Harvard Medical School where he investigated gene amplification and cloning of genes responsible for radiosensitivity. He moved to the Central Research Institute of Electric Power Industry in 1999 to research biological effects of low dose radiation. He joined NIRS in 2006.

Objectives

The Research Center for Radiation Protection was newly established in 2006. The aim of the Center is to provide a scientific basis for radiation protection and safety. Toward this goal, radiation exposure from various sources is measured, the dose-effect relationships for various endpoints are examined, and the mechanisms underlying the effects are investigated. The Research Center disseminates its research results to promote public understanding of radiation effects and to encourage the enactment of more reasonable regulations concerning the use of radiation. The scope of its activity is not limited to Japan. It has been appointed a collaborating center by the International Atomic Energy Agency.

Overview

The Research Center consists of four research groups (Regulatory Sciences Research Group, Experimental Radiobiology for Children's Health Research Group, Radiation Effect Mechanisms Research Group, and Environmental Radiation Effects Research Group), the Nakaminato Laboratory for Radioecology, and the Department of Advanced Technologies for Radiation Protection Research.

The activities of the research groups and the Nakaminato Laboratory are described in their respective sections of this Annual Report.

The Department of Advanced Technologies for Radiation Protection Research consists of four sections. In the Advanced Analytical Technology Section, cooperative projects with other research groups from inside and outside of NIRS have been carried out to measure trace elements in environmental and biological samples. Also, new advanced techniques to determine trace elements those are difficult to measure have been developed.

The Animal Pathology Section has provided histopathology technical and diagnostic supports for NIRS intramural research.

The Advanced Animal Research Section has supported integrated research of molecular and genetic studies with physiological studies in whole animals. Although remarkable progress of radiation biology has been made on genetic, molecular and cellular levels, physiological analysis of whole animal models is inevitable for extrapolation to human health. The section has supported radiobiological research by application of assisted reproductive technologies (ARTs) in genetically modified laboratory mice, including *in vitro* fertilization, embryo transfer, micromanipulation of embryos and cryopreservation. Such technologies have also become essential to efficiently conduct large scale animal experiments by providing a large number of animals synchronously. The Advanced Animal Research Section also has supported research using Medaka fish through providing tumor-bearing fish, preparing samples for analysis, and the quality control of frozen sperms of qualified strains of Medaka fish.

The Environmental Radioactivity Survey Section initiated three collaborative research projects with three universities in Japan. They have involved development of ultra sensitive radon decay products measuring system, establishment of a calibration procedure for radon and its decay products concentrations and development of a new technique (detection of Cherenkov radiation) for radon measurements. In addition to them, two other collaborative research studies were conducted with foreign institutions. This section also carried out twelve commissioned projects, utilizing its technologies and facilities.

The Research Center has been designated by the International Atomic Energy Agency as a Collaborating Centre for Biological Effects of Low Dose Radiation. An annual report for the research outcome in this area was sent to IAEA and highly appreciated.

In FY 2008, the Research Center 61 permanent and 90 temporary members actively conducted research. They produced 65 original papers and 54 reviews and proceedings. The Center held a symposium on damage response and adaptive response after irradiation.

As of July 2008, Dr. Shinichiro Sato was named as the Head of the Planning and Coordination Section of the Research Center to promote its activity further.

5.1 Regulatory Sciences Research for Radiation Safety and Protection

Hidenori Yonehara, Ph.D.
Director of the Regulatory Sciences Research Group

(Outline of Research Career)

Dr. Yonehara received a Ph.D. from Shiga University of Medical Science in 1995 for his study on the issue of risk from exposure to residential radon. He joined NIRS in 1996 and began working on studies related to dose evaluation from environmental radiation. From 2003 to 2006 he worked on development of radiation safety standards as Director for Radiation Protection Policy in the Ministry of Education, Culture, Sports, Science and Technology (MEXT). Since his return to NIRS, he has studied dose evaluation from natural radiation sources as well as issues related to radiation safety regulation. Since March 2007, he has been working as Director of the Regulatory Sciences Research Group.

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Objectives

The objectives of regulatory sciences research for radiation safety and protection are to summarize scientifically based information for radiation safety regulation and to exchange this information among different stakeholders to bridge the gap between science and society. The research programs are focused on the following four points.

1) Summarizing information on radiation protection issues

The group aims to summarize achievements of research projects on radiation protection provided by NIRS, as well as other research institutes to contribute to activities of relevant international organizations such as UNSCEAR and ICRP. The group also constructs a research information network on radiation protection for sharing information with scientific organizations, regulatory authorities and the public.

2) Radiation risk assessment and construction of information databases

The group constructs information databases on risk assessment for people who are exposed to low dose radiation and controllable natural radiation sources. Scientific information on radiological archives of experimental research, on the exposures and health effects of radiation among different human populations, and on effects of environmental radiation from the epidemiological studies are collected for the databases.

3) Development of mathematical models

Using the results of basic research related to the effects of radiation on human health and the environment, the group develops mathematical models for risk evaluation of health effects due to exposure to controllable natural radiation sources, medical exposure, and the models for analysis of radiological effects on the environment.

4) Development of a method for risk communication

The group collects case examples in which risk information on radiation safety is passed on to the public, and the group analyzes social psychology findings.

Progress of Research

1) Construction of information databases for radiation risk assessment

An integrated information database on exposure due to use of naturally occurring radioactive materials (NORM) as industrial raw materials, building materials and consumer products was previously established. In FY 2008, the function of dose estimation due to utilization of NORM was appended. Data for activity concentrations of various materials and consumer products, which were determined experimentally, were added to the database. A method for study on possible health effects associated with medical exposures during childhood was examined. The group has been constructing the archive for long term animal experimental data including information of internal exposure. In this regard, the group has been promoting global data and information exchange as well.

2) Development of mathematical models

The group aims to develop two types of mathematical models for regulatory science. The first type models simulations of carcinogenesis for the main purpose of evaluating the radiation risk at low dose exposure. The second type models evaluations of the effects of ionizing radiation on environmental biota and ecosystems.

Recently, international concerns about protection framework of non-human biota have been increasing and European and North American countries have respectively developed assessment frameworks and tools to evaluate radiological impact for non-human biota. On the other hand, such a framework has not been considered in Japan. Therefore, we examined applicability of the established assessment tools to Japanese environments. In this study, we chose two assessment tools, RESRAD-BIOTA which was developed by US-DOE and the ERICA assessment tools which were developed by EURATOM. We considered a paddy field as a typical Asian environment and used maximum of global fallout nuclide concentrations which were monitored in the Joetsu region of Japan. From our trial calculation for general screening, Tier 1 of ERICA suggested that concentrations of ^{137}Cs in aquatic systems exceeded the general screening level. On the other hand, concentrations of ^{90}Sr were less than screening level 1 of RESRAD-BIOTA , and concentrations of ^{90}Sr in terrestrial systems in ERICA were less than all screening levels. Thus, we proceeded to apply the ERICA Tier 2 using the same parameter set as in Tier 1, and found that each species did not exceed the screening level. Finally, we calculated dosimetries of the most important species living in a paddy field. We tested both tools and we adopted ERICA because of its flexibility in body dimensions of adding organisms to analyses. From our calculation, we concluded that graded approaches which are adopted in RESRAD-BIOTA and ERICA can be effectively applied to Japanese environments.

3) Epidemiological study

The possible effects of exposures to controllable natural radiation and medical radiation are our main research interests. We continued a case-control study of residential radon and thoron and lung cancer among cave-dwelling residents in Gansu Province, China, in cooperation with researchers inside and outside NIRS. Data for a total of 77 cases and 154 controls have been entered in the study so far, and 1-year measurements for radon and thoron and its decay products were

completed for dwellings of 49 cases and 98 controls. Preliminary analysis of data showed an increased risk of lung cancer in relation to radon concentrations as expected. In addition to the case-control study, detailed measurements on temporal variations according to dwelling type were conducted for selected subjects. These data are being analyzed.

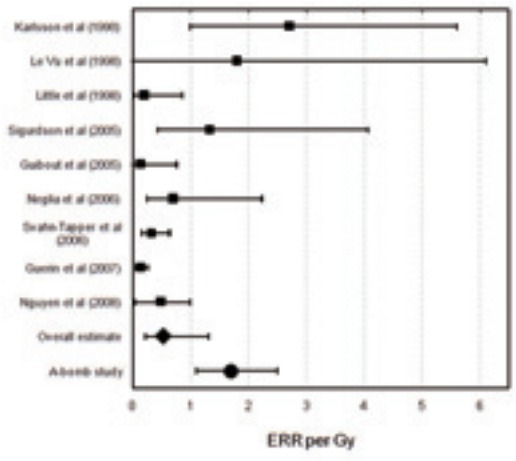
Accurate and precise assessment for exposures is essential for epidemiological studies. We addressed possible influences of uncertainty in exposure assessment on risk estimates in residential radon studies, in terms of both statistical and experimental ways. A simulation study suggested there is an underestimation of radon-related lung cancer risk when using detectors without discrimination of thoron which justifies our on-going case-control study in China.

To assess possible effects of medical exposures quantitatively, we conducted a meta-analysis of studies on second cancer risk among childhood cancer survivors treated with radiotherapy. As shown in Fig. 5-1, 9 relevant studies were identified and analyzed, with an estimate of excess relative risk per Gy (ERR/Gy) from 0.13 to 2.70 among which heterogeneity was suggested ($p<0.001$). Overall the ERR/Gy estimate was calculated as 0.53 (95% CI: 0.22 to 1.31) using a random effects model, which was much smaller than the corresponding estimate of 1.7 (95% CI: 1.1 to 2.5) from the study of atomic bomb survivors exposed as young children. In view of the heterogeneity and the apparent low ERR/Gy estimate, more studies about the risk of second cancers among childhood cancer survivors are needed for further understanding of the carcinogenic effects of radiotherapy on children.

Fig. 5-1. Excess relative risk per Gy (ERR/Gy) of cancer after radiotherapy among children in comparison with that of cancer among A-bomb survivors.

4) Investigation into risk perception of radiation

The surveys of risk perception done in FY 2007 were analyzed using risk ranking techniques. The survey had been done in all parts of Japan using web-based questionnaires and 638 responses were obtained.



Subjects were asked to rank 30 items of various types of technologies and human activities according to their subjective judgments on the order of perceived magnitude of risk. Irrespective of sex, age, occupation and academic majority, all groups examined perceived handguns, nuclear power and cigarettes as having the highest risk, while X-ray exposure was perceived as a moderate risk. Respondents tended to believe the information from TV more than that from public organizations. We also interviewed researchers within NIRS. The NIRS researchers perceived nuclear power as less risky and bicycles and motor vehicles as more risky compared with the perception of the general public.

5) Dialogue seminars for risk communications among stakeholders

A series of meetings called a "Dialog Seminar" on themes of optimization of radiodiagnostic exposure and radioactive waste was held to communicate information on risk among scientists, persons in regulatory authorities, those in relevant companies and the public. In the seminar regarding optimization of radiodiagnostic exposure, international trends, the present circumstances and issues related to protection of medical exposures were discussed among medical doctors, radiological technicians, experts for radioprotection and regulators. In the seminar regarding radioactive waste, fundamental information on high-level waste and radiation effects on humans was provided by experts to the public, and issues related to radiation waste were discussed among stakeholders.

Major publications

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2) R. Kanda, S. Tsuji, Y. Ohmachi, Y. Ishida, N. Ban, Y. Shimada: Rapid and reliable diagnosis of murine myeloid leukemia (ML) by FISH of peripheral blood smear using probe of PU. 1, a candidate ML tumor suppressor, *Molecular Cytogenetics*, 1[1], 22, 2008 (Online Only URL: http://www.molecularcytogenetics.org/home/, 2008-10-16),

3) K. Doi, M. MIeno, Y. Shimada, S. Yoshinaga: Risk of Second Malignant Neoplasms among childhood cancer survivors treated with eadiotherapy: Meta-Analysis of 9 epidemiological sudies, *Paediatric and Perinatal Epidemiology,* in press

4) S. Tapio, P.N. Schfield, C. Adelmann, et al.: Progress in updating the European Radiobiology Archives, *Int. J. Radiat. Biol.,* 84[11], 930-936, 2008

5) S. Tsuji, R. Kanda: Study of views on nuclear energy and radiation among Japanese people. *Japanese Journal of Risk Analysis,* 18[2], 33-45, 2008 (In Japanese)

5.2 Experimental Radiobiology for Children's Health Research Group

Yoshiya Shimada, Ph.D.
Director, Experimental Radiobiology for Children's Health Research Group

(Outline of Research Career)

D r . Shimada received a Ph.D. in 1985 from the University of Tokyo. In the Mizuno Biohoronics Project of JST (1985-1987) and at the Tokyo Metropolitan Institute of Gerontology (1987-1989), he worked on innate immunity in carcinogenesis and aging, respectively. Since 1989 at NIRS, he has focused on molecular and cellular mechanisms of T-cell lymphomagenesis and mammary carcinogenesis from the viewpoint of combined effect of environmental carcinogens and the age-at-exposure effect.

Objectives

With the advent of an era of low birthrate and prolonged longevity, concerns about the safety of fetuses and children have been growing. Programs to protect the health of fetuses and children and the safety of the environment are being instituted, particularly in the USA and Europe. These regulations are mainly directed at foodstuffs and chemicals. Recently, progressive increase in medical uses of radiation for children has forced ICRP, IAEA and WHO to draft global initiatives on radiation protection of children. This group carries out studies to provide information on the risk of carcinogenesis due to radiation exposure during the fetal and childhood periods, for which there are at present insufficient data. Using animal models, we study the effects of radiation exposure on cancer induction and lifespan shortening. Final goals of this research group are to propose age-weighting factors and relative biological effectiveness (RBE) of neutrons and heavy ions for fetuses and children for radiation protection.

Progress of Research

1) Dependency of lifespan shortening by irradiation in B6C3F1 mice

Fifty female and male B6C3F1 mice per each group, which have been used in a wide variety of toxicological studies such as the National Toxicology Program (NTP) in the USA, were exposed to gamma rays (^{137}Cs), carbon ions (13 keV/μm) and neutrons (2 MeV) at various ages during fetal to mature adulthood periods. The ages examined were pre-implantation (3 days post-conception (dpc)), major organogenesis (13 dpc), late fetal (17 dpc), neonatal (1 week after birth), prepubertal (3 weeks), post-pubertal (7 weeks) and mature adult stages (15 weeks). The doses ranged between 0.2 and 4 Gy for gamma rays, 0.2 and 2 Gy for carbon ions and 0.05 and 1 Gy for neutrons. These mice are now being kept under observation. The result of the first experiment for gamma-ray exposure indicated that adult female mice appeared more susceptible to radiation-induced lifespan shortening than male mice. Carbon ions were more potent in reducing lifespan than gamma rays when female mice were exposed at newborn stage. Surprisingly, irradiation with gamma rays at the late fetal stage had little influence on lifespan shortening. This could be ascribed to the early onset of liver tumors and T-cell lymphoma. Irradiation with carbon ions at the fetal stage, however, shortened the lifespan to a similar extent as that at the infant stage. These results suggest a larger relative biological effectiveness (RBE) of carbon ions for fetus.

2) Age dependency of cancer risks in mammary gland, lung, bone marrow, liver, kidney, brain and intestine

Radiation risks are dependent upon both tissue types and the age at exposure. Breast is one of the most susceptible organs to radiation-associated cancer risk. The Sprague-Dawley rat mammary cancer model was used to investigate the age effect on breast cancer risk. In FY 2008, female rats (1, 3 and 7 weeks of age; N = 200) were irradiated with Cs-137 gamma rays and carbon ions (13 keV/μm) at doses of 0.2, 0.5, 1 and 2 Gy. Tentative data indicate that, compared to that at the post-pubertal stage (7 weeks of age), gamma irradiation with 2 Gy at the prepubertal stage (3 weeks of age) resulted in low radiation-associated incidence of cancer. This was evinced by low expression of ovarian steroid receptors and genes downstream from them. Interestingly, genomic copy number alteration was rare in these cancers.

The lung is one of important organs for radiological protection of workers and the public because of its high radiation-associated cancer risks. To elucidate the age dependence of pulmonary carcinogenesis, incidence of radiation-induced lung tumor was compared in 1, 5 and 15 week-old female Wistar rats (total 760 animals) following thoracic X-ray irradiations (0, 1, 3 and 5 Gy). The lung tumor induction increased in a dose-dependent manner, but the dose-effect relationship did not differ much with the age at irradiation.

The age effect on tumor development of kidney, brain and intestine was also examined using mutant and genetically engineered animals such as Eker rats and *Ptc*$^{+/-}$, *Apc*$^{Min/+}$, and *Mlh1*$^{-/-}$ mice. Perinatal and infantile stages were the most sensitive to the development of tumors in kidney and brain. Brain tumors developed in a dose-dependent fashion with showing considerable effects even at low dose of 0.2 Gy. We also found that irradiation at the infantile stage induced more intestinal tumors than that as an adult. Furthermore, the second hit event was intra-chromosomal deletions in tumors of mice irradiated at the infantile stage, but was chromosomal loss and duplication (or mitotic recombination) in those spontaneously developed and irradiated as an adult.

3) Combined effect of radiation with chemical carcinogens on lung and thymic tumorigenesis

The age effect of combined exposure of radiation and a chemical carcinogen has been investigated on pulmonary and thymic carcinogenesis. In order to induce the lung tumors, the thoracic region of female Wistar rats was irradiated with X-rays (3 Gy) at pubertal (5 weeks of age) or adult (15 weeks of age) stages, and then *N*-nitrosobis (2-hydroxypropyl) amine (BHPN) (1.0 g/kg body weight) was intraperitoneally injected. When BHPN was administered alone, the lung tumor was induced at higher incidence in the rats administered at the pubertal stage than at adult stages. Synergistic effects of the X-rays and BHPN were found

in the rats exposed at pubertal and adult stages, and the synergisms were more effective at the pubertal stage. *Gpt*-delta mice were X-ray-irradiated following *N*-ethyl-*N*-nitrosourea (ENU) treatment to see the mode of mutation induction in thymocytes after combined exposure. It was found that ENU treatment increased mutant frequency and accelerated clonal expansion of mutants compared to untreated control mice. Post-irradiation at a low dose of X-rays (0.2 Gy weekly for 4 weeks) decreased clonality, but not the mutation spectrum, suggesting that post-irradiation caused suppression of clonal expansion of ENU-induced mutants.

