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NATIONAL INSTITUTE OF RADIOLOGICAL SCIENCES

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Annual Report
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Dept. of Information Technology
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National Institute of Radiological Sciences
4-9-1,Anagawa, Inage-ku, Chiba-shi, 263-8555 Japan
Tel : +81-43-206-3485 Fax : +81-43-290-1112
E-mail: kagakujohoka@nirs.go.jp
Homepage: http://www.nirs.go.jp/ENG/index.html

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Preface

The National Institute of Radiological Sciences (NIRS) is Japan's leading research institution on radiation protection and promotion of radiological sciences. Since its initial establishment in 1957, NIRS has conducted comprehensive research in science and technology related to radiation and human health. In 2001, NIRS reformed its structure as an independent administrative institution, and has carried out its activities according to the 5-year mid-term plan approved by the national government. This annual report summarizes our accomplishment and research outcome during the past 5 years, corresponding to the second mid-term plan from April 2006 through March 2011.

The main mission for researchers at NIRS is to contribute to human health and to establish a secure and safe society by means of radiological science. During the past five years, we have continued promoting the combined progress of radiation protection and medical uses of radiation. The severe nuclear accident at the Fukushima Dai-ichi Nuclear Power Plant, which was triggered by the East-Japan earthquake and tsunami on March 11, 2011, made NIRS activities more conspicuous to the general public. We directed our maximum efforts and activities toward emergency medical procedures and radiation protection. The Radiation Emergency Medical Assistant Team (REMAT), which we had established in 2010, has made significant contributions in this important mission. NIRS continues to make the utmost efforts for radiation protection during the reconstruction process in the affected areas.

During the past five years, remarkable progress was made in the medical application of radiological sciences, particularly in the establishment of charged particle radiotherapy for cancer treatment utilizing high speed carbon-ion beams. The total number of patients who received this treatment has reached over 5,800 cases since the first clinical trial in 1994. Charged particle radiotherapy is now recognized as the most advanced and effective method among radiotherapies, maintaining excellent quality of life of patients. The technology is now being transferred to other institutions including facilities outside Japan. Molecular imaging, which can visualize detailed molecular processes in a living body, now serves as an essential tool for the accurate diagnosis of cancer. It is being expanded to various other fields, including characterization of cardiovascular diseases, mental disorders, dementia, and other neuropsychiatric diseases, and it is also expected to make a significant contribution in the development of new drugs. NIRS aims to serve as the nation's core institution for development of new technology as well as for quality assurance of radiopharmaceuticals used in clinical research.

NIRS has made expanded international contributions by active collaboration with people in various international organizations and other partners such as universities and institutions. In 2009, the International Atomic Energy Agency (IAEA) designated NIRS as a collaborating center in three fields, low-dose radiation effects, charged particle radiotherapy, and molecular imaging. The results of these collaborations illustrate the importance of taking a comprehensive approach in radiological sciences, which NIRS has pursued for a long time.

As new challenges and opportunities occur, NIRS continues its maximum efforts to establish a solid base as a leading institution promoting comprehensive scientific research in a wide range of radiological sciences; your support is greatly appreciated and necessary to accomplish our mission.

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

President

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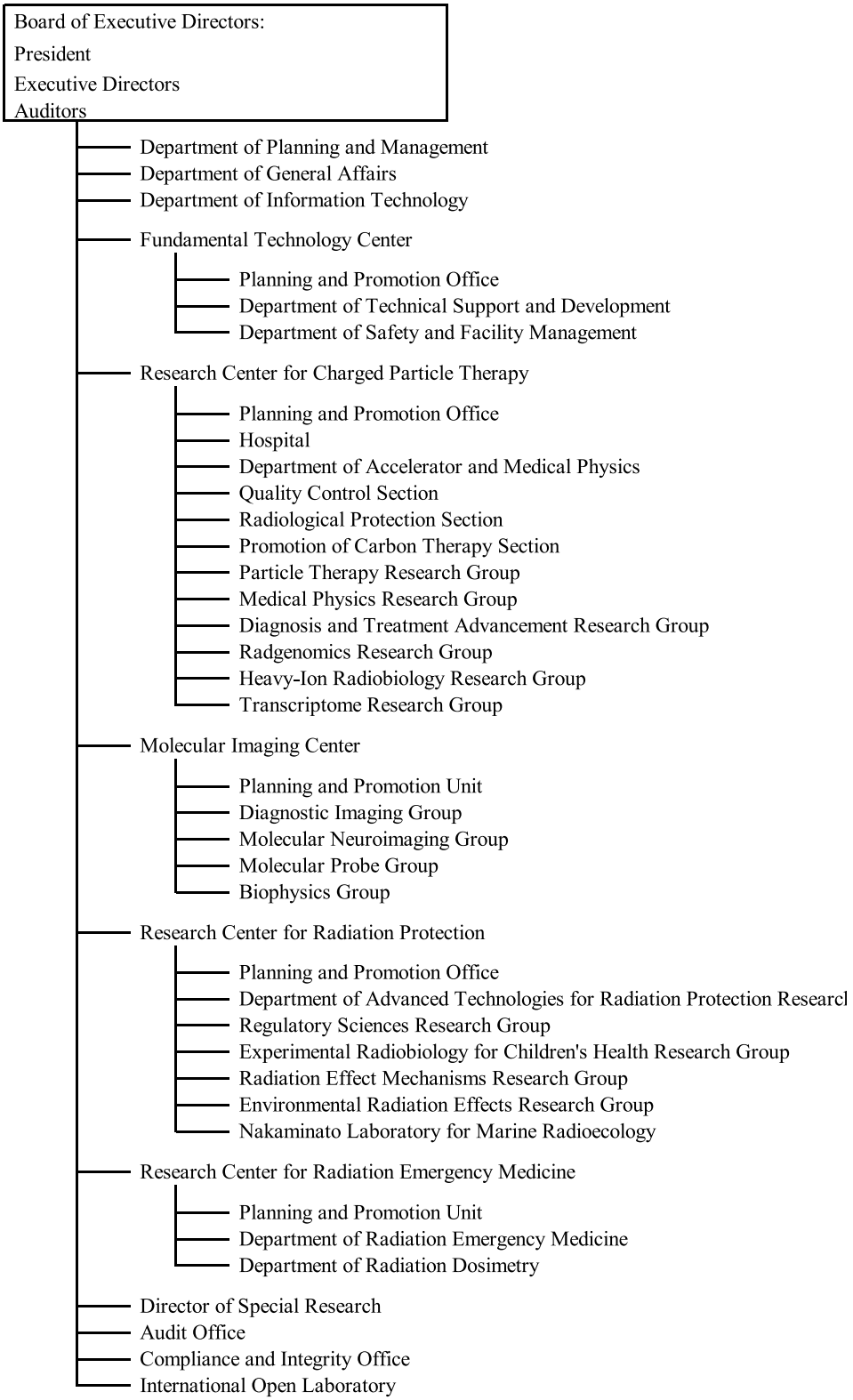
1. Organization Chart



2. Research Center for Charged Particle Therapy

Tadashi Kamada, M.D., Ph.D.

Director, Research Center for Charged Particle Therapy

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 28 years of Dr. Kamada received a Ph.D. from Hokkaido University in 1996 for his study on radiotherapy of bile duct cancer. He has had 30 years of experience in clinical research on radiation oncology, including 14 years of 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 at NIRS since 2008.

Objectives

The Research Center for Charged Particle Therapy (hereafter, abbreviated as "the Center") was established in 1993 when NIRS completed construction of the Heavy-Ion Medical Accelerator in Chiba (HIMAC). Since then it has been carrying out clinical, biological and physics research using heavy ions generated from HIMAC. After accumulating clinical experiences for carbon ion radiotherapy in various types of malignant tumors, the Center was successful in obtaining approval from the Ministry of Health, Welfare and Labor to carry out "Highly Advanced Medical Technology" in 2003. In the meanwhile, carbon ion therapy has achieved for itself a solid place in the general practice of cancer treatment. HIMAC has also provided more than 500 researchers a multi-user utilization facility for medical, biological and physics research.

In 2006, when the second Mid-Term Plan of NIRS was initiated, the Center was reorganized to conduct life science research on ionizing radiation, focusing on carbon ion radiotherapy. This long-term research will eventually contribute to the improvement of the quality of life of human beings. Research plans for the fiscal year of 2010 included: a clinical study on carbon ion radiotherapy for locally advanced tumors; development and improvement of radiotherapeutic techniques; a design study and R&D for a new extension of the treatment rooms for the HIMAC; research on diagnostic imaging; QA and QC for radiotherapy and radiation protection; radiobiological experiments for improvement of radiotherapy; exploration of the variability of radiation sensitivity by investigating single nucleotide polymorphisms (SNPs); and research on a high coverage gene expression profiling (HiCEP) system.