4) Detrimental effect of uranium on the developing kidney

Health effects for children in depleted uranium-polluted areas and uranium mining areas are of recent concerns. Uranium and its compounds have the potential to cause nephrotoxicity. The subcutaneous injection of uranium acetate resulted in a site-selective accumulation of uranium in the downstream of the proximal tubules, where apoptotic cells were concomitantly observed. The dynamics of uranium and incidence of apoptosis in kidney differed between immature and adult animals.

5) Mutation induction in *Aprt* locus

In order to determine the age-dependency of mutation induction, $Aprt^{+/-}$ mice at one or seven weeks old were exposed to 1 Gy or 4 Gy of X-rays. Preliminary observations suggested that the exposure at the younger age with the higher dose resulted in more $Aprt^{-/-}$ mutations in cultured kidney cells derived from the exposed mice.

Major publications

1. Y. Shang, Sh. Kakinuma, Y. Amasaki, M. Nishimura, Y. Kobayashi, Y. Shimada: Aberrant activation of interleukin-9 receptor and downstream Stat3/5 in primary T-cell lymphomas in vivo susceptible B6 and resistant C3H mice, *In Vivo,* 22[6], 713-720, 2008

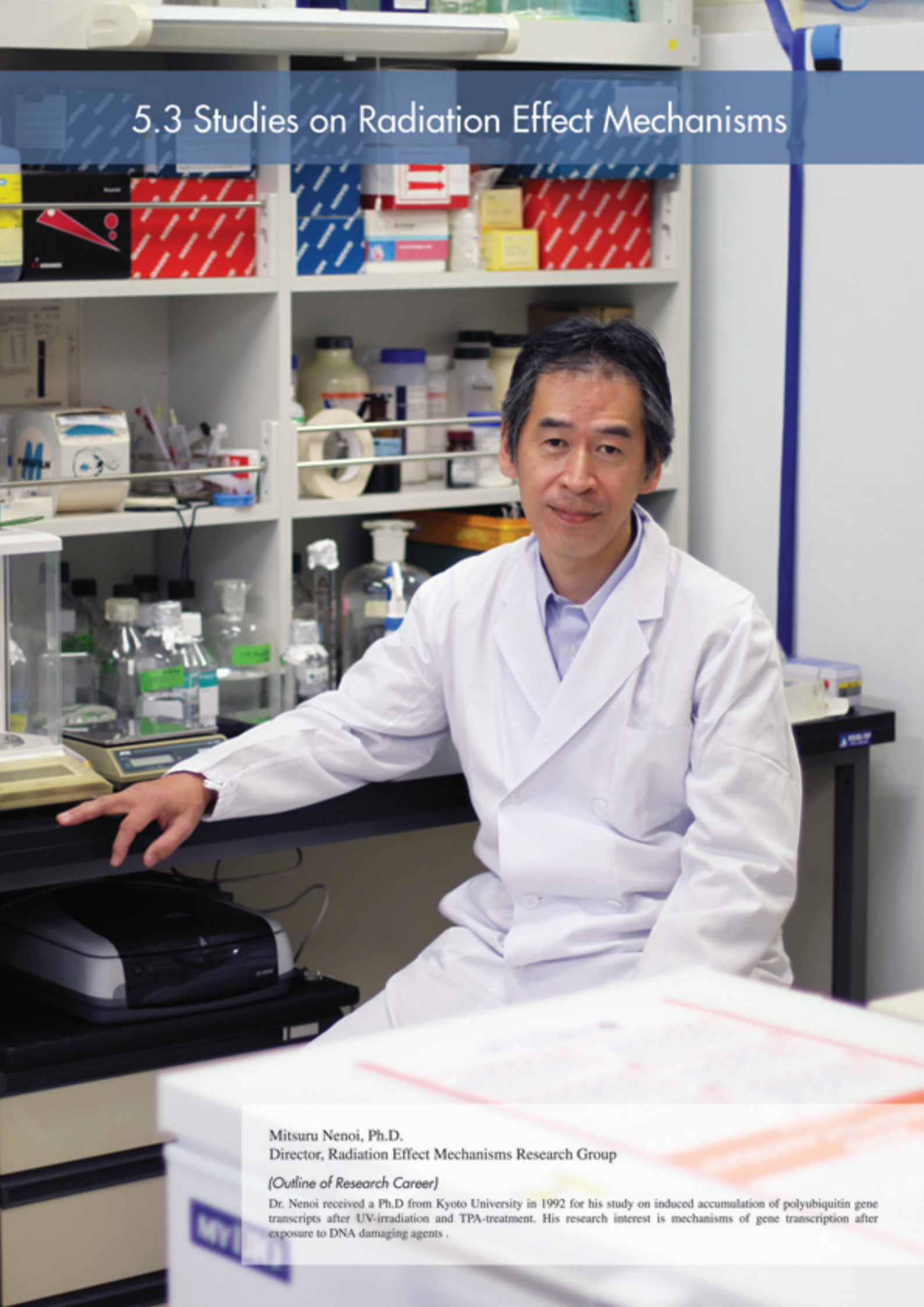
2. S. Homma-Takeda, Mi. Inoue, S. Ueno, H. Iso, T. Ishikawa, Y. Nishimura, H. Imaseki, M. Yukawa, Y. Shimada: Elemental imaging in pancreas of immature rats by micro PIXE analysis, *International Journal of PIXE,* 18[1/2], 53-59, 2008

3. T. Imaoka, S. Yamashita, M. Nishimura, S. Kakinuma, T. Ushijima, Y. Shimada: Gene expression profiling distinguishes between spontaneous and radiation-induced rat mammary carcinomas, *Journal of Radiation Research,* 49[4], 349-360, 2008

4. T. Takabatake, H. Ishihara, Y. Ohmachi, et al. : Microarray-based global mapping of integration sites for the retrotransposon, intracisternal A-particle, in the mouse genome, *Nucleic Acids Research,* 36[10], e59-1-e59-11 2008

5. T. Hirouchi, T. Takabatake, K. Yoshida, Y. Nitta, M.M. Nakamura, S. Tanaka, K. Ichinohe, Y. Oghiso, K. Tanaka: Upregulation of c-*myc* gene accompanied by PU.1 deficiency in radiation-induced acute myeloid leukemia in mice, *Experimental Hematology,* 36[7], 871-885, 2008

5.3 Studies on Radiation Effect Mechanisms



Mitsuru Nenoi, Ph.D.
Director, Radiation Effect Mechanisms Research Group

(Outline of Research Career)

Dr. Nenoi received a Ph.D from Kyoto University in 1992 for his study on induced accumulation of polyubiquitin gene transcripts after UV-irradiation and TPA-treatment. His research interest is mechanisms of gene transcription after exposure to DNA damaging agents .

Objectives

Estimation of low-dose radiation risk has been made using the high-dose data from atomic bomb survivors at Hiroshima and Nagasaki under the assumption that the risk is proportional to the radiation dose without a threshold. However, we do not necessarily have the scientific evidence to support this assumption. We do not have sufficient scientific data on the effects of low-dose radiation on developmental and differentiational anomaly either. Because it is now considered to be difficult to assess the risk of low-dose radiation from animal experiments or in epidemiological data, this research group conducts studies on the mechanism of radiation effects caused by low-dose radiation. The purpose of this research group is to derive findings useful in the risk assessment of low-dose radiation which can be used as a basis for the development of appropriate regulatory frameworks. The following study items are separately investigated by the four teams.

1) Radiation Carcinogenesis Research Team: Evaluation of indirect effects of low-dose radiation on carcinogenesis (carcinogenesis due to changes in the microenvironment caused by irradiation) and examination of the involvement of DNA repair mechanisms in low-dose radiation-induced carcinogenesis.
2) DNA Repair Gene Research Team: Clarification of low-dose radiation risk-modifying factors in nonhomologous end-joining DNA-repair and its molecular mechanism.
3) Developmental and Differentiational Anomaly Research Team: Verification of the validity of radiation regulations relating to developmental and differentiational anomaly by evaluating the effects of low-dose radiation on abnormalities in neural crest cell differentiation.
4) Radioadaptive Response Research Team: Determination of risk modifying factors specific to low-dose radiation by identifying genes associated with biological responses to low-dose radiation, including radioadaptive responses and signal transduction.

Progress of Research

1) Radiation Carcinogenesis Research Team

Radiation risk of cancer induction has been evaluated based on direct effects of radiation on irradiated cells. It is known that radiation causes cancer through two types of damage, DNA damage directly induced in target cells and radiation-induced change of a microenvironment. The contribution of the latter untargeted carcinogenesis to radiation-induced cancer risk has not been evaluated. To elucidate its contribution to radiation risk, we have established the thymus transplantation system for assessment of indirect effects of radiation on carcinogenesis. In the present study, DNA-PKcs-deficient scid mice were thymectomized and nonirradiated or irradiated at 0.1 to 1 Gy γ-rays. Thymuses of new born wild-type mice harboring GFP gene were transplanted in irradiated scid mice under a kidney capsule or subcutaneously. Transplanted scid mice were fed under a specific pathogen-free condition for one year to monitor development of T-cell lymphomas and the incidence of T-cell lymphomas derived from transplanted thymuses was assessed by the expression of GFP in lymphomas. In both transplanted sites, the incidence of T-cell lymphomas of transplanted thymus origin increased with increasing radiation dose and reached a significantly increased value at 0.5 Gy when transplanted under the kidney capsule and at 1 Gy when transplanted subcutaneously. When thymuses of GFP mice were transplanted in thymectomized, 1 Gy-irradiated wild-type mice, T-cell lymphomas of transplanted thymus origin were not induced. The results indicate that under a deficient condition of nonhomologous end-joining repair, untargeted carcinogenesis does occur at relatively low radiation dose in scid mice, which might contribute to radiation-risk of cancer.

2) DNA Repair Gene Research Team

DNA double-strand breaks (DSBs) can arise from multiple sources including ionizing radiation (IR) and DNA replication itself. DSBs are profoundly dangerous lesions to cells, which, if unrepaired, will result in loss of genomic material. Cells, therefore, have invested in at least two pathways to repair DSBs, namely homologous recombination repair (HRR) and non-homologous end-joining (NHEJ). In higher organisms, NHEJ represents the major mechanism for the repair of radiation-induced DSBs. Our chief aim is, in this context, to clarify the induction-mechanism of mutation by radiation. In particular, the identification of the modulatory factor(s) for a low-dose radiation-risk in NHEJ and the elucidation of the molecular mechanism(s) involved with those factor(s) are the focus of our interest. Up to the present, we have established three cell lines having *XRCC4, Artemis* and *MDC1* disrupted, respectively, by a gene targeting technique in a human colon tumor cell line HCT116 to define the biological roles of NHEJ-related genes on DNA damage induced by IR. We then demonstrated higher radiosensitivities of these three NHEJ-related gene deficient cell lines in survival and chromosomal aberration assays than parental HCT116 cells and a decline in the colocalization of phosphorylated ATM and DNA-PKcs foci with γ-H2AX foci, a marker for DSBs, in *MDC1*$^{-/-}$ cells after IR.

In the current study, first, we determined sensitivities of *XRCC4*$^{-/-}$ and *Artemis*$^{-/-}$ cells to chemical reagents

including etoposide, camptothecin, cisplatin and mitomycin C that induce different types of DNA damages by using a survival assay, and we figured out that NHEJ for the repair of DSB may possess two distinct pathways which are dependent upon and independent of *Artemis,* respectively. Next, we studied phosphorylation status of ATM and DNA-PKcs in *MDC1*$^{-/-}$ cells to elucidate dynamics of DNA damage/repair molecules and interactions among repair proteins and MDC1. Phosphorylations of ATM (S1981) and DNA-PKcs (S2056 and T2609) were clearly reduced in *MDC1*$^{-/-}$ cells in comparison with that of parental HCT116 cells 30 min after X-ray (1Gy) exposure. Taken together with the previous findings, these results suggest that a recruitment of phosphorylated ATM to a DSB site is disturbed somehow, and that the activity of ATM and DNA-PKcs is limited at the site of DNA DSBs, in turn DNA repair processes would be torn down in *MDC1*$^{-/-}$ cells. Consequently, MDC1 might be an essential regulatory protein for controlling the phosphorylation, at least, of ATM and DNA-PKcs and for stabilizing the interactions and retention of NHEJ components at the site of DSBs. Meanwhile, we have gotten analysis of gene expression by use of a DNA micro-array technique to find genes influenced by low-dose radiation in *MDC1*$^{-/-}$ cells as well as in parental HCT116.

3) Developmental Anomalies Research Team

To elucidate the mechanism of the effects of low-dose radiations on the development of mice as well as neural crest-derived cells and melanocytes at cellular level, pregnant females of C57BL/10J mice at 9 days of gestation were whole-body irradiated with a single acute dose of iron ions. The effects were studied by scoring changes in the postnatal and prenatal development of mice as well as cutaneous coats 22 days after birth and in the melanocyte development in prenatal hair follicles. The percentages of birth, the survival to day 22 and the body weight at day 22 were reduced in irradiated mice. By comparing the survival to day 22 for iron ions with that of g-rays, iron ions were more than three times as effective as γ-rays. The frequency and the size of white spots (white hairy skin devoid of melanoblasts and melanocytes) in the mid-ventrum were increased in irradiated mice. By comparing the frequency of white spots for iron ions with that of γ-rays, iron ions were more than twice as effective as γ-rays. In 18-day-old embryos, the frequencies of abnormalities in the fore and hind legs, tails and eyes as well as of hemorrhage were increased as dose increased and the number of embryos as well as their body weight were decreased. In 18-day-old embryos, the development of hair follicles was also delayed as dose increased. The number of melanoblasts and melanocytes in the epidermis was also decreased significantly even in mice irradiated with 0.1 Gy iron ions. These results suggest that iron ions seem to have greater effects on postnatal and prenatal development of mice as well as on the melanocyte development than γ-rays.

4) Radioadaptive Response Research Team

Exposure to sublethal doses of ionizing radiation can induce protective mechanisms against a subsequent higher dose irradiation. This phenomenon, called radiation-induced adaptive response (AR), has been described in a wide range of biological models. We previously demonstrated the existence of AR in mice during late organogenesis. In this study, we investigated molecular mechanisms underlying AR in this model. Using DNA microarrays, we performed a global analysis of transcriptome regulations in adapted and non-adapted cells collected from whole mouse fetuses, after *in utero* exposure to priming irradiation. As a result, we identified 861 genes whose expression level was modulated specifically in AR conditions. Our results suggested the involvement of signal transduction and tumor protein (p53)-related pathways in the induction of AR. Our results are in agreement with previous investigations showing that AR could be dependent on p53 activity. The observed gene modulations may also have possible consequences for subsequent developmental process of the fetus.

Major publications

1) M. Koike, J. Sugasawa, M. Yasuda, A. Koike: Tissue-specific DNA-PK-dependent H2AX phosphorylation and gamma-H2AX elimina-tion after X-irradiation in vivo. *Biochem. Biophys. Res. Commun.,* 376, 52-55, 2008
2) M. Koike, A. Koike: Accumulation of Ku80 proteins at DNA double-strand breaks in living cells. *Exp. Cell. Res.,* 314, 1061-1070, 2008
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4) T. Nakajima, K. Taki, B. Wang, et.al: Induction of rhodanese, a detoxification enzyme, in livers from mice after long-term irradiation with low-dose-rate gamma-rays., *J. Radiat. Res.,* 49, 661-666, 2008
5) G. Vares, B. Wang, S. Yi, H. Ohyama, K. Tanaka, T. Nakajima, M. Nenoi, I. Hayata: Adaptive response in embryogenesis: VI. Comparative microarray analysis of gene expressions in mouse fetuses, *Int. J. Radiat. Biol.,* 85, 70-86, 2009

5.4. Studies on Environmental Radiation Effects

Satoshi Yoshida, Ph.D.
Director, Environmental Radiation Effects Research Group

(Outline of Research Career)

Dr. Yoshida received the BE in safety engineering from Yokohama National University in 1983 and the ME and the Ph.D. in environmental chemistry in 1981 and 1989, respectively, from Tokyo Institute of Technology. He joined NIRS in 1989. His main research interests are radioecology, environmental chemistry, and ecotoxicology.

Objectives

The recent rapid changes in energy production systems and life styles of people worldwide have made environmental radiation research even more important. In order to satisfy the needs for radiation safety and regulations, this research group aims to investigate three subjects related to environmental radiation and radioactivity: i.e. 1) effects of radiation on organisms and ecosystems; 2) exposure of public to natural radiation; and 3) marine dynamics of important radionuclides. The group consists of five research teams: Terrestrial Radiation Ecotoxicology Research Team, Aquatic Radiation Ecotoxicology Research Team, Natural Radiation Exposure Research Team, Cosmic Radiation Exposure Research Team, and Marine Radioecology Research Team. The following describes the progress of each of these teams during FY 2008.

Progress of Research

1) Effects on organisms and ecosystems

While the importance of radiological protection of the environment based on scientific principles is increasingly recognized internationally as environmental issues garner more attention, the relevant scientific data are extremely limited. This group conducts studies to evaluate the effects of radiation on representative terrestrial and aquatic organisms as well as studies to estimate radiation dose on those environmental organisms. In addition, the group develops methods to evaluate the ecological effects of radiation using experimental model ecosystems containing various species.

Terrestrial Radiation Ecotoxicology Research Team

To understand the impact of radiation on terrestrial ecosystems, plants, fungi, earthworms and springtails were selected, and the dose-effect relationships for radiation have been studied. The study using a novel technology, high-coverage expression profiling (HiCEP), was started last year to detect radiation responsive genes, and has progressed well. Many transcript-derived fragments (TDFs) up-regulated by irradiation were detected in animals and plants, which have no genome information, such as the springtail (*Folsomia candid*), the cell line was established from a cedar tree and the earth worm (*Enchytraeus Japonensis*).

Since the biological effects of long-term irradiation have more relevance to studies in radiation ecotoxicology, the team started a study on chronic exposure. The model plant, *Arabidopsis thaliana*, exposed to gamma rays for 2 weeks at a dose rate of 20 Gy/day was analyzed for gene expression. The genes up-regulated by the irradiation could be classified into two types by the time-dependent expression patterns; early up-regulation (within 1 day) and late up-regulation (after 3-7 days). The former type included some genes relating to DNA repair, whereas the latter included others relating to metabolism. Each type also included different genes of signal transduction and transcriptional control. These behaviors of gene expression probably reflect the responses of the plants to cope with progression of radiation damages.

The effects of high LET radiation must be also considered because of the presence of alpha and beta emitters in the environment as well as gamma emitters. As the pilot study, the earthworm (*Enchytraeus japonensis*) was exposed to heavy ions (C, Ne, Si, Ar or Fe) at NIRS-HIMAC. Up to now, a larger inhibitory effect of Ar ion on the growth of the earthworm has been observed in comparison with low LET radiation such as gamma rays. The RBE was approximately 3.

Aquatic Radiation Ecotoxicology Research Team

Radiation effects on aquatic ecosystems at various endpoints were investigated in some selected organisms and experimental model ecosystems.

Effects of acute gamma-irradiation on ingestion were investigated in water fleas, *Daphnia magna*. The ingestion of ^{13}C-labelled green algae by *D. magna* was not inhibited at 62.5 Gy while it was significantly inhibited at 125 Gy, and almost completely inhibited at 250 Gy or higher doses. The ingestion was a more sensitive endpoint than mortality, because death of *D. magna* was not observed even at 1000 Gy.

The microbial microcosm consisting of eight identified taxa was acutely irradiated with gamma rays at 100, 500, 1000 and 5000 Gy in the steady state. Populations of most constituent taxa were decreased in a dose-dependent manner. Blue-green algae were, however, more abundant in the irradiated microcosm, which was likely an indirect effect due to interspecies interactions. A comparison of effects between gamma rays and chemicals was carried out using the ecological effect index (EEI), in which degrees of differences in the populations between exposed and control microcosms were represented by the Euclidean distance function. The 50 % effect doses for the microcosm (ED_{M50}s), at which the EEI became 50 %, were evaluated to be 5600 Gy for gamma rays, 6.7 mg/L for benthiocarb (herbicide) and 6.1 mg/L for linear alkylbenze-nesulfonate (LAS, a surfactant).

The flooded paddy soil microcosm was chronically gamma-irradiated at a dose rate of 1.2 Gy/d for 5 days. A brownish discoloration was observed in the liquid phase of the irradiated microcosm, which may have been caused by the change from soluble Fe (II) into insoluble Fe (III). The irradiation also affected a

bacterial community structure, which was detected by denaturant gradient gel electrophoresis (DGGE) based on the 16S rDNA. For example, growth of two bacterial species was stimulated in the irradiated microcosm. Partial nucleotide sequences of 16S rDNA were determined for phylogenetic identification of the constituent bacterial species. Results of this identification will contribute to elucidation of mechanisms of changes in a bacterial community structure, which may have been related with Fe speciation in the irradiated microcosm.

2) Exposure to natural radiation

Since natural radioactive substances and cosmic radiation at high altitude contribute greatly to the radiation dose received by the general public, it is necessary to quantify the actual level of exposure and to document its features. The group therefore investigates the concentration and exposure doses of radon (^{222}Rn), thoron (^{220}Rn), and related radionuclides, mainly in areas with high natural radiation, and analyzes the results together with epidemiological data. The group also aims to collect scientific information on dose and effects of cosmic radiation in aircraft and to provide them in an intelligible and easy to access way for the general public such as on the Internet.

Natural Radiation Exposure Research Team

Recent epidemiological studies indicated that lung cancer risk significantly increases due to exposure to relatively low-level residential radon (100 Bq/m^3). Passive radon detectors are usually used for large scale surveys linked with such epidemiological studies. As the passive detectors give information on average radon concentrations for a long period, radon exposure can be roughly estimated using the average concentrations and a typical occupancy factor (indoor: 0.8 and outdoor: 0.2). However, radon concentration changes diurnally and occupancy factor is different from person to person. These factors should be considered for precise individual dose estimation. We are conducting an epidemiological study in China, cooperating with the Radiation Epidemiology Team of the Regulatory Sciences Research Group. For the precise estimation of individual dose, a detailed survey on indoor radon/thoron and their decay products was conducted using continuous radon/thoron monitors. The individual dose was estimated considering the occupancy factors obtained from questionnaires answered by the residents and diurnal variation of radon concentration.

We are also investigating potential exposure due to natural radionuclides contained in building materials. Building material samples were collected for this purpose and concentrations of natural radionuclides such as radium and uranium were estimated using a high purity germanium detector (HPGe) and ICP-MS. Exposure due to these radionuclides will be estimated following the method adopted in the European Union countries.

Cosmic Radiation Exposure Research Team

More than 16 million Japanese people go abroad every year using aircraft and about 20 thousand persons are working as crew on aircraft of Japanese airline companies. At aviation altitudes, aircraft crew are exposed to enhanced cosmic radiation of which the annual personal dose generally exceeds 1mSv per year. However, the situation and health effects of cosmic radiation exposure are still uncertain. The team thus makes efforts to collect scientific information on dose and effects of cosmic radiation and also to provide them in an easy-to-understand way by the general public. Major tasks are (1) calculation of aviation route doses (effective doses received in aircraft) using the most up-to-date method, (2) development of new detectors to verify calculations in aircraft, and (3) improvement of a comprehensive system for radiation protection dosimetry of aircraft crew. Some research outputs of the team are open to the public as a web program entitled "Japanese Internet System for Calculation of Aviation Route Doses (JISCARD)" on the NIRS home page. In FY 2008, we completed an original program "JISCARD EX" which can calculate effective doses for any flight paths given by users. For verification, the team developed a novel instrument for monitoring of high-energy cosmic-ray neutrons. We also continue to cooperate with airline companies in Japan, regarding management of radiation exposure for aircraft crew.

3) Marine dynamics of important radionuclides

Because many Japanese nuclear facilities are located in coastal areas facing the Pacific Ocean and the Japan Sea, it is very important to predict the environmental behavior, and thus the fate of radionuclides in marine ecosystems. The group focuses on the development of highly sensitive analytical methods for important radionuclides (e.g., plutonium, americium, iodine etc.) for which data are scarce, and provides data on their activities and isotopic ratios to understand their environmental behavior in marine ecosystems.

Marine Radioecology Research Team

The developed analytical method was applied to the study of ^{241}Am distribution in sediment core collected at Sagami Bay, Japan. The ^{241}Am activities in this sediment core ranged from 0.08 to 12.35 mBq/g. We found that ^{241}Am activity and $^{239+240}$Pu activity had

different vertical profiles. A clear subsurface maximum peak, representing the maximum deposition of $^{239+240}$Pu from global fallout in 1963, was seen for Pu isotopes, while ^{241}Am showed constantly high concentrations (10 - 12 mBq/g) from the surface down to the depth of the 1963 deposition peak, in spite of them having a similar oceanic chemical property, i.e. both are highly particle reactive. The relatively constant high activities of ^{241}Am and the continuous increase of ^{241}Am/$^{239+240}$Pu activity ratios observed in the upper layers from the 1963 global fallout peak layer to the surface can be attributed the following processes: (1) continuous supply of seawater with increasingly high ^{241}Am/$^{239+240}$Pu activity ratios due to the oceanic current transportation from the central equatorial Pacific; and (2) the enhanced preferential scavenging of ^{241}Am relative to Pu isotopes.

Seawater samples were collected in the Japan Sea and their $^{239+240}$Pu activities and ^{240}Pu/^{239}Pu atom ratios were determined by sector field high-resolution ICP-MS. The $^{239+240}$Pu inventories were 48.9 ± 0.5 Bq/m^2 obtained for 1984 and 85.2 ± 0.6 Bq/m^2 obtained for 1993 in the Tsushima basin. The inventories obtained for 1993 in the Tsushima basin and Yamato Basin were about two times higher than that (42.2 Bq/m^2) of the expected cumulative deposition density of atmospheric global fallout at the latitudes of 30 - 40°N. The atom ratios of ^{240}Pu/^{239}Pu showed no notable variation from the surface to the bottom with an average ratio of 0.24. The atom ratios of ^{240}Pu/^{239}Pu in water columns of the Japan Sea were significantly higher than the mean global fallout ratio of 0.180 ± 0.014. These high atom ratios proved the existence of close-in fallout plutonium originating from the Pacific Proving Grounds. The contribution of the PPG close-in fallout was calculated to be 34.6 Bq/m^2 obtained for 1993 in the Yamato Basin and the Tsushima Basin, which corresponded to 40 % of the $^{239+240}$Pu inventory in the water column.

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5.5 Office of Biospheric Assessment for Waste Disposal

Shigeo Uchida, Ph.D
Head, Biospheric Assessment for Waste Disposal

(Outline of Research Career)

Dr. S. Uchida received his doctoral degree from Kyoto University. He has about thirty years' experience in the fields of radioecology and environmental radiochemistry, with especial interest in the behaviors of long-lived radionuclides in the environment, e.g., ^{63}Ni, ^{79}Se, ^{90}Sr, ^{99}Tc, ^{129}I, ^{137}Cs, Th, U, etc. He has researched and improved models and parameters for radionuclides in soil-to-crop systems. He has been promoting a project to collect and estimate environmental transfer parameters of radionuclides in relation to radioactive waste management.

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Objectives

The biospheric assessment of radiation dose to human beings related to the releases of long-lived radionuclides from underground nuclear waste disposal sites is very important for the peaceful use of nuclear energy. For the assessment, radioecological transfer models and transfer parameters are needed. Environmental conditions, such as climate, vegetation and soil, affect these parameters. Additionally, agricultural products and food customs in Japan differ from those in Europe and North America. Therefore, we should have our own practical data in Japan using data from European and North American countries as references.

In this office, environmental transfer parameters, such as soil-to-crop transfer factors (TFs) and soil-soil solution distribution coefficients (K_ds), have been collected from agricultural fields throughout Japan. Recently, we also have measured parameters to clarify radon emission mechanisms from soil, as well as to understand the fate of elements in coastal areas in Japan. Analyses of stable isotopes and some natural radioisotopes in soil and edible part of crop sets, and coastal water and seafood sets have been carried out in order to obtain TFs / concentration factors under equilibrium conditions, while radiotracer experiments have been applied for K_ds in various soils. For the case of ^{14}C transfer parameters, radiotracer experiments were carried out to obtain TFs and ^{14}C distribution in soil. In addition, transfer models for predicting radionuclides' behavior in atmosphere-paddy soil-rice plant systems have been developed.

Progress of Research

1) Estimation of soil-soil solution distribution coefficient of radiostrontium using soil properties

Radionuclides reach humans through several transfer paths following their routine and/or accidental release into the environment from nuclear facilities. One of the important paths is by their root uptake from soil solutions to an edible part of a crop which is ingested as food. Thus K_d is an important parameter to describe the behavior of radionuclides in soils for making an environmental safety. In this study, we focused on predicting K_d of Sr because among the released radionuclides, ^{90}Sr (half-life: 28.74 y) is a dominant fission product from ^{235}U at high fission yield of 5.9%. In order to provide more practical and accurate K_d values by prediction, it is necessary to obtain many K_d data for each important radionuclide in various soils, and to determine soil properties which lead to variation in K_d values. Then reduction of uncertainty of each K_d value could be achieved to reduce uncertainty of the transport models.

One hundred and forty-two agricultural soil samples (63 paddy soil and 79 upland soil samples) were collected throughout Japan. The soil samples were dried at room temperature, and then passed through a 2-mm sieve. Exchangeable calcium (ex.Ca) and cation exchange capacity (CEC) were measured by the Schollenberger method. Water soluble ionic and elemental amounts in a solid/liquid ratio of 1 g : 5 mL were measured with an ion chromatograph (IC) (DIONEX, ICS-1500) and ICP optimal emission spectrometer (ICP-OES) (Seiko, Vista Pro), respectively.

Sr-K_d values were obtained by a batch sorption test. Each soil sample was mixed with deionized water (solid/liquid ratio, 3 g : 30 mL) in a plastic bottle and initially shaken for 24 h at 23℃, and then about 10 kBq of ^{85}Sr was added as a tracer. After shaking for 7 days, the suspension was centrifuged at 3000 rpm for 10 minutes, and the supernatant was filtered through a 0.45-μm membrane filter. Activities in the filtrates were measured with a NaI scintillation counter (Aloka, ARC-380).

The distribution of Sr-K_d values for all soil groups were judged as not a normal type ($p < 0.05$), but a log-normal type. Sr-K_d values ranged from 1.0×10^2 to 8.5×10^2 L kg^{-1} (geometric mean (GM) = 2.9×10^2 L kg^{-1}) for Andosol, from 6.2×10^1 to 1.7×10^3 L kg^{-1} (GM = 2.4×10^2 L kg^{-1}) for Cambisol, and from 6.4×10^1 to 1.8×10^3 L kg^{-1} (GM = 2.7×10^2 L kg^{-1}) for Fluvisol. There were no significant differences among soil groups in the t-test. In comparison with the expected Sr-Kd value for loam soil type reported by the International Atomic Energy Agency, 2.0 x 10^1 L kg^{-1}, the GMs of Sr-K_d values for Andosol, Cambisol, and Fluvisol were one order of magnitude higher.

The Sr sorption mechanism in soil is mainly an ion exchange reaction, and sorbed Sr in soil could not exist in the fixation fraction, as indicated by the findings that all of the ^{90}Sr in Chernobyl-contaminated soil could extract strong acid. Therefore, cation exchange capacity (CEC) and electrical conductivity (EC), and pH are important factors. In addition, sorptions of Mg^{2+} and Ca^{2+} which are related to Sr are in competition with sorptions of Sr^{2+}. Thus, Spearman's rank correlation test was used for evaluating correlations between Sr-K_d values and soil properties. In all soil groups, EC and water soluble Ca were important factors affecting Sr-K_d values. These results suggest that Sr can be sorbed in soil by an ion exchange reaction and Ca ion is the strongest competitive ion towards Sr. On the other hand, the highest |Rs| value was less than 0.70. Therefore, it should be difficult to estimate Sr-K_d values from a single soil property.

We suggested a new factor, Ca distribution ratio (CaDR). CaDR focuses on Ca. Since Ca is considered as the most competitive element with Sr, Ca distribution in soil-soil solution system should be more important than the total cation distribution in soil-soil solution system. CaDR, which has the same unit as K_d , is

defined as follows.

$$CaDR = \frac{Ex.Ca}{\text{Ca concentration in water soluble fraction}} \quad (1)$$

Figure 5-2 shows correlations between Sr-K_d values and CaDR for each soil group. There were high correlations with correlation factors of 0.78 for Andosol, 0.78 for Cambisol, 0.58 for Fluvisol, and 0.68 for all soil samples. In addition, simple linear regression equations to estimate Sr-K_d values from CaDRs for Andosol, Cambisol, Fluvisol, and all soil samples were obtained as follows.

(Andosol) $Sr\text{-}K_d = 0.44 \times CaDR + 180$ (2-1)

(Cambisol) $Sr\text{-}K_d = 1.27 \times CaDR - 8.4$ (2-2)

(Fluvisol) $Sr\text{-}K_d = 0.86 \times CaDR + 42$ (2-3)

(All soil samples) $Sr\text{-}K_d = 0.79 \times CaDR + 82$ (2-4)

Regression coefficients of Eqs.(2) differed between soil groups. These regression coefficients would describe the difference in sorption abilities between Sr and Ca in soil. In Andosol, the sorption ability of Sr was about 45% of that of Ca. Additionally, in Cambisol, the sorption ability of Sr was about 130 % of that of Ca. The difference in sorption ability between Andosol and Cambisol could be attributed to differences of soil properties. On the other hand, Pearson's correlation coefficients between estimated Sr-K_d values by Eqs.(2) and observed Sr-K_d values were 0.69 for Andosol, 0.82 for Cambisol, 0.74 for Fluvisol, and 0.72 for all soil samples. Therefore, we think it is possible to estimate more practical Sr-K_d values using CaDR without a classification for soil group. The results in this study point to a relatively easy way to estimate Sr-K_d values. Measurement of Ca is simpler than that of Sr. In addition, ex.Ca is a standard measurement in soil surveys. This estimation method should be useful for long-term dose assessment.

2) Soil-To-Rice Transfer Factor of Uranium by Measuring Naturally Occurring Uranium

TF is a key parameter that directly affects the internal dose assessment for the ingestion pathway. For U, we can use naturally existing U to predict the behavior from radioactive waste disposal sites to the biosphere. However, U concentrations in crop samples are usually low, making it difficult to obtain TF under agricultural field conditions. In this study, U concentrations in rice and associated soil samples have been determined by inductively coupled plasma mass spectrometry (ICP-MS) after chemical separation.

Sixty-three rice grain samples were collected from paddy fields throughout Japan. At harvest, associated soil samples were also collected. Three sub-samples were made for each rice grain sample, i.e., white rice (polished rice), brown rice (hulled rice) and bran. The 189 sub-samples were freeze-dried and thoroughly ground into fine powders. After U extraction on TRU resin (Eichrom) by sample solution loading, tetramethyl ammonium hydroxide was used for U elution behavior from the resin cartridges. Chemical recovery with this method was about 85%. Then U concentrations in three kinds of rice grain samples, brown rice (hulled rice), white rice (polished rice) and bran (63 samples each), were measured by ICP-MS.

The geometric means (GMs) of U concentrations were 7.3×10^{-5} mg kg^{-1}-dry (range: 3.6×10^{-5} to 3.3×10^{-4} mg kg^{-1}-dry) for the white rice samples, 9.7×10^{-5} mg kg^{-1}-dry (range: 3.9×10^{-5} to 9.5×10^{-4} mg kg^{-1}-dry) for the brown rice samples, and 3.7×10^{-4} mg kg^{-1}-dry (range: 8.6×10^{-5} to 4.6×10^{-3} mg kg^{-1}-dry) for bran samples. The bran weight was about 10% of the brown rice weight, and the remaining 90% of the brown rice weight was white rice; thus, about 1/3 of the total U in brown rice was distributed in the bran.