Overview

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

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

① Development of advanced cancer radiotherapy with charged particles

This subject has been studied by the Particle Therapy Research Group (GL: H.Tsuji) consisting of three teams: Clinical Trial Research Team, Clinical Database Research Team, and Radiation Effect Research Team.

According to the long-term objectives, research on developing advanced clinical therapy using carbon ion beams has been aggressively performed in FY 2010 as well as previous years. The Clinical Trial Research Team has succeeded in seeing quite a large number of patients this year; 691 patients, a similar number to that of last year, underwent carbon ion radiotherapy (C ion RT) in FY 2010. So far, a total of 5887 patients have been enrolled in clinical trials of C ion RT and to date, prostate, lung, head and neck, bone and soft tissue, and liver tumors were the leading 5 tumor types in the trials. The outcomes of clinical trials in tumors that were hard to cure with other modalities revealed the quite high probability of local control, a survival benefit, and acceptable morbidity. In addition, clinical trials for establishment of hypofractionated C ion RT in common cancers, such as lung cancer, liver cancer, and prostate cancer have also been successfully achieved. For instance, an ultra-short course C ion RT for lung cancer (single fraction) and liver cancer (two fractions) have been realized. Additionally, advancement of hypofractionation has also been performed in other tumor entities. For instance, the fraction number in the treatment of prostate

cancer could be successfully decreased from 20 to 16, with a lower incidence of late toxicity, but with comparable outcomes in tumor control. The Clinical Database Research Team has improved the coordination among several database systems (Hospital Information System, Therapy Plan Database, Therapy Schedule Management System, Radiology Information System for Radiation Therapy, and two PACSs). The developed information systems conforming to the Integrated Healthcare Enterprise (IHE), Enterprise User Authentication (EUA), and Patient Synchronized Applications (PSA) functions 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 resultant increase of the number of patients. In addition, the functions to analyze the data of the database system were improved and the basic analysis, such as Kaplan-Meier estimates of patient survival, became much easier to make than before. The Radiation Effect Research Team has aggressively performed experiments and analyses as well. Lineal energy information measured by a tissue-equivalent proportional counter in the therapeutic irradiation field was found useful for estimating biological effectiveness of the beam at a point by processing the information with the Microdosimetric Kinetic Model (MKM). This year, the method has been applied for the verification of actual irradiation fields and several subjects have been investigated, including the field effect, oxygen effect, and port characteristics. In addition, the MKM is being employed as a biological model for scanning carbon ion therapy that was started at the new treatment research facility.

② Development of a novel irradiation system for charged particle therapy

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

On the basis of more than ten years of experience with HIMAC, a new treatment research facility was designed and constructed to work toward the goal of implementing "adaptive cancer therapy" with heavy ions, which will make the one-day treatment of lung cancer possible. Further, the new treatment research facility should be able to accurately treat a fixed target, a moving target with breathing, and a target near a critical organ. For these purposes, a phase-controlled rescanning (PCR) method has been studied, especially for treating a moving target. A rotating gantry with the PCR method is also employed in order to increase the treatment accuracy for a tumor near a critical organ through the multi-field optimization method, and to reduce the patient's load. The related R&D work has been carried out with HIMAC since April 2006. In September 2010, the treatment room E, which is one of the treatment rooms in the new treatment research facility, was equipped with both horizontal and vertical fixed beam-delivery systems. After a beam commissioning and pre-clinical study, the clinical study was scheduled to begin on March, 29 2011. The schedule was changed to May 2011, however, due to the massive earth quake on March 11, 2011.

③ Standardization and improvement of therapeutic and diagnostic techniques

This research covers a wide range and has been performed by the Diagnosis and Treatment Advancement Research Group (GL: T. Kamada) consisting of 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, for oncologic imaging. This year, tumor hypoxic imaging using ^{62}Cu-ATSM was continued and metastatic lymph node imaging using C-11-Methionine (MET) was also investigated. For Cu-62-ATSM imaging in tumor hypoxia, the team found that Cu-62-ATSM and FDG did not correlate to each other before CIRT in pancreatic cancer. The change of Cu-62-ATSM uptake did not necessarily correspond to the change of FDG uptake after CIRT. Cu-62-ATSM and FDG uptakes of a patient who died after CIRT were not the highest uptakes, but were relatively high. For metastatic lymph node imaging using C-11-methionine, the team found that MET-PET/CT was useful for diagnosis of neck lymph node metastasis and especially specificity was relatively high. There were very few instances of true positive metastasis in neck lymph node accumulation in the MET-PET/CT study from trunk cancers compared to head and neck cancers. But diagnostic capability for neck lymph node metastasis from trunk cancers was higher than from head and neck cancers. In primary cancer in the head and neck regions, the diagnostic accuracy of cervical lymph node metastasis with MET-PET/CT was better than the diagnostic accuracy reported with FDG-PET.

The Image Processing Research Team analyzed intrafractional organ movement during respiration using 4D CT (256MSCT) for patients with liver, lung, and pancreatic cancers. The team evaluated intrafractional organ motion and dose validation for ungated and gated treatments. Doses to organs at risk were smaller in the gated than the ungated treatment, although the differences were small in pancreatic cancer. The findings suggested that ungated

pancreatic treatment may deliver a sufficient accumulated dose through the treatment course with minimal dose variation due to respiratory pattern variation, and in this regard is therefore preferable to gated treatment. The use of ungated treatment may shorten the total treatment duty time by a factor of three compared with gated treatment in pancreatic cancer. In the liver and lower lung, large organ motions were observed in inferior and anterior directions. The GTV-COM (gross tumor volume-center of mass) displacements due to the treatment position (supine or prone) were compared. The results showed a difference of movement in the left-right directions.

The Radiological Protection Research Team has carried out dosimetry studies for hadron therapy. The team conducted the dosimetric commissioning for the new scanning beam irradiation facility working with members of the HIMAC accelerator group. The technical document for QC in the scanning beam irradiation technique has been prepared. These research activities are expected to contribute to smooth running of other radiotherapy facilities as well as those at NIRS.

The Quality Control Research Team contributes to the field of radiotherapy internationally in cooperation with organizations such as the Forum for Nuclear Cooperation in Asia (FNCA), IAEA, World Health Organization (WHO), International Organization for Standardization (ISO), and International Electrotechnical Commission (IEC).

B. Research on radiation effects for improvement of radiation therapy

① RadGenomics research concerning radiation sensitivity

This subject has been the focus of the RadGenomics Research Group (GL: T Imai) consisting of three teams: Genetic Information Team, Molecular Radio-oncology Team, and Molecular Biostatistics Team. The main research achievements of the group in the second 5-year Mid-Term Plan have been the characterization of radioresistant tumors, the identification of genetic variants associated with adverse reactions after radiotherapy, and the development of a new antimetastatic approach for local combination therapy using carbon ion radiotherapy and immunotherapy.

An important starting point for these studies was the analysis of tumor gene expression profiles. Comprehensive microarray techniques were used to characterize radioresistant tumors by analyzing the gene expression profiles of sequential biopsy samples from cervical cancer patients during fractionated radiotherapy. The FGF2 marker identified by this approach was subjected to a validation study with newly enrolled patients and additional studies of FGF2 expression were also performed. The results suggest that FGF2 expression may be a useful marker to monitor the effectiveness of radiotherapy for cervical cancer, which would improve patient selection for molecular targeted therapies, such as the use of cytokine inhibitors, following standard-of-care treatment.

In the genetic studies of cancer patients, the group showed that prostate cancer patients and cervical cancer patients could be stratified by their particular genetic variation with respect to their radio-sensitivity. The "area under curve-receiver operator characteristic" (AUC-ROC) curve analysis was applied to identify the effective combination of SNPs associated with urinary morbidity in prostate cancer patients. A set of five SNPs from genes including *XRCC6* were identified to reach a maximum AUC-ROC.

A haplotype analysis with a combination of SNPs on the same chromosome was performed. The focus of this study was to identify genetic variants associated with adverse reactions in the gastrointestinal tract of cervical cancer patients who had been treated with pelvic radiotherapy. The analysis identified two haplotypes associated with an increased risk of an adverse reaction. One haplotype was located between the 5' ends of the *NPAT* and *ATM* genes and the second was located in the *AURKA* gene. Furthermore, a third haplotype, associated with a reduced risk, was identified in the *AURKA* gene. The risk of an adverse reaction was significantly higher among patients with both risk diplotypes than in those possessing the other diplotypes. Therefore, individual radio-sensitivity of the intestine can be determined by haplotypes in the *NPAT-ATM* and *AURKA* genes.

In the study using murine tumor models, the group was the first to show that a carbon ion beam upregulates more membrane-associated immunogenic molecules in tumors than gamma-ray irradiation does. In addition, the group showed that lower dose irradiation, which did not inhibit growth of the primary tumor, inhibited lung metastasis significantly. These data emphasize the importance of examining the antimetastatic efficacy of local combination therapy using carbon ion radiotherapy and immunotherapy. The data also showed that combination therapy with carbon ion irradiation and alpha-galactosylceramide-pulsed dendritic cells significantly reduces the incidence of lung metastases in mice, in comparison with the respective monotherapies. The group's studies have clinical implications that could enhance the survival rate of patients after carbon ion radiotherapy.