The U concentration data in brown rice, white rice and in associated soil samples were used to calculate TF. The TF value was calculated using the following equation:

$$TF = C_p / C_s \quad (3)$$

where C_p (mg/kg-dry) is the elemental concentration in plant and C_s (mg/kg-dry) is its concentration in soil. GMs of TFs for white rice and brown rice were 2.7×10^{-5} (range: 6.2×10^{-6} to 7.9×10^{-5}) and 3.6×10^{-5} (range: 5.5×10^{-6} to 4.6×10^{-4}), respectively.

These values were 2 orders of magnitude lower than the TF for cereals of 1.3×10^{-3} proposed by IAEA. The TF values obtained in this study and previously reported values were compared. Our data were slightly lower than other Japanese data but 2-3 orders of magnitude lower than data for India. Compared to other cereals, rice TF values observed in Japan were 1-2 orders of magnitude lower than for temperate zone countries although Japan is also classified as the same zone country.

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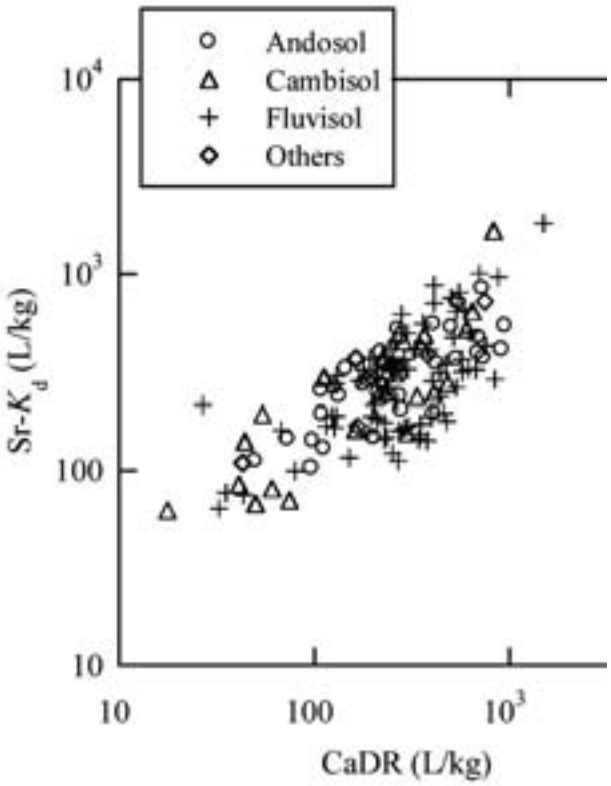
Fig. 5-2. Correlations between calcium distribution ratio (CaDR) and Sr-k_d values for Andsol, Cambisol, Fluvisol, and other.



6. Research Center for Radiation Emergency Medicine

Makoto Akashi, M.D., Ph.D.
Director, Research Center for Radiation Emergency Medicine

(Outline of Research Career)

Dr. Akashi started his medical career at Jichi Medical School (Tochigi Prefecture) as a junior resident of internal medicine in 1981. He worked as a senior resident at the Division of Hematology of Jichi Medical School before moving to the Division of Hematology/Oncology at UCLA School of Medicine in 1987. He received a Ph.D. from Jichi Medical School in 1988. He became a staff member of NIRS in 1990. His major interests are: 1) establishment of radiation emergency medical preparedness; 2) research on radiation injuries, including molecular and cellular mechanisms; and 3) development of methods for mitigation of radiation injuries. He has treated patients of the criticality accident in Tokai-mura.
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Objectives

This Research Center had the unique experience of receiving three victims heavily exposed to radiation at the JCO criticality accident of Tokai-mura in September 1999, because the Center has been assigned as the National Center for Radiation Emergency Medical Preparedness and Response by the Nuclear Disaster Prevention Plan of the Japanese government since 1980. The Center is responsible for, and has established a solid system for dealing with a radiation emergency from the medical viewpoint. Our required aims are as follows:

1) To receive victims exposed to radiation and/or contaminated with radioactive materials who require specialized diagnosis and treatment.
2) To dispatch a radiation emergency medical team to local emergency medical headquarters.
3) 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.
4) To maintain and reinforce an efficient radiation emergency medicine system under usual conditions.
5) To promote technical development and research on radiation emergency medicine.
6) To develop skilled manpower for a radiation emergency.

As an additional objective, we are carrying out fundamental research on radiation emergency medicine. Details are given elsewhere; only the subjects are presented here.

1. Research for diagnosis and treatment of exposure to high-dose radiation and/or contamination with radioactive materials.
   1-1 Studying mechanisms of radiation injuries leading to development of new agents for treatment, with the focus on the skin and gastrointestinal tract.
   1-2 Studying indicators of radiation exposure dose from biological specimens.
2. Research on dose assessment for victims in radiation accidents.

Overview

In 1997, the Central Disaster Prevention Council (CDPC) in the Prime Minister's office added a section on emergency preparedness for dealing with a nuclear power station emergency to the Basic Plan for Disaster Prevention. This plan was reinforced in 2000 following the criticality accident at Tokai-mura the previous year. The plan was also revised in 2008 after the Niigata-Chuetsu-Oki Earthquake caused damage to a nuclear power plant in 2007.

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 victims heavily exposed to radiation and/or contaminated with radioactive materials due to nuclear or radiological accidents. In 2000, NSC published the guideline for radiation emergency medical preparedness and revised it in 2008 to clarify the role of hospitals for radiation emergencies.

From January 2004 the Research Center has served as a liaison institution of WHO/REMPAN (Radiation Emergency Medical Preparedness and Assistance Network). The Research Center carries out the following activities to maintain and enhance or strengthen the emergency preparedness system required to fulfill its role as the tertiary radiation emergency hospital.

1) Network System

The primary goal is strengthening the institutional system to prepare for radiation emergencies by establishing three nation-wide network councils, 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 to treat the victims at the time of a nuclear disaster or a radiation accident. In an emergency, the cooperation involves sending an expert in the specific field, 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 considers the necessity arises) to respond to radiation emergencies. This council worked effectively at the time of the JCO criticality accident in 1999. In FY 2008, a communication exercise was done for members of the council as a general drill for radiation emergencies (October) and the council annual meeting was held (December).

1-2) Chromosome Network Council

This council forms a network among a limited number of experts having dose evaluation capability based on chromosome analysis. Through this network, NIRS can strengthen the capability of the dose estimation by chromosome analysis, and also establish technical standards of dose estimation method by chromosomes.

An inter-comparison study on the dose estimation by chromosome analysis was performed by members of

the Chromosome Network Council, when the national drill for radiation emergencies was held. Two blood samples experimentally exposed to 2 different does were sent to the members without informing them of the doses. The doses estimated by these investigators were similar. Members reached a consensus that the dose estimation should be applied to the PCC-ring methods when high dose exposure is suspected in the accident. Thus, the Chromosome Network Council has started to analyze the rings in prematurely condensed chromosomes of irradiated lymphocytes and the criteria for the selection of PCC were suggested.

NIRS held the NIRS-ISTC Asian Workshop on cytogenetic dosimetry on 27-28 November 2008 in cooperation with WHO. Recent progress in studies in radiation cytogenetics was introduced by researchers and case reports of dose estimation in radiation accidents were also presented by the participants from various Asian countries including Russia, Ukraine, Armenia and Belarus. Furthermore, an inter-comparison study was performed among these participants by distributing three slides prepared from experimentally irradiated lymphocytes.

A staff member of the section of biodosimetry was invited to the consultation meeting at Dartmouth University (USA) for the establishment of an international cytogenetic dosimetry network on 6 September 2008 by WHO. This NIRS member staff was elected as a member of the steering committee, and several task groups were established at the meeting.

1-3) Physical Dosimetry Network Council

This council is a network of experts in physical dose evaluation. The network is expected to respond to emergencies through collaboration among experts and related institutions for prompt and precise dose estimation. It is also responsible for accumulating dose evaluation technology and for fostering followers.

In FY 2008, an inter-comparison study for the quantitative and qualitative analysis on radioactive materials in urine samples and its dose evaluation were performed in the Physical Dosimetry Network Council; this study was conducted by four organizations (JAEA, Hiroshima University, NIRS, and JCAC) who are members of the Network Council.

A 100 ml urine sample spiked with radionuclides ^{54}Mn, ^{60}Co, and ^{90}Sr was sent to these member organizations without providing any information on spiked radionuclides. Each organization was asked to analyze radionuclides in the sample quantitatively and qualitatively and to report analytical results 1 h, 6 h, and 3 days after receiving. In these organizations, γ-radionucides were first qualitatively measured by γ-spectr-ometry with a Ge(Li) detector for a short time and then analyzed in detail. Two organizations 8 uantified the nuclides 6 h and the other two completed the analysis in 3 days. Average radioactivity levels of ^{54}Mn and ^{60}Co were 0.33+0.04 and 0.051+0.002 Bq/ml-urine, respectively; these radioactivities were almost identical to the spiked values (^{54}Mn: 0.31+ 0.01 and ^{60}Co: 0.049 + 0.001). Two organizations analyzed the β-nuclide ^{90}Sr by the liquid scintillation method and one organization completed its activity estimation in 1 day and the other finished in 2 days. Chemical separation was also performed in the latter organization. The activity obtained by this organization (0.025+0.001) was almost identical to the spiked value (0.029+0.001).

From the study, several issues in the event of an emergency were discussed: 1) samples containing radioactive materials should be sent legally, 2) information should be provided on the chemical and physical forms of radioactive samples and also their preservation and pretreatment.

The Physical Dosimetry Network Council also carried out an investigation on a whole body counter (WBC) in the secondary level hospitals for radiation emergencies. The WBC is used for measurement of internal contamination. However, it cannot work without proper calibration. The secondary level hospitals for radiation emergencies have WBCs and victims internally contaminated with radionulides are transported to them. The estimation of committed effective dose is important for making decision of whether these victims should be transferred to NIRS. We checked WBCs in nine hospitals by using the BOMAB phantom containing the standard radioactivity of either ^{137}Cs, ^{60}Co, ^{133}Ba or ^{40}K which NIRS had developed based on the ANSI standard. Using the phantom with ^{137}Cs, we found that the deviation from the standard ranged from -37% to +128%. One of the main reasons for this variation is that the methods of calibration were different among manufactures of WBCs; phantoms used by these makers were too small for calibration of these WBCs. Thus, a committee has been constructed for establishment of a standard calibration method in Japan.

1-4) Local Medicine Network Council

In Japan, the medical system for radiation emergencies is 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, establishment of a specific collaboration system with NIRS is mandatory and it must specify the steps to be performed in the smooth transfer of patients from an accident site to a hospital, including radiation protection management.

In FY 2008, discussions were held in Miyagi, Ibaraki, and Fukushima Prefectures on assistance from NIRS and treatment of internally-contaminated victims. Moreover, the desk-top study using the different scenarios such as combined injuries was introduced in Fukushima, Niigata, Aomori, and Kanagawa Prefectures and Hokkaido. In an annual meeting of 19 local governments, with actual or nearby nuclear facilities, held in Tokyo in March, discussion was focused on transport of contaminated victims to NIRS in cooperation with the Ministry of Defense (MOD). Relevant ministries and agencies such as the Ministry of Education, Culture, Sports, Science and Technology (MEXT), and Fire and Disaster Management Agency (FDMA) also attended this meeting.

2) Training

The primary goal for training is the development of radiation emergency medicine skills for medical professionals and disaster response personnel; these include doctors and nurses involved in nuclear disaster medical care, emergency crews, and nuclear establishment employees. For that purpose, the following training courses are regularly held in addition to our participation in nuclear disaster prevention training, seminars on medical response and other activities conducted by local governments to provide the relevant information and skills to deal with a radiation emergency.

2-1) Radiation emergency medicine course (hospital course)

This 3-day course is designed for physicians, nurses, and radiological technologists who may receive victims exposed to radiation and/or contaminated with radionuclides. The course is held 3 times a year with 20 participants in each course. More than 380 participants have been trained so far. Many of them are working actively in primary or secondary levels of radiation emergency hospitals and playing an important role in local radiation emergency exercises. In FY 2008, lecturers were invited from Asian countries to provide more information on medical response to radiation accidents. In FY 2008, 60 persons attended the course.

2-2) Emergency rescue training course (pre-hospital course)

This 3-day course is primarily designed for first responders such as fire or police department personnel, paramedics, and emergency planners at nuclear facilities. The course is held 4 times a year with 30 participants in each course. In FY 2008, 116 persons attended the course.

2-3) Training course for the whole body counter measurement

This 3-day course is intended for personnel of health physics, medical physics, radiation safety and others who have radiation dose assessment responsibilities. The course presents an advanced level of information on radiological/nuclear event reconstruction and dose assessments/estimations, focusing on internal contamination. Topics related specifically to radiation emergency medicine include internal and external contamination. Other topics covered include internal and external dosimetry and bioassay techniques. In FY 2008, 8 persons attended the course.

3) Emergency Exercises

National and local governments annually hold drills for nuclear emergencies. NIRS sent staff members to these drills to give advice from the viewpoints of medical care and radiation protection. On 21-22 October 2008, the Japanese government conducted a nuclear drill at the Nuclear Power Plant of Tokyo Electric Power Company (Fukushima Prefecture) to enforce readiness for an accident; 2,126 people from 113 organizations participated and some experts from France and IAEA/ANSN members observed the drill. The 2-day long drill assumed that trouble occurred in the cooling system, which caused radioactivity leaks. From NIRS, medical doctors and experts on radiation protection participated. In this drill, a mock victim was transferred from the plant to NIRS by a helicopter of the Chiba City Fire Department. Following the drill, NIRS conducted an additional exercise to simulate emergency handling, especially decontamination and dose assessment. The drill activities at NIRS were opened to the public via observations made by media representatives.

4) Follow-up Studies

The center carries out medical follow-up for the victims who were exposed to radiation in the thermonuclear weapon tests on Bikini Atoll, patients with thorotrastosis, and the surviving JCO accident victim.

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

On 1 March 1954, the 23 crew members (18 to 39 years old at the time) of the Japanese fishing vessel Daigo Fukuryu Maru (which means "Lucky Dragon") from Yaizu City, Shizuoka Prefecture saw bright light in the South Pacific resembling a sun rise. Seven or eight minutes later there was a terrific sound. They did not know what it was at the time. The blast, equivalent to about 12 million tons of TNT, was 750 to 1,000 times more powerful than the atomic bomb released over Hiroshima. All 23 people were hospitalized after returning to Japan. One of them died of liver failure

seven months later. Several hundred inhabitants of the Marshall Islands in the Pacific, as well as nearly 30 U.S. army personnel involved in the tests, also were injured from the nuclear fallout. Their medical follow-up aims at examining the health states of these victims over a long period of time to study late radiation effects. The follow-up examinations that have been conducted for 50 years provide important information. The type of exposure was external and also internal, whereas internal doses were thought to be relatively small. The estimated whole body doses were 1.7 to 6.9 Gy. In FY 2008, a medical check-up of survivors was conducted for 6 victims at Yaizu City Hospital. Among 23 victims, 14 have now died. Details on cause of death are as follows: 6 died of liver cancer, 2 of liver cirrhosis, 1 of liver fibrosis, 2 of colon cancer, 1 of heart failure, 1 in a traffic accident, and 1 of an aortic aneurysm rupture. Malignancies were suspected in two of these people. Many of them have evidence of infection with hepatitis viruses since all 23 victims received transfusions in 1954. Thus, transfusion might be the most important factor for infection by hepatitis viruses, although transfusion was one of the best treatments for bone marrow suppression at that time.

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

Thorotrast is an alpha emitting thorium dioxide colloid, which was used clinically in the 1930s and 1940s as a radiographic contrast medium. It was injected intra-vascularly for the visualization of vascular structures. Long-term retention of thorotrast in the reticulo-endothelial system, in the liver, spleen and bone marrow produces lifetime alpha particle irradiation of these organs and considerable epidemiological follow-up work has been performed. The major cohorts that can be used for risk evaluation are German, Danish and Japanese patients subjected to thorotrast. The incidence of leukemia has increased among these persons. 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. 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 carcinogenesis, and elucidates the effects of long-term internal radiation exposure on human bodies. This year, a medical check-up was carried out for only one patient.

5) Database

Since radiation accidents requiring medical care are extremely rare, the medical information must be collected from each accident and accumulated to help medical professionals to make decisions for strategies to treat victims, and establish and improve therapeutic methods. A medical database including the cases of radiation exposure at Bikini Atoll in the South Pacific and cases of thorotrastosis is being constructed. Today, there are many database systems on radiation accidents and their victims, but most are only accessible from the related countries. Under the supervision of the WHO, an international program called REMPAN 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 Daigo Fukuryu Maru accident in the SEARCH database. In addition, the 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. This year, medical data on treatment of internal contamination with radionuclides were collected from China and Russia.

6) Operation of 24 h Emergency Call System and Telephone Consultation for Radiation Effects System

For more than 10 years, NIRS has provided medical assistance to hospitals, radiation facilities, companies, and other interested groups. However, NIRS could not answer phone calls at night, on weekends or on national holidays, since a 24-hour on call emergency system had not been established. In FY 2008, NIRS established the 24-hour on call emergency system for hospitals and first responders including fire department personnel. This system is for direct or consultative assistance regarding medical and health physics problems associated with radiation or nuclear accidents. This consultation assistance on a 24-hour basis can be reached by phone. After usual business hours, the phone call is automatically transferred to 3 or 4 staff members (which include a medical doctor and a health physicist) of the Research Center for Radiation Emergency Medicine.

NIRS has another consultation assistance system by phone. The number of phone calls for consultation of radiation effects is increasing. This year we received 39 consultations. Of those, 26 were consultations on radiation exposure (7 cases were about exposure to radiation in medical use and 19 were accidental exposure). 11 were questions about radiation or the radiation emergency medicine system. Two other 2 cases were from the persons who believed that they had been exposed to radiation without reasonable evidence. Since some events occurred in Japan last year which were about uncontrolled or stolen

radioactive sources, some consultations or questions we received were associated with these cases. To deal with these situations, NIRS also released important information about each event to the public on the Institute's homepage.

7) International Cooperation

7-1) Training courses for foreign medical staff organized by NIRS

Upon a request, NIRS Training Course for Korean Medical Professionals on Radiation Emergency Medical Preparedness was held from 11-13 November 2008 and 25 medical professionals attended.

7-2) Organization of meetings

a) NIRS Workshop on Cytogenetic Biodosimetry for Asia and 46th ISTC Japan Workshop Organized by NIRS and ISTC in cooperation with WHO from 27-28 November 2008.
b) NSC/NIRS workshop on medical response to nuclear accidents in Asia Organized by the Nuclear Safety Commission (NSC) and NIRS in cooperation with the WHO Regional Office for South-East Asia from 17-19 February 2009. As a part of this workshop, information on recent accidents and other topics was exchanged; in all 21 people (14 from 10 Asian countries, 6 from other area countries, and 2 from IAEA and WHO SEARO) were invited.

7-3) Invited lectures

Our staff was invited to give lectures in the following meetings and training courses.

a) 6th International Conference on Isotopes held in Seoul, Korea, 12-16 May 2008.
b) Ehrlich II-2nd World Conference on Magic Bullets Celebrating the 100th Anniversary of the Nobel Prize Award to Paul Ehrlich held in Nurnberg, Germany, 2-7 October 2008
c) 3rd International Training on Emergency and Disaster Management held in Surabaya and Bali, Indonesia, 18 - 31 August 2008.
d) 12th International Congress of the International Radiation Protection Association (IRPA12) held in Buenos Aires, Argentina, 19-24 October 2008.
e) BATAN-JAEA Joint Training Course on Radiological Emergency Preparedness and Response held in Jakarta, Indonesia, 3-7 November 2008.
f) Japan-United States Chemical and Biological Collaboration Conference held in Tokyo, Japan, 17-19 February 2009.
g) Tokyo Symposium on Disaster Medical Management - To Share Knowledge and Information Between Japan, China and South Korea- held in Tokyo, Japan, 26-27 March 2009.

7-4) International meetings / Conferences

NIRS staff members attended the following meetings and exercises.

a) AACR 2008 Annual Meeting held in San Diego, CA, USA, 12-16 April 2008.
b) International Investigative Dermatology 2008 held in Kyoto, Japan from 14-17 May 2008.
c) BioDose 2008 held in Hanover, NH USA, 7-10 September 2008.
d) WHO BioDoseNet 1st Coordination and Planning Meeting held in Hanover, NH USA on 7 September 2008.
e) 12th International Congress of the International Radiation Protection Association (IRPA12) held in Buenos Aires, Argentina, 19-24 October 2008.
f) ConvEx-3, International Exercise, 9-11 July 2008.

7-5) Members of international committees

NIRS staff members participated in the following committees.

a) ICRU Low Dose Report Committee meeting held in Washington DC, USA from 17-18 April 2008.
b) Particle Therapy Co-Operative Group (PTCOG) 47 held in Florida, USA, 19-24 May 2008.
c) OECD/NEA CRPPH EGIR-8 held in Paris, France, 2-3 October 2008.
d) 12th Coordination and Planning Meeting of the WHO-REMPAN Collaborating Centers and Liaison Institutions held in Buenos Aires, Argentine, 15-17 October 2008.
e) Global Health Security Initiative (GHSI) Meeting held in Brussel, Belgium, 1-5 December 2008.
f) International Commission on Radiation Units and Measurements (ICRU) Annual Meeting held in Nyon, Switzerland, 22-27 September 2008.
g) Small group meeting for ICRU Ion Beam Report held in Heidelberg, Germany, 16-17 January 2009.
h) FNCA FY 2008 Workshop on Radiation Oncology held in Surabaya, Indonesia, 28-31 January 2009.
i) ICRU Low Dose Report Committee held in Bethesda, MD, USA, 5-7 March 2009.
j) ICRU Ion Report Committee small group meeting held in Lyon and Paris, France, 16-18 March 2009.
k) WHO Consultation on Harmonization of Medical Countermeasures for Radiation Emergencies: Management of ARS/MODS held in Geneva, Switzerland, 16-18 March 2009.
l) 2009 GHSI Rad/Nuc Threats Working Group Workshop Harmonization of Medical

Countermeasures and Triage for Radiological/Nuclear Events held in Geneva, Switzerland on 19 March 2009.

7-6) Other Visitors

a) Participants in the JICA Medical Management in Disaster for Andean Countries on 30 October 2008.

b) Colorado State University researchers on 17 November 2008.

c) Participants in programs of JICA for Radiation Diagnosis and Radiation Therapy for Cancer (Fundamental Medical Sciences) , Radiation Protection & Safety, Radiation Diagnosis, Radiation Therapy (IAEA board member states in Africa) on 1-19 December 2008. (Under the assistance of JICA).

6.1 The Study for Medical Treatment for High Dose Exposure

Makoto Akashi, M.D., Ph.D.
Director, Department of Radiation Emergency Medicine

(Outline of Research Career)

Dr. Akashi started his medical career at Jichi Medical School (Tochigi Prefecture) as a junior resident of internal medicine in 1981. He worked as a senior resident at the Division of Hematology of Jichi Medical School before moving to the Division of Hematology/Oncology at UCLA School of Medicine in 1987. He received a Ph.D. from Jichi Medical School in 1988. He became a staff member of NIRS in 1990. His major interests are: 1) establishment of radiation emergency medical preparedness; 2) research on radiation injuries, including molecular and cellular mechanisms; and 3) development of methods for mitigation of radiation injuries. He has treated patients of the criticality accident in Tokai-mura.

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Objectives

This department conducts studies that are usually not performed by other research institutions, emphasizing the diagnosis and treatment of radiation injuries due to high dose exposure. The members try to clarify the mechanism of injuries in cells and tissues exposed to high doses of radiation and its effects on survival, repair, and maintenance of function. In these studies, we are evaluating candidate substances for therapeutic drugs particularly for gastrointestinal and skin injuries. For gastrointestinal injuries due to radiation, we use experimental animals, primary cultured cells, and tissues to develop quantitative evaluation systems. In addition, we studied medical treatments with cytokines, natural products, and synthetic compounds that decrease the severity of injury.

To develop accurate diagnostic dose assessments for high-dose exposure to radiation, we also try to find markers for radiation exposure from bio-molecules contained in samples which can be collected less invasively, such as blood. We are attempting to determine genes, proteins, and other constituents of a living body that can provide a guide to treatment for radiation exposure.

Progress of Research

1) Effect of FGFC on intestinal injuries due to high doses of radiation

Fibroblast growth factors (FGFs) play important roles in numerous biological events such as angiogenesis, wound repair and so on, suggesting their ability to protect the intestines against radiation injuries. FGF receptor 2 IIIb (KGFR) is expressed only in epithelial cells and serves as a high-affinity receptor for FGF1, FGF7 and FGF10, while FGF1 binds to all subtypes of FGFRs. However, the structural instability of wild-type FGF1 and its dependence on exogenous heparin for optimal activity diminishes its potential for practical use. We have created an FGF1:FGF2 chimera (FGFC) that is able to stimulate heparan-bearing cells in the absence of exogenous free heparin. This study aimed at evaluating the protective activity of FGFC against radiation-induced intestinal damage. Using BaF3 transfectants overexpressing each FGFR subtype, we showed that FGFC was able to activate all of the FGFR subtypes similar to FGF1. When FGF1, FGF7, or FGF10 was administered with heparin intraperitoneally to BALB/c mice at 24 h before total body irradiation (TBI) at a dose ranging from 8 to12 Gy, FGF1 most effectively increased crypt survival at 3.5 days after TBI. In the same setting FGFC was equally as effective as FGF1, whereas it was even superior to FGF1 when administered without heparin. Finally, the effectiveness of FGFC was also observed without heparin when it was administered 24 h after irradiation. These findings suggest that FGFC is useful in clinical applications for both prevention and post-treatment of radiation injuries.

2) Cell-permeable PIDD (773-917)-TAT protein inhibits ionizing radiation-induced activation of pro-death caspase-2

PIDD (p53-induced protein with a death domain) plays a critical role in the activation of caspase-2 to trigger DNA damage and to induce apoptosis through the formation of a PIDDosome, which contains the adaptor protein RAIDD and caspase-2. We found that transcription of PIDD was induced by exposure of ionizing radiation in rat small intestinal epithelial cell line (IEC6) . Yeast two-hybrid analysis indicated that the death domain of PIDD interacts with RAIDD. Overexpression of rat C-terminal PIDD fragment (residues 773-917) containing the death domain dominant-negatively inhibited the PIDD-mediated activation of caspase-2 after ionizing irradiation. In order to use the PIDD (773-917) fragment as an antiapoptotic drug, we purified a recombinant PIDD (773-917) fragment fused with a basic 11-amino acid peptide derived from HIV-TAT which facilitates the uptake of the protein into mammalian cells with high efficiency. When PIDD (773-917)-TAT was added to the IEC6 cells, PIDD (773-917)-TAT was delivered into the cells within 1 hour. Furthermore, we observed the inhibition of caspase-2 activation when PIDD (773-917)-TAT was added to the IEC6 cells 1 hour after irradiation. These results suggest possibility of PIDD (773-917)-TAT for protection from ionizing radiation-induced gastrointestinal cell death.

3) The roles of endogenous TNFα in leukemia cells and mice exposed to radiation

Tumor necrosis factor alpha (TNFα) is a unique pro-inflammatory cytokine whose signaling pathways are linked to both pro- and anti- apoptotic responses in many types of cells and tissues, and it is produced upon radiation exposure. Previously we have shown that radiation induces apoptosis through the caspase pathway requiring TNFα production in human Jurkat T leukemia cells lacking functional p53. TNFα expression is regulated by a transcription factor, early growth response-1 (Egr-1) in cell lines lacking p53. To better understand the mechanism of TNFα expression after high dose radiation, we used inhibitors of the MEK (PD98059), p38MAPK (SB203580), PI3K (LY294002) and JNK (SP600125) pathways and examined Egr-1 and TNFα expression in these cells. Pretreatment of these cells with an inhibitor of MEK, p38 MAPK or JNK blocked the expression of Egr-1 and TNFα mRNAs by 10 Gy radiation. In contrast, inhibition of PI3K blocked the TNFα but not Egr-1 mRNA expression induced by radiation. Furthermore,

cAMP response element-binding protein (CREB) linking to the transcription of Egr-1 was phosphorylated by radiation. Radiation-induced phosphorylation of CREB was blocked by pretreatment of each inhibitor. Our results suggest that the radiation-induced TNF α expression is mediated through the MEK, p38 MAPK, PI3K or JNK pathway via Egr-1 induction requiring activation of CREB in Jurkat cells. Further studies on mechanisms are in progress.

We also compared the wild-type of TNF α (WT) and its knockout (K/O) balb/c mice and found that the survival durations in WT were significantly longer than those in K/O mice and administration of TNF α increased the survival rate in K/O mice. Since autopsies failed to find difference in causes of death between both groups, we compared injuries of bone marrow and small intestine. Numbers of red blood cells were significantly reduced in K/O mice 15 days after exposure with concomitant higher levels of serum iron and lower unsaturated iron binding capacity as compared to those in WT mice. Administration of TNF α significantly improved those in irradiated K/O mice. Assays for crypt microcolony and apoptosis in small intestine showed no difference between both irradiated groups. Interestingly, administration of either TNF α or lipopolysaccharide (LPS) significantly inhibited the apoptosis in WT but not in K/O mice. The serum levels of TNF α were increased following the TNF α challenge in both groups, but that in WT was higher than that in K/O mice. LPS increased the levels of TNF α in WT but not in K/O mice. We also studied the expression of Bax and Bcl2 proteins in intestinal crypt cells. Radiation increased the Bax/Bcl2 ratio in both mice. However, administration of TNF α before radiation reduced the ratio in irradiated WT but not in K/O mice. Our results suggest that endogenously-produced TNF α plays an important role in radiation injury.

4) Lithium chloride protects and rescues the small intestinal epithelial cells from radiation-induced apoptosis through PI3K/Akt and MEK/ERK pathways

High dose radiation induces apoptosis of intestinal epithelial cells and subsequent depletion of the cells, resulting in lethal intestinal injury. However, effective treatment of this injury has not been established yet. Lithium chloride (LiCl) is well known as an inhibitor of glycogen synthase kinase 3 (GSK3), which has been shown to be associated with apoptosis. We studied the effect of LiCl on intestinal radiation injury. Rat small intestinal epithelial cell line, IEC-6 cells and intestinal epithelial cells in primary culture obtained from fetal rat duodenum were treated with LiCl for 1 h and then exposed to γ-radiation of 20 Gy; 24 h after irradiation, the apoptosis was evaluated by Hoechst staining. Pretreatment with 10 mM of LiCl markedly inhibited radiation-induced apoptosis in both cells. Furthermore, addition of LiCl after irradiation blocked the apoptosis. Inhibition of either phosphoinositide 3-kinase (PI3K)/Akt or mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) kinase (MEK)/ ERK pathway abrogated the anti-apoptotic effect of LiCl. We administered LiCl to balb/c mice 1 h before total-body irradiation (TBI) with 8 Gy. Administration of LiCl blocked the radiation-induced apoptosis in intestinal crypts. Moreover, either pre- or post-administrations of LiCl increased the number of surviving crypts in mice 3.5-day after TBI. In the present study, we found that LiCl protects and rescues intestinal epithelial cells from radiation-induced apoptosis through activation of pathways involving PI3K/Akt and MEK/ERK. Our results also showed that LiCl prevents radiation-induced intestinal injury in vivo.

5) Suppressive effect on ionizing radiation-induced intestinal epitherial cell apoptosis by a cell penetrating peptide bound Survivin

Survivin is a member of the inhibitors of apoptosis (IAP) family and contains signature motifs termed baculovirus IAP repeat (BIR). Survivin is aberrantly expressed in cancer but undetectable in normal differentiated adult tissues. Although the precise mechanism remains to be elucidated, it has a role in cell division and apoptosis (caspase-dependent and caspase-independent apoptosis). In response to inducers of cell death, mitochondrial survivin is rapidly released into the cytosol, where it prevents caspase activation and inhibits apoptosis. These findings suggest that survivin might be effective for protection from ionizing radiation-induced gastrointestinal cell death. We used rat small intestinal epitherial cell line (IEC-6) to investigate the effect of survivin. When survivin was over-expressed, it localized in mitochondria and it functioned as an inhibitor of caspase-9 activation, indicating that it might function as an inhibitor of caspase-3 and caspase-2 activation after ionizing radiation. We synthesized survivin bound to a cell penetrating peptide (TAT-survivin), which is known to facilitate the uptake of the protein into mammalian cells with high efficacy. An investigation of the effect of the protein on the intestinal injury induced by high dose radiation is now in progress.

6) Study on the effect of pharmaceutical agents on the recovery of intestine damaged by radiation

The aim of the study is to obtain basic results to select favorable pharmaceutical agents against intestinal damage caused by exposure to high-dose radiation in accidents. We examined drugs which contribute to recovery from lethal intestinal damage

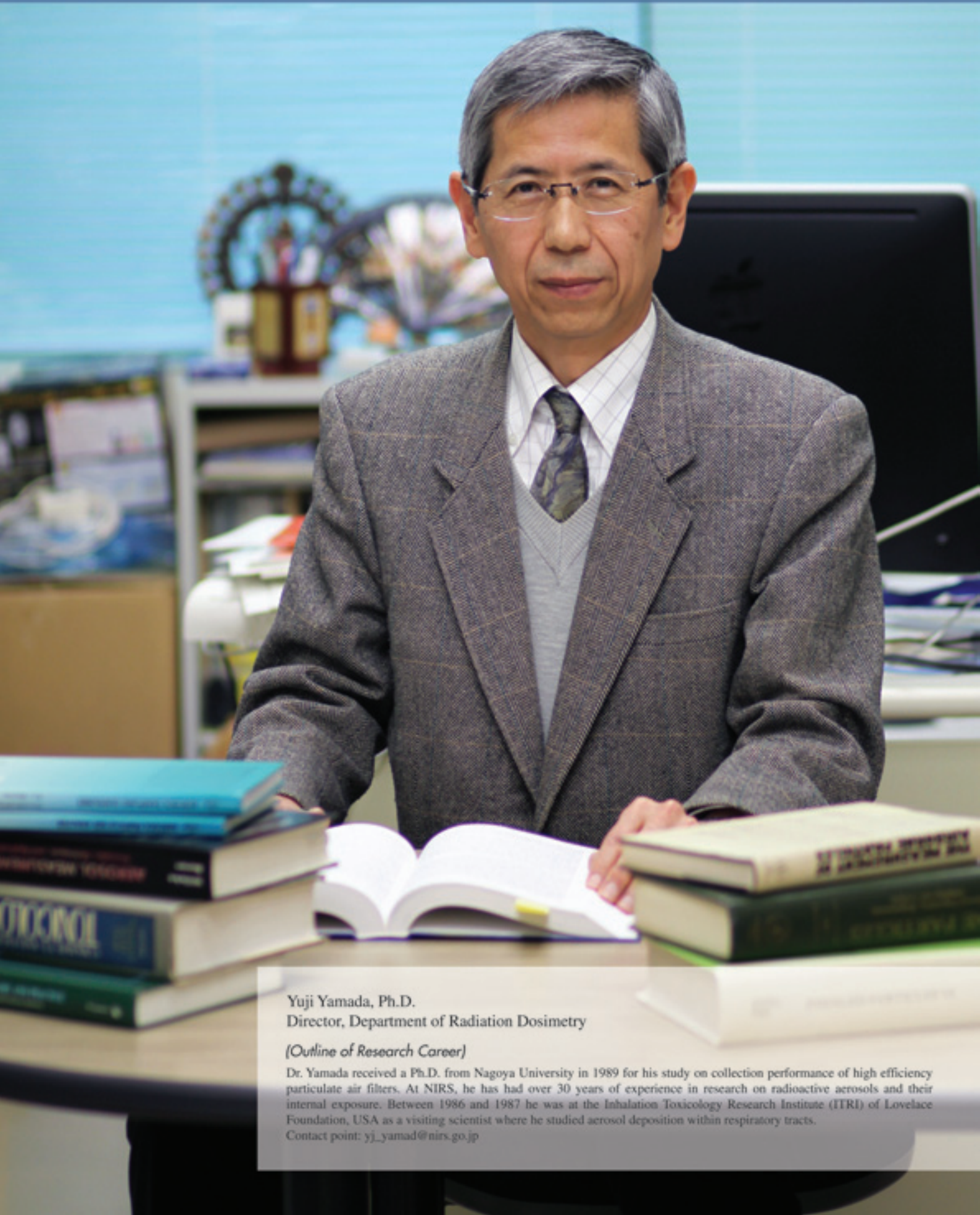
following radiation exposure using an experimental animal model.