② Biological research concerning the improvement of radiation therapy

This subject has been pursued by the Heavy-Ion Radiobiology Research Group (GL: R. Okayasu) consisting of four teams: Biophysics Team, Experimental Therapy

Team, Cellular and Molecular Biology Team, and Radiation Modifier Team.

The group has successfully completed the three mid-term plans set for the past five years. Two main goals of this group have been to biologically validate the ongoing carbon ion treatment and to suggest further effective radiotherapy protocols by studying cells and animals with heavy ions and conventional X-rays and gamma-rays. Studies included radiation modifiers such as radio-sensitizers and radio-protectors. Indirect effects of radiation and oxygen effects have also been studied. The mid-term plans were investigated by four teams: Biophysics Team; Experimental Therapy Team; Cellular and Molecular Biology Team; and Radiation Modifier Team. The group's extensive efforts and world-wide collaborations resulted in 147 peer-reviewed publications and 23 external awards in the last 5 years.

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 various radiation sources (LET: 10-500 keV/μm) were applied for the study. Clear splits of the LET-RBE spectra were found among ion species. The parameters used were found to be defined as functions of atomic numbers (or atomic mass numbers) of the accelerated ion beams. This method is applicable to estimate overall RBE in therapeutic beams. Efforts have been made to extend these studies for various cell lines and other end points such as DNA damage and mutations.

Animal data collected by the group indicated 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 a 20% tumor formation frequency for irradiated mice. This suggests that carbon ion treatment might be safer than the conventional radiotherapy in terms of secondary cancer occurrence. Furthermore, it was 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.

Biological differences between X-ray and heavy-ion irradiations were demonstrated using assays such as immune staining and chromosome aberrations, focusing on the molecular mechanism for the early stage of DNA damage response at therapeutic level doses. The obtained data revealed that homologous recombination repair inhibitors can sensitize cells and tumors implanted in mice exposed to high LET radiation. Using HiCEP, an NIRS original comprehensive gene expression technique, the expression of ASPM (a microcephaly gene) was found to be significantly downregulated by ionizing radiation (IR) in human and murine cells. This finding will be applied to find a new target for radio-sensitization.

The mechanism of "melatonin" radio-protection was found to be free radical scavenging by an electron transfer reaction. Protective effects of γ-TDMG on radiation-induced dermatitis were investigated; however, more studies are necessary to reach a definitive conclusion. The distribution and density of hydroxyl radicals caused by IR was investigated. The total amount of hydroxyl radicals generated by carbon ion irradiation was lower than that by X-ray irradiation at the same dose, while the density of hydroxyl radicals caused by heavy ions was higher than that by X-rays. The redox mechanism of nitroxyl radical was studied. The glutathione dependent reduction of nitroxyl radicals depended on pH of the reaction mixture, and this reaction can be accelerated by other free radicals coexisting in the reaction mixture. Using a mouse model, oral administration of an herbal drug "Daikenchuto" was shown to reduce intestinal and/or colonal inflammation-indexes increased after X-ray irradiation.

③ Transcriptome Research for Radiobiology

This subject has been the objective of the Transcriptome Research Group (GL: Abe) consisting of three teams: Stem Cell Research Team, Gene Expression Profilling Team, and Model Organism Research Team.

During the second mid-term plan the three teams in the research group have been concerned mainly with three issues. First, they focused on improvement of the HiCEP method which was developed by this group. HiCEP has several clear advantages compared to previous transcriptome analyzing procedures. The number of cells required for analysis is greatly reduced from 10 million to just 20 cells, and even an analysis using a single cell was quantified as approximately 5,000 transcripts (~1/4 entire transcriptome). In addition, the group developed a high-throughput system for various analyses, especially for human molecular epidemiology. The system allows 96 samples to be analyzed simultaneously, resulting in 15,000 analyses per year.

Second, using an improved procedure the group members have developed a new method for diagnosis using blood. They established a system by which more than three entire transcriptome analyses can be conducted with 1.0 mL of peripheral blood, and more that 20,000 transcripts can be detected. Not only the lymphocyte fraction but also the whole blood without any fractionation can be used for the analysis. Furthermore, it was demonstrated that some tumors including solid tumors could be detected using

only a blood sample. Tumors could be detected at very early stages due to the extremely high sensitivity of the developed diagnostic method.

Third, group members also focused on iPSCs (induced Pluripotent Stem Cells). Recently, it has been demonstrated that somatic cells can be converted into pluripotent stem cells by ectopic expression of four transcription regulation genes, Oct3/4, Sox2, Klf4 and c-Myc. Such somatic cell reprogramming has suggested the possibility of generating patient-specific pluripotent stem cells. A great potential for therapeutics of radiation-induced injuries is offered by replacing or adding tissues prepared from patient-specific stem cells. While elucidating the molecular mechanisms underlying iPSC generation is a key issue for efficient preparation of safe iPSCs that can be applied for various medial uses, it has been quite difficult due to the unique characteristics of generation, that is, the extremely low efficiency and stochastic manner in which the generation occurs.

The Stem Cell Research team first succeeded in directly observing the emergence of iPSCs from somatic cells. They developed a new investigation system by improving a pre-existing time-lapse system that allows precise investigation of iPSCs generation at short intervals of about 2 weeks and the identified the conversion process from the somatic cell lineage to stem cell lineage. Interestingly, it was revealed that the onset of the cell lineage conversion had already initiated within 48 hours after the gene transduction in most generations of iPSCs. In addition, the team found that c-Myc plays a crucial role in iPSCs generation via histone acethylation controlling. It had been considered previously that c-Myc transduction is non-essential for the generation of iPSCs, and in addition not suitable for subsequent medical application, because various tumors frequently occur in the mice developed from iPSCs by the reactivation of c-Myc. Team members established a large number of iPSC lines from the inbred mouse strain, C57BL/6J, to conduct a precise comparison among the cell lines. Analysis of 22 iPSC lines with a chimeric mice generation test revealed that c-Myc has positive effects on iPSC generation, particularly in terms of achieving their pluripotency. In addition, trichostatin A, a HDAC (histone deacethylase) inhibitor, rescues the defects of iPSCs that were established without c-Myc transduction. Thus new light has been shed on the iPSC generation mechanism.

C. Research Projects with Heavy Ions at NIRS-HIMAC

In FY2010 135 proposals were accepted and were carried out at HIMAC. The beam time of 5,480 hours was supplied to those research projects. A total of 85 papers and 62 proceedings were published, and 362 papers were presented at various meetings. A total of 673 researchers participated in projects at HIMAC, including 107 foreign researchers for 20 international projects.

2.1. Developing Advanced Clinical Therapy with Charged Particles

Hiroshi Tsuji, M.D., Ph.D.

Program Leader, Hospital

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 28 years of experience in clinical reseach on radiation oncology, including 15 years experience in carbon ion radiotherapy at NIRS. Since 2008, he has been group leader of the Particle Therapy Research Group for developing an 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.
- Study optimizing irradiation methods by disease and by region, using clinical investigations of therapies in which radiation is combined with drugs and surgery.
- Develop a comprehensive database on treatment, clinical course and other factors and compare and analyze domestic and foreign data on particle beam therapy.
- Carry out the annual treatment of 500 patients to maximize the therapeutic effects of charged particle technology and disseminate information about them. This is the target number combining patients taking part in clinical studies and those receiving high-technology treatments, in 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 viewpoint of quality of life (QOL) and therapeutic costs. For this objective, patients' 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. All the teams are performing R & D on charged particle therapy. Progress of research in each team is summarized below.

1) Clinical Trial Research Team

From June 1994 to February 2011, a total of 5887 patients were enrolled in clinical trials using carbon ion beams generated by HIMAC. Carbon ion radiotherapy of these patients was carried out by more than 50 different phase I/II or phase II protocols and highly advanced medical technology. Figure 2.1 lists the number of the patients for each tumor site treated with carbon ion beams.

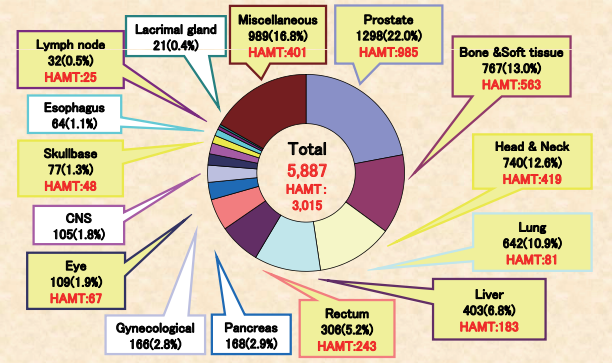


Fig.2.1. The number of patients treated with carbon ion beams for different tumor sites.