Since it was difficult to find the regions of lethal damage in the large intestine, survival rate was used as an indicator. Damage to the whole intestine was induced by abdominal exposure of anesthetized C3H/He mice to 15.7 or 17.6 Gy of x-rays. Parenteral nutrition and drugs were concomitantly injected to the mice from day-1 to 10 after the irradiation. Even though the nutrition was administered to the mice, the body-weight decreased until day-7. Although mice that showed increasing weight on day-8 survived at least until day-28, others died within 10 days. Using at least 3 different lines of mice, the effects of the drugs on the survival rate were determined. Various drugs including alpha-adrenergic receptor stimulators (salbutamol and phenylephdrine), parasympatholytic agents (scopolamine butylbromide and atropine) and antispasmodic (papaverine) showed an effect on the survival rate. In contrast, their antagonists such as sympatholytic drugs (reserpine and propranolol), parasympathomimetic agents (pilocarpine and neostigmine) and benzodiazepine derivatives (such as antianxiety agents diazepam and tofisopam) decreased the survival rate. These results showed that relaxation of smooth muscle during the recovery of damaged mucosal tissue of intesine may inhibit recovery of radiation-induced damages.

Major publications

1) K. Motomura, A. Hagiwara, A. Komi-Kuramochi, et al.: An FGF1:FGF2 chimeric growth factor exhibits universal FGF receptor specificity, enhanced stability and augmented activity useful for epithelial proliferation and radioprotection., *Biochimica et Biophysica Acta. General Subjects,* 1780[12], 1432-1440, 2008
2) F. Nakayama, A. Hagiwara, T. Yamamoto, M. Akashi: Hydrogen peroxide as a potential mediator of the transcriptional regulation of heparan sulphate biosynthesis in keratinocytes., *Cellular & Molecular Biology Letters,* 13[3], 475-492, 2008
3) T. Tamura, X. Cui, N. Sakaguchi, M. Akashi: Ginsenosides Rd Prevents and Rescues Rat Intestinal Epithelial Cells From Irradiation-Induced Apoptosis, *Food and Chemical Toxicology,* 46[9], 3080-3089, 2008
4) F. Nakayama, K. Muller, A. Hagiwara, R. Ridi, M. Akashi, V. Meineke: Involvement of Intracellular Expression of FGF12 in Radiation-Induced Apoptosis in Mast Cells, *Journal of Radiation Research,* 49[5], 491-501, 2008
5) T. Yamamoto, N. Sakaguchi, M. Hachiya, F. Nakayama, M. Yamakawa, M. Akashi: Role of catalase in monocytic differentiation of U937 cells by TPA: hydrogen peroxide as a second messenger, *Leukemia,* 23[4], 761-769, 2008

6.2. Reseach on Radiation Dose Assessment for Radiation Emergency Medicine



Yuji Yamada, Ph.D.
Director, Department of Radiation Dosimetry

(Outline of Research Career)

Dr. Yamada received a Ph.D. from Nagoya University in 1989 for his study on collection performance of high efficiency particulate air filters. At NIRS, he has had over 30 years of experience in research on radioactive aerosols and their internal exposure. Between 1986 and 1987 he was at the Inhalation Toxicology Research Institute (ITRI) of Lovelace Foundation, USA as a visiting scientist where he studied aerosol deposition within respiratory tracts.

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Objectives

Radiation accidents can be divided into those resulting from external exposure and those resulting from internal exposure. For severe accidents, bone marrow transplantation may be considered depending on the external exposure dose received, or drug administration may also be considered to inhibit deposition and promote excretion of radioactive substances incorporated into the body. Dose assessment of victims in radiation accidents must be made within a short time in combination with the details of the accident to estimate the radiation effects and to initiate appropriate medical treatment.

Major subjects in radiation dose assessment research are: 1) collection and analysis of information on the occurrence of radiation accidents, radiation type, and radioactivity; 2) determination and evaluation of the amount of radioactivity in the body and excreta; and 3) biological evaluation of the effects resulting from exposure on the body. Our aims are to shorten the time needed for analysis and dose determination, and to improve the accuracy of comprehensive assessment, which combines physical and biological dose assessments.

In the area of radiation emergency medicine, we have made basic and application studies for clinical use of agents in removing radionuclides, especially alpha emitters like plutonium or uranium that are incorporated into the body.

Progress of Research

1) Development of ESR dosimety using human nail clippings

Electron spin resonance (ESR) dosimetry is a method to measure radical numbers produced by radiation in substances and to estimate exposure dose. This method is useful for dose estimations when workers are exposed while not wearing personal monitors and when the general public is exposed accidentally. Tooth enamel is typically used for this purpose. However, teeth cannot be extracted easily from persons in all cases. It is necessary to find other human tissues or substances around exposed persons for estimating personal exposures. Nail clipping samples are more easily obtained from exposed persons than tooth enamel samples. Therefore, nail samples were applied to ESR dosimetry in the case of γ-irradiation. Relationship of ESR sensitivity and absorbed dose (Gy) in nails was found to be linear. Unknown dose of γ-exposed nail was estimated using the modified calibration curve at room temperature for 1-2 weeks. However, it was found both ambient temperature and humidity have an affect on this calibration curve more than individual sensitivity differences from radiation. Those problems must be solved to establish nail ESR dosimetry.

2) Chromosome aberration analysis

In order to maintain the quality level in chromosome analysis for the dose estimation, the dicentric chromosome was analyzed in the lymphocytes which were irradiated by gamma-rays at the doses of 0, 0.5, 1.0, 2.0, 3.0, 4.0, and 5.0Gy. The frequencies of the dicentric chromosome at each dose point in these analyses were almost identical with those obtained from the analysis in all previous years. This means that the quality level for the detection of dicentric chromosome was maintained and the standard curve for dose estimation was also not changed.

In the process of dose estimation by dicentric chromosome analysis, the slide preparation seems to be very important to obtain the value of radiation dose more accurately. Therefore, in the present study, we analyzed the effect of the concentration of Colcemid which is the chemical agent to stop the cell cycle at the M-stage on the chromosome condensation. No relationship was observed at concentrations of 0.03, 0.05 and 1.0 μg/ml. However, the chromosomes were significantly elongated at the concentration of 0.01 μg/ml in the case of a 2-hour treatment.

Furthermore, in order to establish an assay system to estimate the radiation dose in the case of partial body exposure, we used the human hair root as the target organ for dose estimation. The comet assay was applied for the detection of DNA damage in the hair root cells after irradiation and we detected a slight relationship between tail length indicating DNA damage and irradiated dose. This suggests the possibility that the comet assay in hair root cells will be useful for dose estimation in partial body exposure.

One of the purposes in our laboratory is to develop and improve automated systems of facilities used for chromosome studies. The metaphase finder is an automated optical microscope system which automatically scans and finds metaphase cells on the slide glass and relocates metaphase cells to the center of the field of view of the microscope to observe chromosomes in high magnification. The software of this metaphase finder uses mathematical morphology filters in most of the image recognition process. In addition, mathematical morphology filters for grey-level images are used in the most recent version. This year, the performance of this metaphase finder was tested and the results were presented at an international meeting. It was proven that the false positive rate was improved to 2%.

3) Development of a semi-tissue equivalent Si semiconductor for local dose estimation

The majority of persons have non-uniform exposure in the case of high dose external exposure. For such a case, it is indispensable to reconstruct the local dose in

the early stage for determining the radiation emergency medicine treatment. One of the optimum methods to estimate the dose is geometrical simulation by Monte Carlo calculation. To construct the basic data, a semi-tissue equivalent Si semiconductor detector to be inserted in a physical phantom for the bench mark test on the Monte Carlo calculation was developed. This detector consists of a Si sensor (1mm square) which is connected to the Si substrate on which a super-thin amplifier circuit is formed directly with the MEMS technique, and a tissue-equivalent medium which is composed of hydrogen (8.2%), carbon (66.2%), nitrogen (2.2%), oxygen (20.7%), chlorine (0.4%), and calcium (2.3%). Using mono-energetic photons from 10kev to 70keV and ^{137}Cs and ^{60}Co sources, it was confirmed the Compton spectrum which would be used in an unfolding technique could be measured.

4) Nasal swab for alpha emitters

To improve the first estimation of intake activity, the quality of a nasal swab measurement was experimentally investigated. Alpha spectrometry was used to examine the experimental nasal swab samples which had been added a plutonium solution or particles. It was observed that the alpha energy spectrum had a quite different shape among samples, and it was characterized by the type of contaminant. The detection ratio for samples was almost 30% for the counting efficiency of the detector. To define the reason for the low detection ratio and the different shape of the spectrum for experimental swab samples, an AASI (Advanced Alpha-Spectrometric Simulation) was used. According to the AASI simulation, alpha radiation emitted from more than 80 μm below the surface hardly penetrated the filter medium. The count for 80 μm below the surface decreased to about 5% of that for no absorber. This means that the filter is infinitely thick with respect to the alpha particles at 5.15MeV. Since the thickness of the filter paper was 210 μm, the alpha radiation could be detected up to about 30% in depth. This simulated result supports that the detection ratio for the experimental sample was about 30% for the counting efficiency of the detector. The radioactive contaminant would also soak into the filter medium filled with distilled water. These results suggest that the absorption of alpha radiation should be considered to determine an accurate alpha activity for nasal swab samples. When the activity of particle and solution sample were adjusred, the park coumt in the alpha anergy spectra showed remarkble difference among them. The park area count was determind by deducting the count of the solution sample from that of particle sample. The ratio of the peak area count to the total was calculated as 30%. For the simulated spectrum, the ratio of the peak area count to the total was estimated to be 31% when the ratio was determined by deducting 35% as the ratio of the particle from 4% as that of the solution. The 31% for the simulated result was very close to 30% for the experimental result. This means that the difference in the detection ratio reflects the nominal energy without any shielding of the filter fiber. Therefore, the shape of the alpha energy spectrum would give an advantage to distinguish between the particle and solution samples. These results of a simulated analysis indicated that alpha spectrometry would give a sufficient detection ratio result to distinguish between radioactive substances.

5) Development of lung phantom for *in-vivo* measurements

A thorax model was designed and made for realistic shape of lungs and Japanese body size. This year, we compared the model with Lawrence Livermore National Laboratory phantom (LLNL phantom). First, the distribution of the radioactivity was compared by using the mapping measurement of 59.5keV gamma rays from ^{241}Am inside a low background room using a one-inch NaI detector that rolled the collimator of the lead 1mm. As a result, LLNL phantom gathers when seeing ahead and the radiation source will have gathered in the narrow area. The difference of the each distribution was caused by the difference of a flat extension of lung models. Moreover, they were measured by the lung monitor and compared by count efficiency. Because the view was expected to be almost the same in both models, a big difference would not be seen in the count efficiency in the lung monitor of NIRS.

6) A rapid analysis technique of Sr, Am, and U in urine samples

Internal dose evaluation is more complicated than external dose evaluation. Especially internal dose estimation due to α- and β-emitters is more difficult compared with that of γ-emitters. For this purpose, chemical analyses of urine and feces (bioassay) are conducted to estimate the input and accumulation volumes of radioactive nuclides of human bodies. However, the chemical analyses are usually complicated and time consuming. In a radiation emergency, early analytical results are requested for medical treatment of exposed persons.

In this study, three kinds of extraction resin columns and a liquid scintillator or alpha-spectrometer were combined to develop a rapid measurement system for strontium, americium, and uranium in human urine samples. After spiking an aliquot of ^{90}Sr into the urine sample, the ^{90}Sr fraction was purified by a Sr-specific resin column and detected by a liquid scintillator. Am and U were separated by UTEVA and TRU resin columns and measured by an alpha-spectrometer. A good recovery (above 80-99 %) was obtained in all cases. The total analysis time for a urine sample was

within a work day (ca. 8 h.) This system would be an effective bioassay method on radiation emergency.

7) Acute toxicity of uranium and the effects of chelating agents in simulated wounds model of rats

The initial behavior and acute toxicity of depleted uranium (DU) via wounds in which uranium was injected into femoral muscles of rats were compared with those by subcutaneous (SC) injection in previous studies. There were differences in the uranium behavior and excretion rates in feces from that of SC injection, probably due to the differences in diffusion speed of uranium from the DU injected site. The CBMIDA by local treatment, in which infused into the DU injected site , particularly for decreasing dysfunction of kidneys, was as effective as that by SC injection. This time, new effects of two lactoferrins by oral administration were examined. The lactoferrin with Fe has efficacy for excreting uranium and decreasing uranium accumulation in organs, and the lactoferrin without Fe enhanced the effects of CBMIDA, although either effects were lower than that of CBMIDA. The results indicated that local treatment by CBMIDA has efficacies for decreasing acute toxicity of uranium via wounds, when CBMIDA is infused within 2 h, and lactoferrin might be used in prolonged treatments in radiation emergency medicine. Findings of these studies were published.

Major publications

1) S. Fukuda, M. Ikeda, M. Nakamura, A. Katoh, X. Yan, Y. Xie, G. Kontoghiorghes: The effects of bicarbonate and its combination with chelating agents used for the removal of depleted uranium in rats, *Hemoglobin,* 32[1-2], 191-198, 2008
2) R. Wilkins, M. Yoshida, P. Pataje, et al.: Interlaboratory Comparison of the Dicentric Chromosome Assay for Radiation Biodosimetry in Mass Casualty Events, *Radiation Research,* 169[5], 551-560, 2008
3) S. Fukuda, M. Ikeda, M. Nakamura, X. Yan, Y. Xie: Efficacy of oral and intraperitoneal administration of CBMIDA for removing uranium in rats after parenteral injections of depleted uranium, *Radiation Protection Dosimetry,* 133, 12-19, 2009
4) K. Shiraishii, S. Ko, H. Arae, K. Ayama, P.V. Zamostyan, N.Y. Tsigankov, I.P. Los, and V.N. Korzun: Dietary intakes of radioactive cesium for Ukrainians, *J. Radioanal. Nuc. Chem. Art.,* 275, 411-415, 2008
5) W.F. Blakery, Z. Carr, M.C-M. Chu, et al.: WHO 1st consultation on the development of a global biodosimetry laboratories network for radiation emergencies (BiodoseNet), *Radiation Research,* 171, 127-139, 2009

7. Fundamental Technology Center

Masashi Kusakabe, Ph.D.
Director, Fundamental Technology Center

(Outline of Research Career)

In 1980 upon completion of his Ph.D. research in Hokkaido University, Dr. Kusakabe moved to University of Southern California, Los Angeles, to study the behavior of radionuclides in the ocean. In particular, his research focused on cosmogenic nuclides such as ^{10}Be and U-Th series radionuclides. In 1992, he joined the Japan Agency for Marine-Earth Science and Technology (then called Japan Marine Science and Technology Center), where he studied the carbon cycle in the ocean by using radionuclides. Since 2002, he has been a director of the NIRS Nakaminato Laboratory for Marine Radioecology in Ibaraki Prefecture. Since 2008, he has been concurrently Director of the Fundamental Technology Center which now occupies a considerable amount of his workload.

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Objectives

The Fundamental Technology Center was newly established in 2006 to support and promote the wide variety of research activities done at NIRS. It consists of two departments with seemingly different natures, the Department of Safety and Facility Management and the Department of Technical Support and Development. They work sometimes in complementary manner to each other. While the Center provides state-of-art technology to and helps NIRS scientists, it also secures the safety of the working environment. An outline of the Center activities and structure follows in the next section.

Overview

The Center consists of one office, two departments and seven sections. Figure 7-1 shows the organizational structure of the Center. The Planning and Promotion Office is responsible for planning and management of work in the Center. It also manages common use facilities. In addition, the Office sponsors meetings to facilitate the technical development of NIRS and to provide a bridge between scientists and technologists.

The Department of Technical Support and Development consists of three sections: (1) Technical Advancement of the Radiation System Section; (2) Radiation Measurement Research Section; and (3) Laboratory Animal Science Section.

The Department of Safety and Facility Management consists of four sections; they are shown below with their operations.

(1) Safety and Risk Management Section
- Planning and promotion of safety assurance
- Training of employees on safety issues
- Assurance of safety on campus
- Protection of the public from nuclear power accidents

(2) Radiation Safety Section
- Legal management of radiation and radioactive materials
- Radiation exposure management
- Training of employees who deal with radioactive materials and radiation
- Assurance of safety with respect to radiation
- Management of radiation related facilities and radioactive waste

This Section includes the subdivision, Nuclear Fuel Control Office, which is concerned with the management of radionuclides used in nuclear fuel.

(3) Safety Control Section
- Planning of fire control measures
- Establishing safety controls of gene recombination experiments and hazardous chemicals
- Safety assurance in working environments

(4) Facility Management Section
- Management of energy consumption, working environments, and general wastes
- Construction and maintenance of buildings

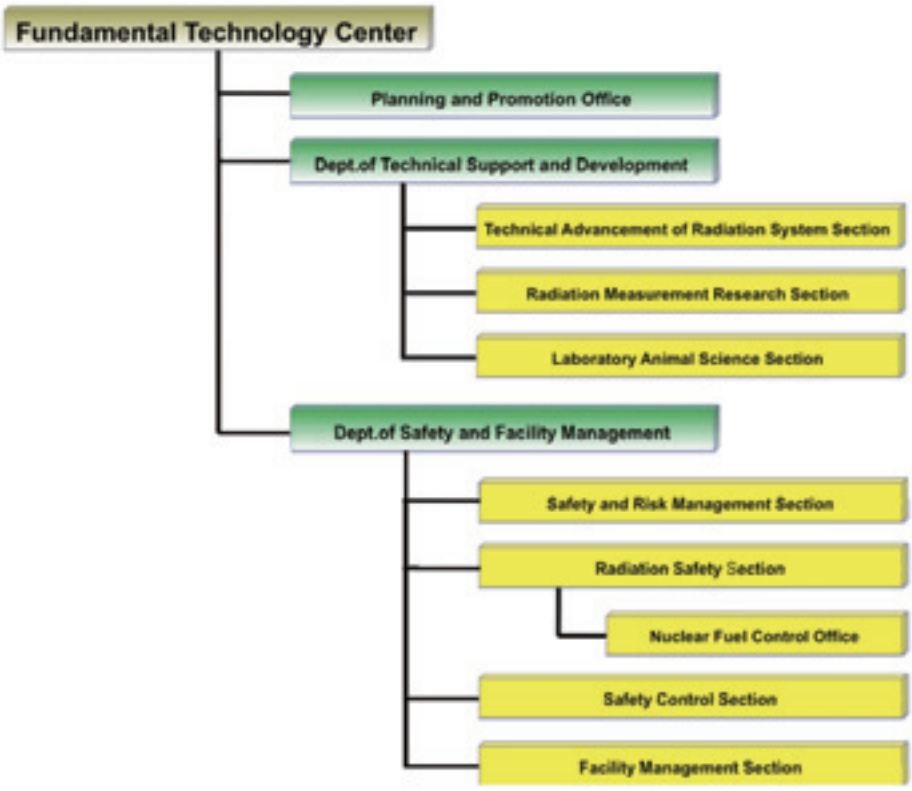

Fig. 7-1 Organization of Fundamental Technology Center.

7.1. Department of Technical Support and Development of Fundamental Technology Center

Hitoshi Imazeki, Ph.D.
Director, Department of Technical Support and Development

(Outline of Research Career)

Our department staff consists mainly of technologists who support researchers in the other research centers in NIRS and domestic and international institutions with knowledge, experiences and technologies. Inherited or newly developed technologies have been enhanced in order to provide better facilities, devices and animals for various research projects in biology, medical and physics. Our department is composed of three sections, Technical Advancement of Radiation Systems Section, Radiation Measurement Research Section and Laboratory Animal Sciences Section.

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Technical Advancement of Radiation Systems Section

This section provides technical supports for radiobiological researchers along with advancing developments of radiation systems. This section provides a variety of radiation sources, such as X-ray, gamma-ray, and neutron sources, and our mission is to ensure the quality of those radiation fields, such as dose, dose rate, and field uniformity. We also have two electrostatic accelerators. The original one is called PASTA (PIXE Analysis System and Tandem Accelerator), which accelerates protons and helium ions for multi-elemental analysis in biological and other environmental materials. There is a beam line is installed in PASTA, which is called SPICE (Single Particle Irradiation system to Cell) and this is a microbeam irradiation system exclusively designed for radiobiological studies such as research concerning radiation risk assessments. The second electrostatic accelerator facility is called NASBEE (Neutron exposure Accelerator System for Biological Effect Experiments), and it generates a neutron beam at an average energy of 2.0 MeV at high dose rate. Neutron beams are introduced into the SPF-conditioned room, which enables researchers to work with radiation-induced carcinogenesis using mice. These accelerator facilities are available for collaborative research projects. We also provide technical assistance for the single cell analysis sorter (flow cytometer), the XRF (X-ray fluorescence) analysis system and other analysis systems that are highly technical and require experience for their successful operation.

Radiation Measurement Research Section

Dosimetery and radiation measurements are required for radiation biology and physics research projects. In order to respond to this need, we characterize the radiation fields and provide data of radiation parameters using radiation dosimeters and detectors. Also, brand-new detectors and dosimeters are developed utilizing new technologies.

Our section is composed of 3 permanent staff members, 2 full time technical and scientific staff members, 1 post-doctoral fellow and 3 support staff members. And, many national and international collaborators support our work as well.

Laboratory Animal Science Section

It is absolutely necessary to use experimental animals in animal experiments to advance biomedical and radiological research and education. There are 11 institutes using experimental animals in Japan and our section has various animal species, for example mice, rats, Mongolian gerbils, rabbits, and monkeys. Those animals are humanely taken good care of by our staff. Our staff is composed of nine permanent members, five animal technicians (including two veterinarians), four clerical workers and 50 non-permanent staff members.

In April 1999, the guidelines concerning the care and control of experimental animals were revised. All animal researchers at NIRS must adhere to these new guidelines. The Laboratory Animal Care and Use Committee (LACU) acts as the cornerstone of our system of self-regulation. LACU has to examine animal research protocols in order to ensure that all animal research projects are in compliance with the guidelines. No animal research projects can be carried out without approval by the LACU.

7. 2. Current status of the microbeam irradiation system for mammalian cells, SPICE

INTRODUCTION

Single-cell microbeam irradiation systems have become significant tools in the field of radiation biology. Recently, many microbeam facilities have been developed, and are available for biological research worldwide. Also in Japan , there are many microbeam facilities with different types of radiation sources that are now available for biological studies, such as low-dose effects, hyper radio-sensitivity, bystander effects and so on. The single particle irradiation system (SPICE) of NIRS generates 3.4 MeV protons with an approximately 2 μm diameter beam, and is the only microbeam irradiation system in Japan with low-LET parti-cles irradiation. SPICE is currently operative for biological studies.

This year, the "8th International Workshop on Microbeam Probes of Cellular Radiation Response" was organized and held at NIRS and the Extended Abstracts were published (8th International Workshop on Microbeam Probes of Cellular Radiation Re-sponse. Extended Abstracts, *J. Radiat. Res.*, 50: Suppl., A81-A12, 2009).

There were a total of 113 participants, including researchers from overseas. Recent developments and biological research in microbeam facilities in Europe, U.S, and Asia were also reviewed in the workshop. This workshop series has been highly successful in bringing together groups interested in developing and applying micro-irradiation techniques to the study of cell and tissue damage by ionizing radiations and provided a forum to assess the current state of microbeam technology and current biological applications, and to discuss future directions for development, for both technological and biological aspects. (See poster, Fig. 7-2)

Fig. 7-2. Poster of the 8th International Workshop on Microbeam Probes of Cellular Radiation Response.

OUTLINE OF SPICE

The electrostatic accelerator facility of NIRS supplies protons and helium ion beam by a Tandetron accelerator. In this facility, there are four beam lines, and three horizontal beam lines are available for PIXE analysis PASTA. The fourth beam line, SPICE is a vertical beam line, the beam of which is transported upward after passing by a 90-degree bending magnet installed in the middle of the microbeam scanning PIXE beam line. The main characteristic of SPICE is that a beam is focused by a Q-magnet lens (Oxford Microbeam Ltd.). The number of protons traveling through the cells is counted using a scintillation detector equipped on the microscope system which is set above the cell dish. The computer that controls the voice coil motor stages gives a high-speed trigger pulse to the beam deflector to turn the beam on and off. It is possible to irradiate from a single to an arbitrary number of protons per position or cell. Cells are dyed with Hoechst 33258, and their fluorescent image is captured with a CCD camera. This system computes the X-Y coordinates of the cell position according to their fluores-cence. All of the irradiation procedures can be performed automatically after setting some parameters, such as a preset number of protons.

BEAM-SIZE MEASUREMENT USING CR-39

Beam size has been measured by the plastic track detector, CR-39 (HARTZLAS TD-1). A thin CR-39 film was adhered to a cell dish, and then the dish was set on the stage. The image of 〈Fugaku 36ヒ drawn by Katsushika Hokusai was reprinted as a microbeam drawing as shown in the Workshop poster (see Fig.? -1). This microbeam drawing was performed automatically according to the text file of a preset number of protons and the X-Y coordinates of the sample stage position, which consisted of 14,000 irradiation positions. This system allows from 6 to 8 positions to be irradiated per second, therefore the irradiation of CR-39 shown in figure was ac-complished within approximately 30 min.

FUTURE AIM AND DEVELOPMENTS

We have developed the microbeam irradiation system, SPICE. An approximately 2 μm in diameter beam was real-ized and the 5 μm diameter beam is now available for daily irradiation. Irradiation with a single proton can also be per-formed and the maximum speed for cell irradiation is over 400 cells per minute. Most of the irradiation procedures can be performed

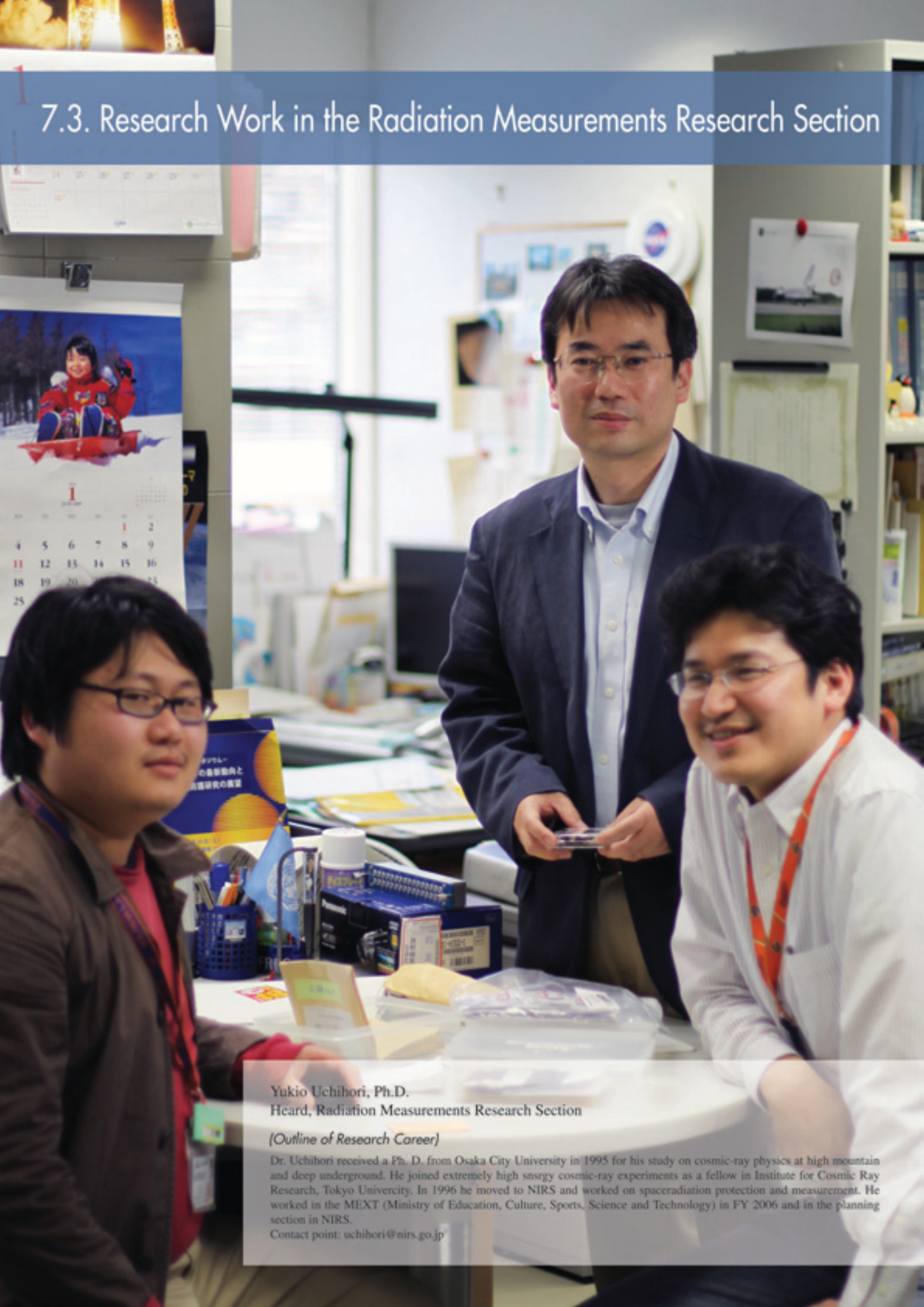
automatically by setting some parameters. Further improvements are underway, such as an off-line microscopic system for post-irradiation biological analysis, improve-ments of targeting accuracy and reduction of the beam size below 2 μm in diameter.

SPICE and PASTA are now available as an open facility for collaborative research projects. Contact infopixe@nirs.go.jp for beam time schedules and other detailed information.

Major publications

1) Y. Kobayashi et al., *J . Radiat. Res.* 50: Suppl., A29-A47, 2009
2) H. Imaseki et al., *Nucl. Inst. Meth. B* 260: 81, 2007
3) H. Yamaguchi et al., *Nucl. Inst. and Meth. B,* 210: 292, 2003
4) T. Konishi et al., *Nucl. Inst. and Meth. B,* in press
5) H. Imaseki et al., *Int. J. PIXE,* 10: 77-90, 2001
6) T. Ishikawa et al., *Nucl. Inst. and Meth. B,* in press

7.3. Research Work in the Radiation Measurements Research Section



Yukio Uchihori, Ph.D.
Heard, Radiation Measurements Research Section

(Outline of Research Career)

Dr. Uchihori received a Ph. D. from Osaka City University in 1995 for his study on cosmic-ray physics at high mountain and deep underground. He joined extremely high snsrgy cosmic-ray experiments as a fellow in Institute for Cosmic Ray Research, Tokyo Univercity. In 1996 he moved to NIRS and worked on spaceradiation protection and measurement. He worked in the MEXT (Ministry of Education, Culture, Sports, Science and Technology) in FY 2006 and in the planning section in NIRS.

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Objectives

Research work done in Radiation Biology and Physics needs reliable dosimetery or measurement data in the radiation field. Our members support the activities of NIRS researchers using conventional and/or the latest radiation detectors. And, we also propose new research topics in various new radiation fields like micro-beam and low dose neutron facilities to biologists and physicists in order to open new areas of the sciences.

Several detectors have been developed by leading-edge techniques and calibrated in various radiation fields like that of HIMAC, cyclotrons, neutron fields, precise radiation sources, and so on. Not only detectors themselves but also analysis methods including hardware and software, simulation code and electronics have been developed.

Dosimetery of space radiation is another object of interest and several detectors for space radiation measurements were developed. Under a collaboration with the Institute of Bio-Medical Problems (IBMP), Russian Academy of Science, there were several opportunities to measure space radiation in the International Space Station (ISS). Also, the international intercomparison program of space radiation detectors, the ICCHIBAN (InterComparison for Cosmic-rays with Heavy Ion Beams At NIRS) Project, is ongoing to understand and standardize detectors for space radiation dosimetery.

Progress of Research

Passive detectors (Nakahiro Yasuda, Satoshi Kodaira, Shuya Ota, Iva Jadrnickova, Mieko Kurano, Hajime Kawashima, Hisashi Kitamura, Yukio Uchihori)

Development of a fluorescent nuclear track detector technique

A novel fluorescent nuclear track detector (FNTD) was verified as a possible spectroscopic technology for heavy charged particles with wide range linear energy transfer (LET). The technique uses a luminescent aluminum oxide single crystal having aggregate oxygen vacancy defects and doped with Mg (Al_2O_3: C,Mg) as the detector in combination with a laser scanning confocal fluorescence microscope. We found that the lower detection limit for LET in water was less than 0.5 keV/μm (corresponding to 160 MeV protons). A previous study showed the higher limit would be more than 9,000 keV/μm. This indicates that the method has a very large dynamic range for LET measurements, and has enough capability to be applied as a personal monitor for space use. Based on the result, we designed a compact reader for this application as an on board instrument. For further study, we will verify the detector response to a mixed field radiation field such as heavy ions with X/γ ray or high energy neutrons. [Done in collaboration with: Landauer Inc. (USA) and Nagase Landauer Inc. (Japan)]

Development of the new CR-39 detectors for the precise measurement of high LET particles

Precise LET measurement of higher LET radiation is necessary to estimate dose equivalent for astronauts. Recently, the dose contribution of high LET components (> 50 keV/μm) originated from target fragmentation reactions has been discussed. We have developed the new type copolymer detector of CR-39 and DAP resin detectors and the new chemical etching method using PEW solution for control of the detection threshold of LET. The CR-39/DAP copolymer has the unique characteristic to degrade the sensitivity to the high LET particles. The new etching technique using PEW solution could make it easy to control the detection threshold and to improve the charge resolution of high LET particles.

Development of the particle tracking algorithm in CR-39 detectors

A new method to trace heavy ion trajectories in a stack consisting of interleaved CR-39 detectors and target material layers was developed and verified for the use in the precise measurement of projectile charge changing cross sections of heavy ion fragmentation reactions. A high speed imaging microscope with sophisticated track analysis software was utilized to extract the charge information from multiple ion tracks belonging to a single fragmentation event. The projectile total charge changing cross sections for Fe ions on a carbon target was estimated and compared with previous experiments at initial beam energy of 1 GeV/n, was and results were in good agreement with those obtained by other investigators. This method allows precise and fast measurements of the projectile charge changing cross section with higher statistics, and will be applicable to the precise measurement of LET spectrum in particle therapies and space dosimetry.