We treated 691 new patients in FY 2010. Prostate, lung, head and neck, bone and soft tissue, and liver tumors are the leading five tumor types in the trials. 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 treat with other modalities. Using carbon ion beams, we could implement hypofractionated radiotherapy, with application of larger doses per fraction and a reduction of overall treatment times as compared to conventional photon radiotherapy. Since November 2003, carbon ion radiotherapy has been approved by the Ministry of Health, Labor and Welfare of Japan as a

"Highly Advanced Medical Technology (HAMT)". Nearly 70 % of the patients receiving carbon ion radiotherapy were treated by HAMT in 2010.

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. We developed a new MLC with thinner leaves and proved that the leakage dose of the MLC was comparable to the present MLC. Therefore, it is possible to use the new MLC for more precise field shaping without the patient collimator; however, it is necessary to design a new treatment control system prior to installing the new MLC into the beam line for the actual patient treatment. We have already started to design the new treatment control system that will be suitable for the new treatment research facility.

Range compensators are also essential in the broad beam method. A new method for manufacturing range compensators, employing a punch technology, has been developed. 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 takes half an hour or less. Use of the range compensators made with this new method was started in actual treatments.

Use of the new field localization system using a flat panel detector (FPD) was started in 2009. Localization images with the FPD have higher resolution than a conventional radiograph, therefore the setup procedure has become easier and faster than ever.

2) Clinical Database Research Team

In October 2006, we implemented the Electronic Medical Record (EMR) 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, Radiology Information System for Radiation Therapy, and two PACSs). These systems are connected to each other and necessary data are transmitted.

We also developed the information systems that conform to the Integrated Healthcare Enterprise (IHE), Enterprise User Authentication (EUA), and Patient Synchronized Applications (PSA) functions. These functions make it easy to operate multiple systems. Two PCs (EMR and PACS viewer) are commonly used for the Hospital Information System in one clinical unit. Physicians have to enter a user ID and password to log into these systems. The IHE, EUA and PSA functions 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. Because EUA and PSA functions are 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 as well 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 delivery of the software. We implemented the document source, document repository, document registry, and document consumer that were defined by the IHE XDS. We are now designing and developing an interface function that communicates between the existing systems, such as the EMR, and the PACSs and IHE XDS system. We think that it is very important to establish a new IHE integration profile which will enable the Treatment Management System to receive and send radiotherapy orders.

We have a clinical database system which contains information for over 5,200 patients who have been treated with heavy particle radiation therapy and over 22,800 patients who have been treated with photon radiation therapy. We improved the processing speed and ease of operation of this database system. Physicians can analysis patients by the heavy particle radiation therapy protocol and generate the survival curves in a few seconds using this system. The clinical database can manage data concerned with the disease history, staging, radiation schedule, radiation dose/days, adverse effects and follow-up information.

The current Medical Information System at the NIRS is shown in Fig.2.2.

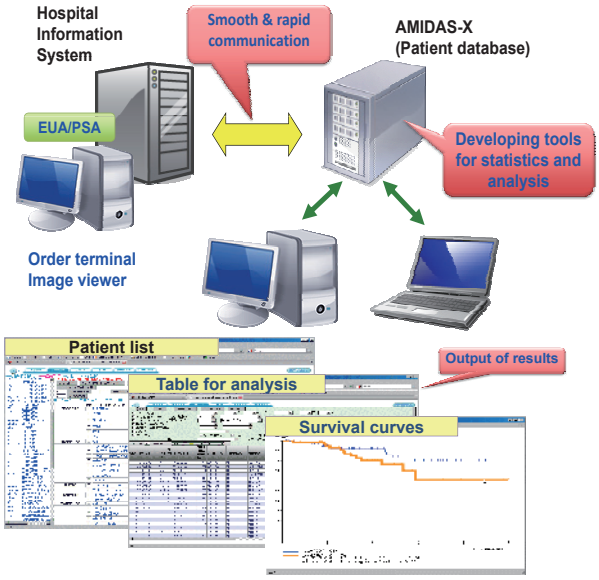


Fig.2.2. Current configuration of the Medical Information System in NIRS.

3) Radiation E ffect Research Team.

Radio-sensitivity analysis based on the TCP model has been applied for the analysis of toxicity on benign tissue. Late toxicity on the genitourinary (GU) tract which was 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; this was more than 2 times larger than the literature value against photons (3.0). 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 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 dose given to patients significantly differs individually. From this viewpoint, we have investigated skin reaction through the reaction observed on mice. Through the fractionated irradiation of carbon beams to mouse leg, we found that the effect of a single fraction irradiation differs uniquely from those by multiple fractionations: the efficacy tends to be small for single fractions. In order to analyze the response, the applicability of the commonly-used LQ model was investigated together with the RCR (repairable -conditionally repairable) model and multi-target two components model. While the LQ model failed to express the decrease in response by single irradiation, RCR showed good agreement with the experimental observation.

In addition, we have started a fractionated cell irradiation experiment with carbon ions by adjusting the time gap between irradiations from 0 to 120 min in order to clarify the initial repair of damages for better understanding of clinical outcomes.

Lineal energy information measured by a tissue-equivalent proportional counter in the therapeutic irradiation field was found useful for estimating biological effectiveness of the beam at a point by processing the information with the Microdosimetric Kinetic Model (MKM). This year, we applied the method for the verification of actual irradiation fields. In addition, MKM is being employed as a biological model (Fig. 2.3) for the scanning carbon ion therapy that was started at the new treatment research facility.

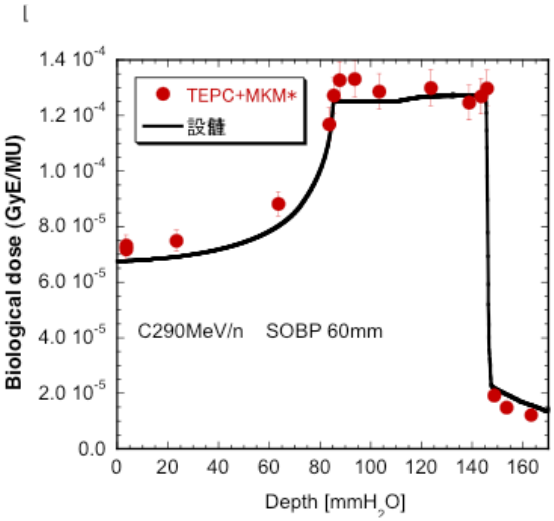


Fig.2.3 Estimated biological dose distribution by the MKM and measured biological dose with the TEPC Using the MKM method we obtained the following results in verification of actual irradiation fields.

Field effect

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

Port characteristics

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

Oxygen effect

The MKM was applied for the estimation of cell survival estimation of hypoxic cells based on the response under the oxic condition. By adjusting the domain size as half that for the oxic condition, we could get a good estimate of the cell survival of hypoxic cells.

Major Publications (Last 5 years)

1. Tsuji H, Ishikawa H, Yanagi T, Hirasawa et al: Carbon-ion radiotherapy for locally advanced or unfavorably located choroidal melanoma: A Phase I/II dose-escalation study, *Int J Radiat Oncol*, 2006
2. Imai R, Kamada T, Tsuji H, et al: Cervical spine osteosarcoma treated with carbon ion radiotherapy, *Lancet Oncol*, 2006
3. Mizoe, J, Tsujii, H, Hasegawa, H, et al: Phase I/II clinical trial of carbon ion radiotherapy for malignant gliomas: combined X-ray radiotherapy, chemotherapy, and carbon ion radiotherapy, *Int J Radiat Oncol* , 2007
4. Miyamoto T, Baba M, Sugane T, et al: Carbon Ion Radiotherapy for Stage I Non-small Cell Lung Cancer Using a Regimen of Four Fractions during 1 Week, *J Thoracic* Oncol, 2007
5. Ishikawa H, Tsuji H, Kamada T, et al: Adverse Effects of Androgen Deprivation Therapy on Persistent Genitourinary Complications after Carbon Ion Radiotherapy for Prostate Cancer, *Int J Radiat Oncol*, 2008
6. Sugane T, Baba M, Tsujii H, et al: Carbon ion radiotherapy for elderly patients 80 years and older with stage I non-small cell lung cancer, *Lung Cancer*, 2008
7. Yanagi T, Mizoe J, Hasegawa A, et al: Mucosal malignant melanoma of the head and neck treated by carbon ion radiotherapy, *Int J Radiat Oncol* , 2008
8. Imai R, Kamada T, Tsuji H, et al: *Int J Radiat Oncol*, 2009
9. Imada H, Katou H, Yasuda S, et al: Comparison of efficacy and toxicity of short-course carbon ion radiotherapy for hepatocellular carcinoma depending on their proximity to the porta hepatis, *Radiother Oncol*, 2010
10. Jingu K, Tsujii H, Mizoe J, et al: Carbon ion Radiation Therapy Improves the Prognosis of Unresectable Adult Bone and Soft Tissue Sarcoma of the Head and Neck, *Int J Radiat Oncol* , 2010

2.2. Medical Physics Research Group

Koji Noda, Ph. D.

Director, Medical Physics Research Group.

Outline of Research Career

Dr. Koji 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 in the Institute for Nuclear Study, University of Tokyo, on the development of a PET cyclotron from 1981 to 1989, and he also studied accelerator physics from 1985 to 1989. In 1989, he joined the HIMAC project at NIRS, where 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 Director of the Department of Accelerator and Medical Physics, and he holds the additional post of Director of the Medical Physics Research Group.

Contact point: noda_k@nirs.go.jp

Objectives

On the basis of more than ten years of experience with HIMAC, we have designed and constructed a new treatment research facility toward "adaptive cancer therapy" with heavy ions, which makes the one-day treatment of lung cancer possible. Further, the new treatment research facility will accurately treat a fixed target, a moving target with breathing, and a target near a critical organ. For these purposes, a phase-controlled rescanning (PCR) method has been studied, especially for treating a moving target. A rotating gantry is employed with the PCR method in order to increase the treatment accuracy for a tumor near a critical organ through the multi-field optimization method、and to reduce the patient's load. The related R&D work was carried out with HIMAC from April 2006. In September 2010, the treatment room E, which is one of the treatment rooms in the new treatment research facility, was equipped with both the horizontal and vertical fixed beam delivery systems. After a beam commissioning and pre-clinical study, the clinical study was scheduled to begin on March 29, 2011. This was changed to May 2011, however, due to the mega earthquake that occurred on March 11, 2011.

Progress of Research

1) Planning of the new treatment research facility

The new treatment research facility, as shown in Fig. 2.4, is connected with 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, three treatment rooms are prepared in order to treat 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 a 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 that of a fixed target, the PCR method, which completes the irradiation on one slice during one respiration-gate opening, was proposed and verified through a computer simulation. The scanning speed should be faster than conventional scanning method in order to provide a tolerable treatment time, because the rescanning naturally takes a longer time. Thus we have developed the fast 3D rescanning with gating. We have also designed a fixed beam delivery system, a rotating gantry system, a treatment management system, a patient positioning system and a treatment planning system. For the rotating gantry, superconducting technology is introduced in order to reduce its weight and size. Based on the design and R&D work, both the horizontal and vertical beam delivery systems were installed in treatment room E, as shown in Fig. 2.5. The beam commissioning and pre-clinical study were successfully completed.

The specification of the facility is summarized at Table 2.1.

Table 2.1. Specifications of the new treatment facility

Basic parameters	
Ion species	^{12}C, ^{16}O (^{11}C, ^{15}O)
Delivery beam intensity	10^7 – 10^9 pps for ^{12}C
Treatment room	2 fixed beam rooms (horizontal & vertical), 1 rotating gantry room
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: 50 mm/ms
Spot size	2 – 4 mm at 1-sigma
Lateral-field/SOBP/Range size	22 cm in square/ 15 cm/ >25 cm at ^{12}C
Irradiation-port length	9 m
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 – 4 mm at 1-sigma
Lateral field/SOBP/range size	15cm×15cm/ 15 cm/ >25 cm for ^{12}C
Displacement of iso-center	< 1 mm
Size and weight	Length, 16.5 m; radius, 7.1 m; weight, 350 ton

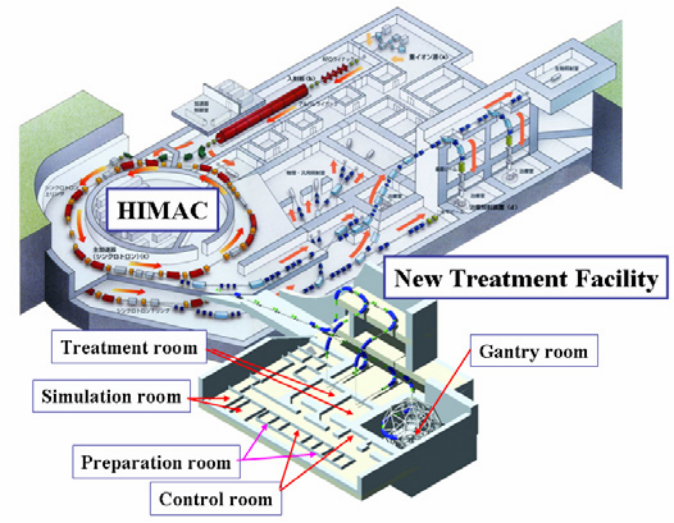


Fig. 2.4. Schematic view of the HIMAC and the new treatment research facility.

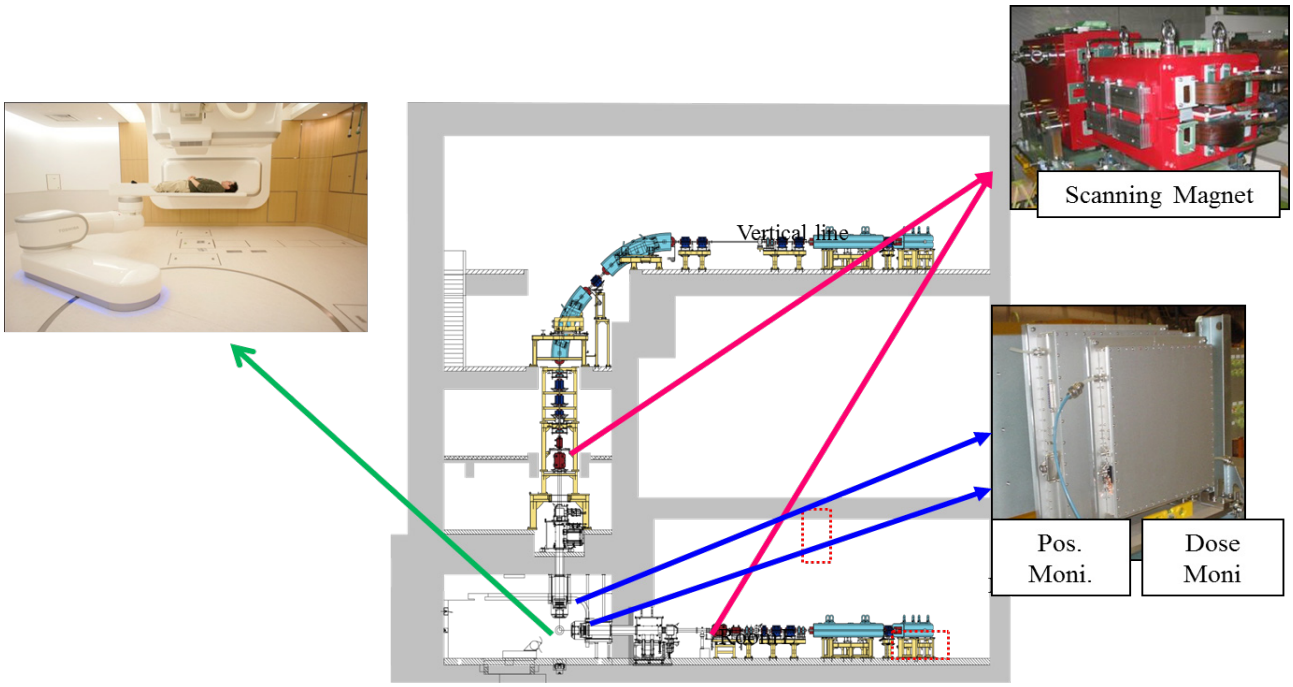


Fig. 2.5. Layout of the treatment room E.

2) Pre-clinical study

We have carried out the pre-clinical study for the clinical trial with fast 3D rescanning and the physical dose distribution and survival rate of HSG cells were measured. The physical dose distributions are shown in Fig. 2.6 (a) shows the depth dose distribution and (b) is the lateral dose distribution. The measurement results in both the depth and lateral dose distributions are in good agreements with the plans. The measured survival rate the planned survival rate based on the MKM (Microdosimetric Kinetic Model) are shown in Fig. 2.7. the good agreement verified that our biological effect planning method could be used in the fast 3D scanning.

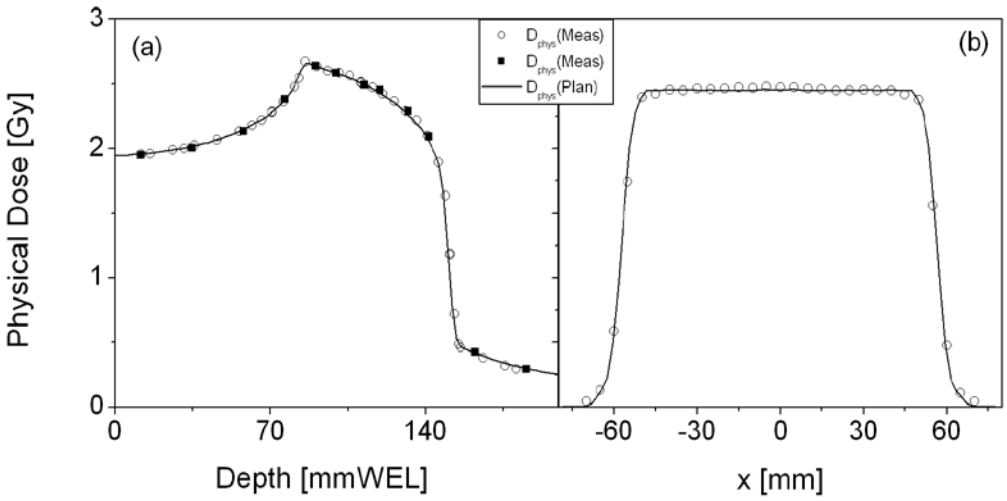


Fig. 2.6 Physical dose distributions. (a) Depth dose and (b) lateral dose.