Measurements of high LET components in space radiation

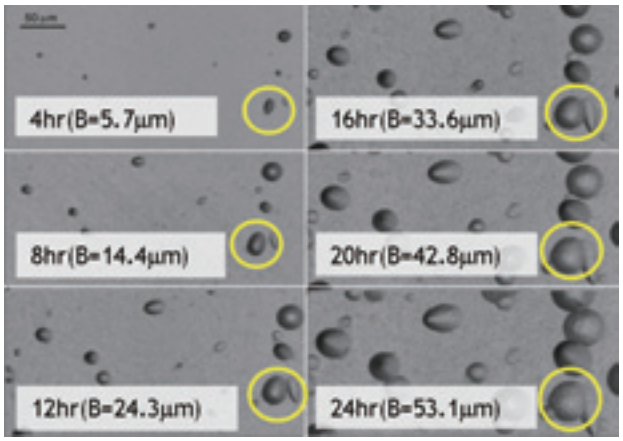
We conducted a radiation monitoring experiment for passive radiation dosimeters as a part of the BRADOS experiment on the International Space Station (ISS) for 269 days in 2004. In this study, we employed the CR-39 detector HARZLAS TD-1 and verified the variation of the LET spectra for several bulk etch conditions (multi-step) from 5 - 53 mm at the same position as a TD-1 detector. All etch pits were traced at each step of the etching time as shown in Fig. 7-3. Many high LET particles with short range are observed in the CR-39

detector, which are considered to be produced by target fragmentation reactions with high energy protons. They should make a significant dose effect in inner regions of the human body (e.g. bone consisting of Ca).

Fig. 7-3. The same etch pits were traced on several CR-39 detectors using the multi-etching method.

Neutron detectors (Masashi Takada)

Pocket-size dosimeters with long-life batteries are the preferred device in order to measure cosmic-ray neutrons in aircraft with good accuracy. The possibility to measure the neutron exposure doses in the radiation field produced by cosmic rays in aircraft was investigated with these devices. In long haul flights, the



dosimeters were observed to give values 10 times larger neutron ambient dose equivalents than those estimated by the EPCARD code.

In order to investigate dosimeters that can meet this requirement, irradiation experiments were done using 18, 30 and 70 MeV proton and 25 MeV/nucleon alpha-particle beams at the cyclotron facility in NIRS. Measured deposited energies in the silicon detector were about 2 to 5 times larger than calculated deposited energies in the original depletion layer. The large discrepancy in energy deposition in the partially depleted silicon detector used in this study is well explained by considering the funneling effect for high LET particles.

The charge-collection lengths are found to be independent of particle species, energies and stopping powers but dependent on the original depletion layer thickness. An empirical equation as a function of the depletion layer thickness is introduced to calculate the charge-collection length and the deposited energy in the silicon detectors.

The empirical equation will be used to calculate energy responses of personal neutron dosimeters using silicon detectors for neutrons and charged particles in the design of a dosimeter for aircrews that can be used at cruising altitudes although the detector response to neutrons and charged particles can not be calculated from the deposited energy in the original depletion layer. The equation will be applied to high-energy and heavier particles and electrons because the charge-collection length is independent of particle species, energies and stopping powers.

Energy deposition of X, γ and electron dosimeters would also be calculated.

Scintillation detector (Hidehito Nakamura)

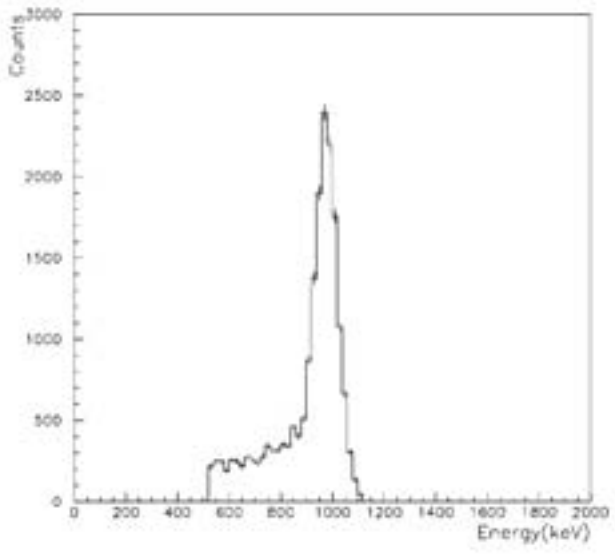
A new method was developed to obtain reliable calibrations using radioisotope sources. This has proven to be a powerful tool to obtain a detector response with high accuracy. Not only conversion electrons but also α particles, β particles, γ rays and X rays from radioisotope sources can be studied with this method. The method was validated with a plastic scintillation plate in the developed clinical scanner CROSS using a ^{207}Bi source and a ^{137}Cs source (Fig. 7-4). With this method, the energy resolution of the plastic scintillator plate was $\sigma = 3.7/E^{1/2}\%$ with E in units of MeV, which is a good energy resolution compared to other plastic scintillator detectors.

The method will be feasible for use not only for scintillation detectors but also for other detectors. There is a possibility that the method reported here will improve calibration methodology for radiation detectors, because it outperforms other methods used for radiation measurement.

FIG. 7-4. Energy spectrum of 976 K conversion electron line from the ^{207}Bi source. It can be seen that the peak is asymmetrical due to loss of the energy deposited in the ^{207}Bi source.

ICCHIBAN program (Yukio Uchihori, Nakahiro Yasuda, Hisashi Kitamura, Satoshi Kodaira)

The 3rd Space Intercomparison Experiment in the Russian Service Module in the ISS was performed within the ICCHIBAN project. In the last fiscal year, the



2nd Space Intercomparison Experiment was performed and this 3rd experiment was planned to research more details of the responses of passive detectors.

For this 3rd experiment, passive detectors (TLD, OSL, CR-39 and so on) from 13 institutes and universities in 10 countries were sent to NIRS and the package which contained these detectors was launched in the ISS with support by the Institute of BioMedical Problems, Russia. These detectors were recovered and distributed to the participants. These detectors have been analyzed and the participants will report these results in the near future.

From March, 2009, a Japanese astronaut was staying for three months, a rather longer period than past Japanese astronauts. And in the near future, Japanese astronauts may stay for longer periods in the space environment for lunar space bases or Mars explorations. For longer stays, we should research radiation effects for humans; some members have joined the Space Radiation Research Unit in the International Open Laboratory in NIRS.

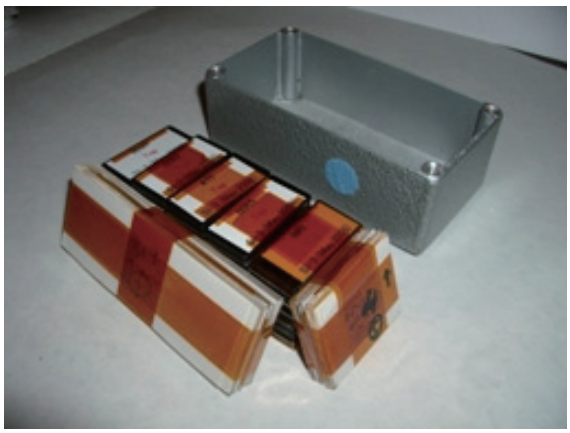
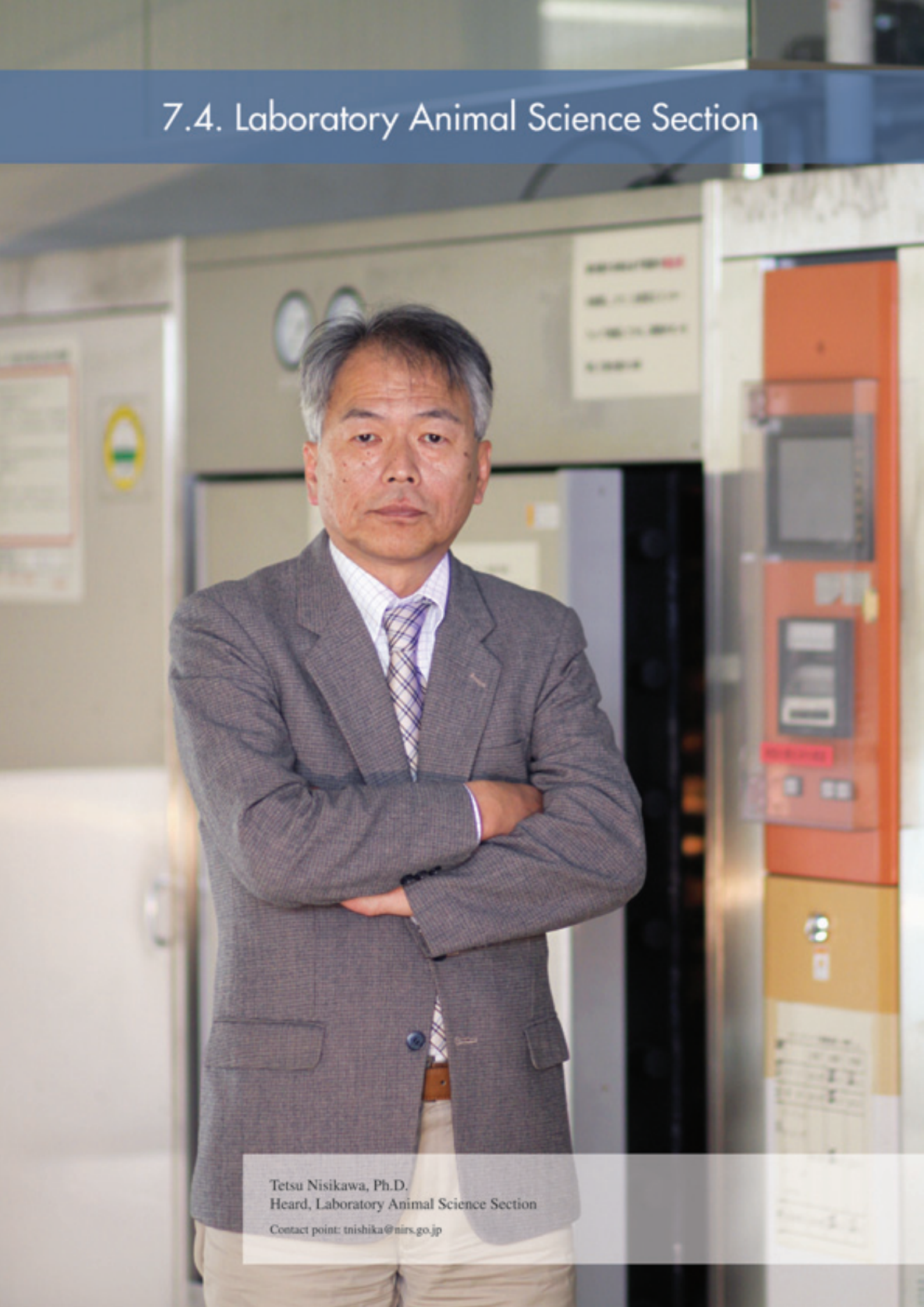


Fig. 7-4. Photograph of a detector package in the 3rd Space-Intercomparison Experiment.

Major Publications

1. G.J. Sykora, M.S. Akselrod, E.R. Benton, N. Yasuda, "Spectroscopic properties of novel fluorescent nuclear track detectors for high and lowLET charged particles", *Radiat.Meas.,* 43, 422-426, 2008.
2. S. Kodaira, N. Yasuda, et al., "Track detector of CR-39-DAP-copolymer with variable threshold to detect trans-iron nuclei in galactic cosmic rays", *Radiat. Meas.,* 43 S52, 2008.
3. S. Ota, S. Kodaira, N. Yasuda, et al., "Tracking method for the measurement of projectile charge changing cross section using CR-39 detector with a high speed imaging microscope", *Radiat. Meas.,* 43, S195 2008.
4. M.Takada, T.Nunomiya, et al., Charged - Collection Length Induced by Proton and Alpha Particle Induced in to Silicon Detectors due to Funneling Effect. *IEEE Transasctions on Nuclear Science,* 56, 337-345, 2009.
5. H. Nakamura, H. Kitamura et al., A New Method for Calibration and Response Measurement of a Scintillation Detector Using Radioisotope Sources, *Rad. Res.,* 170, 811-814, 2008.

7.4. Laboratory Animal Science Section



Tetsu Nisikawa, Ph.D.
Heard, Laboratory Animal Science Section
Contact point: tnishika@nirs.go.jp

Now, we are carrying out the following research projects.

・The cannibalism of mouse-strain differences; examining on foster parents eating foster infants.

To research the mouse-cannibalism by mothers which nurse foster infants, we compared the incidences among three ICR sub-strains (Slc:ICR, Jcl:ICR,Crlj:ICR), Slc:ddY, and four inbred strains (BALB/c, C3H/He, C57BL/6, DBA/2). Ten mice from each sub-strain were used as foster mothers. Experimental designs were as follows;

1 Five mother mice nursed only foster infants.

2 Five mother mice nursed two of their own infants plus 2 to 8 foster infants.

Three ICR sub-strains nursed three C3H/He sub-strains and three C57BL/6 sub-strains.

Slc:ddY nursed C3H/HeSlc and C57BL/6CrSlc sub-strains. Four inbred strains nursed only Slc:ICR. We found 81.1% of infant mice were cannibalized by foster mothers within 24 hours, regardless of the strains of mothers.

In the case that when Slc:ICR、Jcl:ICR and Crlj:CD1 mice were used as foster mothers and they nursed C3H/He-sub strains, the cannibalism ratios (number of cannibalized infants / number of fostered infants) were 100%, and 20.0 to 56.0%, respectively. In the case that when the same foster mothers nursed three C57BL/6 sub-strains, the ratios were 82.0 to 100%, and 16.1 to 50.0%, respectively. In the case that when Slc:ddY mice were used as foster mothers and they nursed C3H/HeSlc, the cannibalism ratios were 37.0%, and 27.6%, respectively. In the case that when the same foster mothers nursed C57BL/6CrSlc, the ratios were ˜86.6%, and ˜60.9% respectively. In the case that when C3H/HeSlc and C57BL/6CrSlc mice were used as foster mothers, both 1 and 2 showed the same ratio: 0 to 7.5%.

In the case that when BALB/cCrSlc and DBA/2CrSlc mice were used as foster mothers, both 1 and 2 showed the same ratio: 3.3 to 22.5%.

Cannibalism ratios of four inbred strains of mice were lower than those of outbred strains of mice in both 1 and 2. As a result, we concluded that inbred strains are more suitable as foster mothers than outbred strains.

・Establishment of the genetic monitoring system of the mouse using microsatellite markers

We established the genetic monitoring system using microsatellite markers of 15 inbred strains of mice. These markers offered good advantages regarding of time, labor, economy, efficiency, validity, and accuracy, compared with the biochemical and the immunological markers.

This experiment showed that there are chromosomes which are not inspected, and chromosomes which have only one gene locus in themselves. Next, we will use new microsatellite markers to invent them. And this experiment also showed that in a certain microsatellite marker, it is difficult to make judgments, because the sizes of DNA products are not so different from one another. We will exchange the marker for others ones to establish an easier system.

・An improvement for shortening the operation time of an Isolator

-A trial manufacture of a new metal stopper-

The rubber stopper is used to adhere the inner cover to the sterile lock in a vinyl isolator (VI).We prototyped a new kind of a metal stopper in order to reduce the working time. Then we measured the average times for installing a rubber stopper and a metal stopper respectively.

Rubber stopper

3 workers with 2 to 3 years' experience in handling VIs-----21.6 seconds.

5 workers with no experience in handling VIs-----46.4 seconds.

Experienced workers needed 20 seconds less than inexperienced workers on the average for installing the rubber stopper. In the case of the metal stopper, 3 persons with VI-work experienced and 5 persons with no experience d in VI-work needed 25.4 seconds and 26.4 seconds, respectively.

Metal stopper

3 experienced workers-----25.4 seconds

5 inexperienced workers-----26.4 seconds

Unlike the rubber stopper, the average times for installing the metal stopper were almost the same between experienced workers and inexperienced workers. We also carried out a microbiological test for 6 months regarding VIs with the rubber stopper and the metal stopper. The result showed that the insides of all the VIs were kept (negative and) germ-free. Based on the results mentioned above, we concluded that the prototype metal stopper is as useful and practical as the rubber stopper.

8. List of Original Papers

This list includes main publications by the staff members issued during the period from April 1, 2007 to March 31, 2008

* Outside Co-research

Research Center for Charged Particle Therapy
Developing Advanced Clinical Therapy with Charged Particle

1. Akihiro Niwa*, Kyosuke Suzuki*, Shingo Kato, Hiraki Kajiyama*, Kiyosumi Shibata*, Kazuhiko Ino*, Hisao Nakamura*, Fumitaka Kikkawa*: Carbon beam therapy in recurrent ovarian cancer, Annals of Oncology, 19(1), 192-194, 2007
2. Masaharu Hata*, Kouichi Tokuue*, Yoshiyuki Shioyama, Satoshi Nomoto, Nobuyoshi Fukumitsu*, Hidetsugu Nakayama, Shinji Sugahara, Kiyoshi Ohara, et.al: Malignant Myoepithelioma in the Maxillary Sinus: Case Report and Review of the Literature, Anticancer Research, 29(2), 497-501, 2009
3. Daisuke Nakamoto, Nobuharu Yamamoto*, Ryo Takagi, Akira Katakura*, Junetsu Mizoe, Takahiko Shibahara: Detection of Microsatellite Alterations in Plasma DNA of Malignant Mucosal Melanoma Using Whole Genome Amplification, Bulletin of Tokyo Dental College, 49(2), 77-87, 2008
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Ohtsura Niwa, Ph.D., Deputy Director
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Hospital
Jun-etsu Mizoe, M.D., Director
Administration Section
Yoichi Kawamura, Head and 7 staffs
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Gen Kobashi, M.D.
Masami Mukai, M.S.
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Naoyoshi Yamamoto, M.D.
Hiroshi Imada, M.D.
Azusa Hasegawa, M.D.
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Takeshi Yanagi, M.D.
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Kyosan Yoshikawa, M.D., Head
Tokuhiko Omatsu, M.D.
Riwa Kishimoto, M.D.
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Junko Noguchi
Kaztsunori Shimizu
Taijyu Yamada
Mari Motomura
Nursing Section
Yoko Nakamura, Head
Sadayo Saito, Chief Nurse
Kiyoko Tahara, Chief Nurse
Yoko Yamasita, Chief Nurse
Yayoi Daigo, Chief Nurse
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Pharmacy Section
Shin Watanabe, Head and 5 staff
Radiological Technology Section
Kazuhiro Watanabe , Head and 18 staffs

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Satoshi Yamada, Ph.D., Head of Special Research
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Naruhiro Matsufuji, Ph.D.
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2) Visiting Researcher
3) Postdoctoral Fellow

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