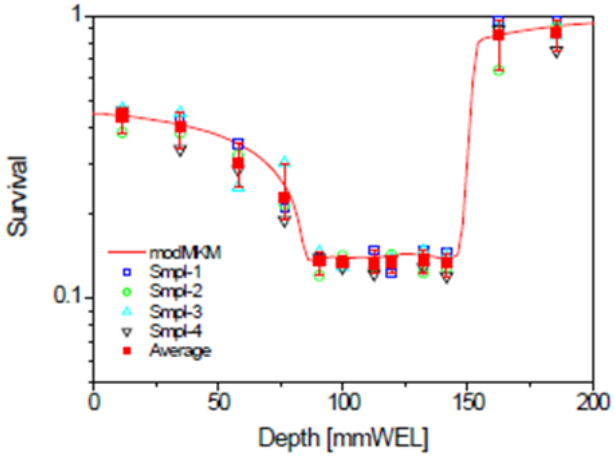


Fig. 2.7. Planned (solid line) and measured (symbols) survival rates of HSG cells obtained with 3D scanning.

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1. Amemiya N, Ogitsu T, Noda K, et al: Multi-Pole Components of Magnetic Field in Dipole Magnets Wound With High T-c Superconductor Tape and Feasibility of Their Accelerator Applications, *IEEE Transactions on Applied Superconductivity*, **20**, 364-367, 2010
2. Minohara S, Fukuda S, Kanematsu N, Takei Y, Furukawa T, Inaniwa T, Matsufuji N, Mori S, Noda K: Recent Innovations in Carbon-Ion Radiotherapy, *J Radiation Research*, **51**, 385-392, 2010
3. Furukawa T, Inaniwa T, Sato S, Shirai T, Takei Y, Takeshita E, Mizushima K, Iwata Y, Himukai T, Mori S, Fukuda S, Minohara S, Takada E, Murakami T, Noda K: Performance of the NIRS fast scanning system for heavy-ion radiotherapy, *Medical Physics*, **37**, 5672-5682, 2010
4. Furukawa T, Inaniwa T, Sato S, Shirai T, Mori S, Takeshita E, Mizushima K, Himukai T, Noda K: Moving target irradiation with fast rescanning and gating in particle therapy, *Medical Physics*, **37**, 4874-4879, 2010
5. Iwata Y, Uchiyama H, Fujimoto T, et al: Multiple-energy operation with extended flattops at HIMAC, *Nuclear Instruments & Methods in Physics Research Section A*, **624**, 33-38, 2010
6. Takada E: Carbon Ion Radiotherapy at NIRS-HIMAC, *Nuclear Physics A*, **834**, 730c-735c, 2010.
7. Inaniwa T, Furukawa T, Kase Y, Matsufuji N, Toshitou T, Matsumoto Y, Furusawa Y, Noda K: Treatment planning for a scanned carbon beam with a modified microdosimetric kinetic model, *Physics in Medicine and Biology*, **55**, 6721-6737, 2010
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9. Dobashi S, Sugane T, Mori S, Asakura H, Yamamoto N, Kumagai M, Kandatsu S, Baba M: Intrafractional Respiratory Motion for Charged Particle Lung Therapy with Immobilization Assessed by Four-Dimensional Computed Tomography, *J Radiation Research*, **52**,96-102,2011
10. Kanematsu N: Dose calculation algorithm of fast fine-heterogeneity correction for heavy charged particle radiotherapy, *Physica Medica*, doi:10.1016/j.ejmp.2010.05.001(2010-06-25)

2.3. Standardization and Improvement of Therapeutic and Diagnostic Techniques

Tadashi Kamada, M.D., Ph.D.

Director, Diagnosis and Treatment Advancement Research 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 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 Director of the Research Center for Charged Particle Therapy, NIRS since 2008.

Contact Point : t_kamada@nirs.go.jp

Objectives

- Develop software to create integrated clinical images, determine early therapeutic effects and analyze prognostic factors using a combination of multiple diagnostic imaging techniques.
- Improve treatment plans by using integrated images obtained from advanced dynamic imaging devices such as 4-dimensional CT.
- Carry out 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.
- Advance and standardize 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, the Image Processing Research Team, the Quality Control Research Team and the Radiological Protection Research Team, and it performs research into the advancement and standardization of radiation therapy and diagnostic methods. The 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 and tissue metabolic indicators leading to treatment effects especially of carbon ion radiotherapy (CIRT).

Cu-62-ATSMis a well-known hypoxic imaging PET tracer. We performed a preliminary investigation of Cu-62-ATSM tumor hypoxia PET/CT imaging in comparison with FDG PET/CT for pancreas cancer. The purpose of this study was to delineate the differences in intratumoral uptake and the tracer distribution of Cu-62-ATSM and F-18 FDG in patients with pancreatic cancer. Two males and two females (mean age, 62.5 y; range 52-69 y) with pancreatic cancer underwent both Cu-62-ATSM and FDG PET/CT before the CIRT initiation, and a set of PET/CT studies was done one month after CIRT termination. Tumor uptake of each tracer was analyzed semi-quantitatively by the tumor to normal tissue ratio (TNR) for Cu-62-ATSM and by the standardized absorption value (SUV) for FDG. The Cu-62-ATSM uptake did not correlate with FDG uptake before CIRT, but it inversely correlated with FDG after CIRT because FDG uptake tended to decrease in all cases. Correlation coefficients of tumor uptake between Cu-62-ATSM and FDG before and after CIRT were 0.022 and -0.965, respectively. In three out of four patients, before CIRT they had high Cu-62-ATSM uptake that might reflect the tendency to be hypoxic. After CIRT, one patient showed an increase of Cu-62-ATSM uptake, but FDG uptake of the same patient did not increase and was almost stable. This might indicate that the change of Cu-62-ATSM uptake did not necessarily correspond to the change of FDG uptake after radiotherapy. Only one patient died after CIRT, and his Cu-62-ATSM and FDG uptakes before therapy were not the highest among the four patients, but both these intakes were relatively high. In conclusion, Cu-62-ATSM and FDG did not correlate with each other before CIRT in pancreatic cancer patients. After CIRT, the change of Cu-62-ATSM uptake did not necessarily correspond to the change of FDG uptake. Cu-62-ATSM and FDG uptakes of the patient who died after CIRT were not the highest uptakes, but they were relatively high.

Studies using C-11 methionine with PET have been under taken. We performed a study about the diagnostic performance of MET-PET/CT with respect to cervical lymph node metastasis which was a study on the diagnostic accuracy for each primary cancer tissue in the head and neck region. In particular, we looked at the issue of whether or not there are differences in diagnostic performance depending on the tissue type of the primary lesion. In this study, 49 patients were selected as subjects: they had cancers in the head and neck regions and had undergone MET-PET/CT scans in which one or more nodular accumulations were observed in the cervical region. Regarding the diagnosis of cervical lymph node metastasis, pathological diagnoses had been verified or clinical comprehensive evaluations had been provided in all 49 cases involving 67 sites. There were 14 malignant melanoma (MM), 12 squamous cell carcinoma (SCC), 8 adenoid cystic carcinoma (ACC), and 15 cases of other types. In the study of all 67 sites, the diagnostic accuracies were 60 % for the sensitivity, 69% for the specificity, and 64% for the accuracy. In addition, the diagnostic accuracies by tissue type (SCC, MM, ACC) with cut-off value of TNR=2.7 were 56%, 100%, and 63%, respectively, for SCC; they were 60%, 50%, and 53%, respectively for mm; and they were 67%, 83%, and 78%, respectively, for ACC. In contrast, optimal cut-off values were calculated for each tissue and diagnostic accuracy per tissue type was recalculated. The optimal cut-off value for ACC was 2.7 and it matched the value of all sites. The diagnostic accuracies were 75%, 100%, and 79%, respectively for SCC with a cut-off value of TNR=2.1, and for MM with a cut-off value of TNR=5.1, they were 40%, 100%, and 82%, respectively. Improvement was observed in the rates of accurate diagnosis in the two tissues. We concluded that, in the primary cancer in the head and neck regions, the diagnostic accuracy of cervical lymph node metastasis with MET-PET/CT was better than the diagnostic accuracy reported with FDG-PET., Assessment using a cut off value for each tissue type was particularly useful.

2) Image Processing Research Team

We have two main themes: fusion imaging between multi-modalities; and analysis of respiratory movement of viscera using 4D imaging.

(a) Fusion imaging between multi-modalities

Modalities, such as CT, MRI, PET, ECHO, etc., have their individual characteristics. Malignant tumors are comprehensively diagnosed taking the characteristics into consideration. We tried to fuse imaging between multi-modalities by using an image processing tool so that we can more precisely diagnose the tumor extent, the tumor character, differentiation from inflammation, and metastases.

We have studied fusion imaging between CT and MRI. Although in the neck and pelvic area, fusion was completed using linear image processing, fusion was incomplete in upper abdominal and lung area because of the respiratory movements. Previously, although we used non-linear processing for solution of the image gap due to respiratory movements, we were not satisfied with the results. In FY 2010, we changed the sequence of examination and we obtained new results.

Using Modality 1.5T MRI (Philips), 16-row MDCT (Siemens), and the Image Processing Workstation (Fuji), we carried out fusion imaging for 33 patients having a tumor in the upper abdomen which were scheduled for heavy-ion therapy.

We obtained useful results by fusion of the MRI diffusion and contrast enhanced CT images in the upper abdominal tumors. We used fusion imaging for the differentiation between benign and malignant lesions and diagnosed the tumor extent more precisely. After completing the fusion imaging, small metastatic nodules were clearly seen (Figs.2.8 and 2.9).

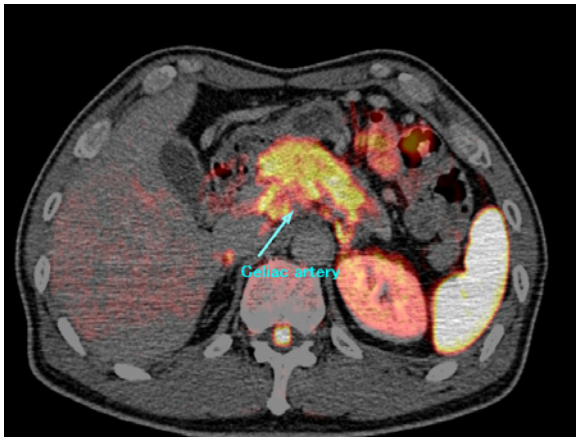

Fig.2.8. Pancreas carcinoma. Fusion image of enhanced CT and MRI diffusion. clearly shows tumor extent.

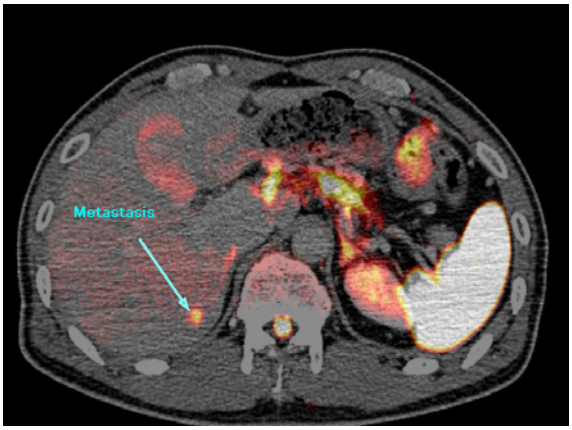

Fig.2.9. Pancreas carcinoma. Fusion image of enhanced CT and MRI diffusion shows small metastasis in the liver.

(b) Analysis of respiratory movements of target organ for heavy particle therapy

Recent improvements in radiotherapy techniques have ensured doses given to the tumor are more accurate. Intra- and inter-fractional changes, however, remain as a fundamental problem in the abdominal area treatment. Normal tissues and tumor positions change as a function of respiration; as a result, this can lead to tumor movement in and out of the treatment beam field. An understanding of the motion characteristics in radiotherapy planning is useful in determining the internal margin and optimizing beam parameters (beam angle etc.), because the degradation of image quality due to respiratory motion affects radiotherapy planning and delivery of the treatment beam.

A charged particle beam can provide complicated dose distributions; however, it is very sensitive to intra-fractional motion. We evaluated organ motion using 4DCT due to intra-fractional motion.

We quantified lung, liver and pancreas tumor movements due to respiration using 256 multi-slice CT (256MSCT). The 4DCT acquisition was done immediately after CT simulation to keep the same situation as in the treatment. Each patient reclined on the CT couch and the position was kept by using a low-temperature thermoplastic immobilization device (Shellfitter; Kuraray Co., Ltd., Osaka, Japan). The respiratory signal was acquired by a respiratory sensing system (Toyonaka Kenkyoujo, Osaka, Japan) and an infrared-emitting light marker was put on the abdomen except when in the beam fields. Slice collimation was 1.0 mm and rotation time was 0.5s/rotation. Scan time was set to cover a single respiratory cycle (but limited to less than 6 s). CT image reconstruction was done with a voxel size of 0.78 mm x 0.78 mm x 1.0 mm. 4DCT data were equally subdivided into 10 phases (T0: peak-inhalation, T30: mid-exhalation, T50: peak-exhalation) based on the respiratory signal amplitude. Gross tumor volume (GTV) was manually contoured 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. In the lung region, we examined the GTV-COM and the results showed that immobilization decreased the mean range of displacement by 0.4 mm, 1.6 mm, and 2.4 mm in the respective directions compared with our previous study based on 4DCT data obtained without immobilization. The quantitative evaluation of lung tumor motion using an immobilization device is useful in particle beam therapy as well as external photon beam therapy, where tumor motion significantly affects dose distribution. In the pancreas region, respiratory-induced organ motion was observed mainly on the anterior abdominal side rather than on the posterior side. Average GTV-COM (ungated/gated phases) were 0.7 mm/0.2 mm in both the left and right directions, and 2.5 mm/0.9 mm in the anterior, 0.1 mm/0 mm in the posterior, and 8.9 mm/2.6 mm in the inferior directions. Average pancreas COM displacement relative to that at peak exhalation was mainly in the inferior direction, at 9.6 mm in the ungated phase and 2.3 mm in the gated phase (Fig.2.10).

In the liver region, large organ motion was observed in inferior and anterior directions. We compared the GTV-COM displacements due to the treatment position (supine or prone). The result showed the difference of movement in the left-right directions.

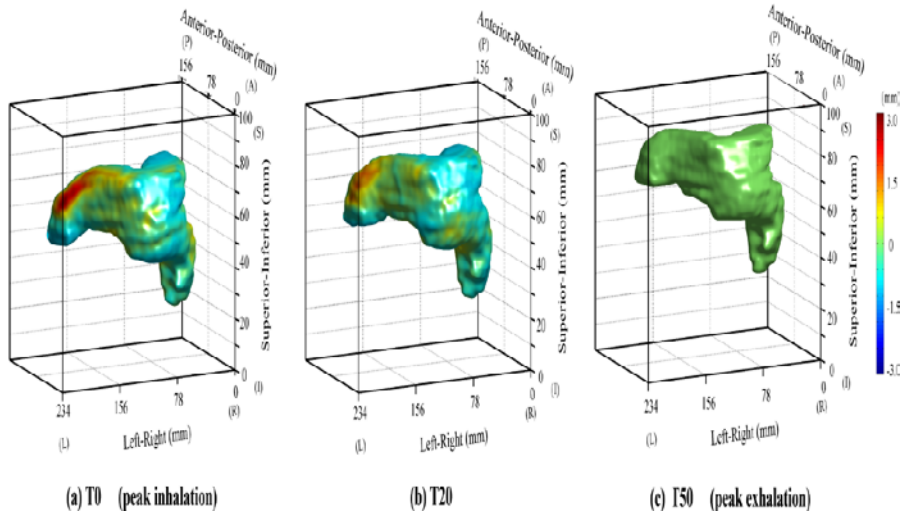

Fig.2.10. 3D-visualized pancreas and the magnitude of geometrical variation from peak exhalation as a function of respiratory phase. (a) T0: peak-inhalation. (b) T20: mid-inhalation. (c) T50: peak-exhalation.

3) Quality Control Research Team

The importance of quality control in radiotherapy has been increasingly recognized as the techniques have become more complex. The Quality Control Research Team tries to meet the expectations for safe and reliable radiotherapy mainly 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. More than 700 therapy-level dosimeters from hospitals were calibrated with the NIRS ^{60}Co standard field in FY 2010. The team has established the standard field of absorbed dose to water and made a dosimetry intercomparison with International Atomic Energy Agency (IAEA). To improve the quality of radiotherapy in Japan, the team has developed the dosimetry audit system using radiophotoluminescent glass dosimeters (RGDs). The regular dosimetry audit service for radiotherapy facilities with a commercial base has been successfully managed by the Association for Nuclear Technology in Medicine, in collaboration with the National Cancer Center and NIRS. However, the audits were limited to the reference irradiation condition. The team measured the RGD response for non-reference conditions and succeeded in expanding the audit application to large and small field beams and wedged beams. The audit service for non-reference irradiation conditions was initiated in April 2010. In addition, the team has carried out studies with regard to dosimetry for hadron therapy. The team conducted the dosimetric commissioning for the new scanning beam irradiation facility in cooperation with the HIMAC accelerator group. The technical document for QC in the scanning beam irradiation technique has been prepared. These research activities are expected to contribute to smooth operations in other radiotherapy facilities as well as in NIRS. The Quality Control Research Team also contributes to the field of radiotherapy internationally in cooperation with organizations such as the Forum for Nuclear Cooperation in Asia (FNCA), IAEA, World Health Organization (WHO), International Organization for Standardization (ISO), and International Electrotechnical Commission (IEC).

4) Radiological Protection Research Team

We performed a nationwide survey on medical radiation use, estimated exposure doses and risks, and studied radiation protection of particle radiotherapy. Radiation uses in radiotherapies were surveyed by sending questionnaires on the frequencies and exposure conditions to 809 medical facilities. The data were collected and analyzed. As a study on dose and risk estimations, radiation doses for pediatric patients in X-ray CT examinations were measured by using an anthropomorphic phantom of a one-year-old infant and placing radiophotoluminescense glass dosimeters under the head, chest, and abdomen-pelvis regions; the cardiac CT scan conditions routinely used at two medical facilities were employed for the measurements. The doses varied with the differences in the types of CT scanners and scan parameters used at the two medical facilities. The organ dose measurements of an anthropomorphic phantom of a baby under the age of one have also been started for comparison between different body sizes. Undesired doses outside of the target volume in carbon ion and proton radiotherapies were assessed by measurements with a tissue equivalent proportional counter and water phantoms. In addition, Monte Carlo simulations of neutrons produced in carbon ion radiotherapy have been verified by comparing with measurements. The successful simulations of the neutrons will lead to an accurate assessment of the organ doses in the non-target volume during carbon ion radiotherapy.

Major Publications

1. Yonai S, Kase Y, Matsufuji N, Kanai T, Nishio T, Namba M, Yamashita W: Measurement of absorbed dose, quality factor, and dose equivalent in water phantom outside of the irradiation field in passive carbon-ion and proton radiotherapies, *Medical Physics*, **37**, 4046-4055, 2010
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5. Hayakawa M, Moritake T, Kataoka F, Takigawa T, Koguchi Y, Miyamoto Y, Akahane K, Matsumaru Y: Direct measurement of patient's entrance skin dose during neurointerventional procedure to avoid further radiation-induced skin injuries, *Clin Neurol Neurosurg*, **112**, 530-6, 2010

2.4. 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 a fellowship position 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.

Contact Point: imait@nirs.go.jp

Objectives

The RadGenomics Research Group consists of three teams: the Genetic Information Team, the Molecular Radio-oncology Team, and the Molecular Biostatistics Team. These teams use different approaches to address the overall research aims of the research group.

There is an ongoing need for improved efficiency of radiotherapy and the group has focused on investigating the genetic characteristics of cancer patients as well as the tumors. Important research objectives of the group have been the improvement of tumor therapy and the reduction in adverse reactions by modification of therapeutic conditions for individual patients. The main research achievements of the group in the second 5-year Mid-Term Plan have been the characterization of radio-resistant tumors, the identification of genetic variants associated with adverse reactions after radiotherapy, and the development of a new antimetastatic approach for local combination therapy using carbon ion radiotherapy and immunotherapy.

Progress of Research

1) Study population

Between October 2001 and March 2011, 2,818 patients were registered including 775 breast cancer patients, 436 cervical cancer patients, 925 prostate cancer patients, and 324 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/ 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 (radio-sensitive and radio-resistant) according to the grades determined by the above scoring systems.

2) Radiotherapy-responsive markers expressed in cervical tumors

To refine treatment strategies and thereby improve the clinical outcomes, it is essential to use markers that will help assess the outcome of a treatment method. The currently available markers are insufficient to differentiate between patients who require further therapy and those who require only standard-of-care treatment. Therefore, it is necessary to identify additional markers that will help evaluate the treatment outcome.

First, we identified specific radiotherapy-responsive genes including *FGF2, CD44, CDKN1A* and *BAX* using comprehensive microarray techniques by analyzing the gene expression profiles of sequential biopsy samples from cervical cancer patients during fractionated chemo/ radiotherapy. Then, we confirmed that FGF2 expression in tumor (FGF2-T) was significantly higher in midtreatment samples ($P = 0.0002$), and a high ratio of midtreatment/ pretreatment FGF2-T was related significantly to a better prognosis ($P = 0.025$, $n = 82$). These results suggest that FGF2 expression may be a useful marker to monitor the effectiveness of radiotherapy for cervical cancer, which would improve patient selection for molecular targeted therapies, such as the use of cytokine inhibitors, following standard-of-care treatment.

3) Genetic factors associated with a risk of adverse reactions to radiotherapy

In the second mid-term plan, mainly three studies have been performed: (i) searching for single nucleotide polymorphisms (SNPs) associated with a risk of late urinary

morbidity after carbon ion radiotherapy in prostate cancer patients; (ii) searching for haplotypes, i.e., combinations of SNPs on the same chromosome, associated with adverse reactions in the gastrointestinal tract of cervical cancer patients who had been treated with pelvic radiotherapy; and (iii) searching for microsatellite markers associated with acute adverse reactions following radiotherapy.

In the first study, the "area under curve-receiver operator characteristic" (AUC-ROC) curve analysis was applied to identify the effective combination of SNPs associated with urinary morbidity in prostate cancer patients. When the SNP markers in the *SART1, ID3, EPDR1, PAH,* and *XRCC6* genes were subjected to AUC-ROC curve analysis, values of the obtained AUC-ROC curves were 0.86 in the training set and 0.77 in the test set, respectively. 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.

The second study revealed two of three haplotypes were associated with an increased risk of early gastrointestinal reaction (EAR). The first haplotype, comprised of four SNPs, rs183460C, rs228589T, rs189037A, and rs625120G, is located between the 5' ends of *NPAT* and *ATM* (OR = 1.86; 95% CI, 1.21-2.87), while the second is located in the *AURKA* gene and is comprised of two SNPs, rs2273535A and rs1047972G (OR = 1.75; 95% CI, 1.10-2.78). The third haplotype, with two SNPs, rs2273535T and rs1047972A, and located in *AURKA*, was associated with a reduced EAR risk (OR = 0.42; 95% CI, 0.20-0.89). The risk of EAR was significantly higher among patients with both increased-risk diplotypes compared to those possessing the other diplotypes (OR = 3.24; 95% CI, 1.52-6.92). Therefore, individual radio-sensitivity of the intestine can be determined by haplotypes in the *NPAT-ATM* and *AURKA* genes.

In the last study, a total of 360 cancer patients treated with radiotherapy were analyzed. Pooled patients' DNA was screened using 23,244 microsatellite markers, which cover the whole human genome. Two-rounded screenings and the following individual typing data showed 47 autosomal markers with a false discovery rate < 0.05. One of these markers is within the proximal promoter region of the *SEMA3A* gene. Knockdown of this gene expression in a normal human skin fibroblast caused a significant change in the radio-sensitivity of these cells.

These studies suggest that stratification of the cancer patients is expected based on their genetic background association with radio-sensitivity.

4) Combining carbon ion radiotherapy and local injection of alpha-galactosylceramide-pulsed dendric cells

Distant metastases after local treatment remain a major challenge to overcome for improvement of long-term survival. We, first, studied *in vivo* biological effects induced by carbon ion irradiation using comprehensive expression analysis. The gene expression data showed that irradiation with a carbon ion beam upregulates more membrane-associated immunogenic molecules in murine tumors than gamma-ray irradiation. We also investigated the effects of irradiation on distant metastases using the murine model. Furthermore, we observed that surgical resection of the primary tumor after local tumor irradiation significantly decreased distant metastases whereas surgical resection without irradiation showed no inhibitory effect on the distant metastases. These results led us to hypothesize that local carbon ion radiotherapy has a potentially high curative effect, even for distant metastases, when combined with systemic immunotherapy.

Tumors of mouse squamous cell carcinoma (NR-S1) cells inoculated in the legs of C3H/HeSlc mice were locally irradiated with a single 6-Gy dose of carbon ions (290 MeV/nucleon, 6-cm spread-out Bragg peak). Thirty-six hours after irradiation, alpha-galactosylceramide-pulsed dendric cells (α-GalCer-pulsed DC) were injected into the leg tumor. The data showed that the combination therapy with carbon ion irradiation and α-GalCer-pulsed DCs significantly reduces the incidence of lung metastases in mice, as compared with the respective monotherapies. Increased concentration of intracellular adhesion molecule 1 (ICAM-1), which activates DCs, was observed 6 h to 36 h after irradiation in the local tumors of the carbon ion-irradiated group. The expression of S100A8 in lung tissue, a marker of the lung pre-metastatic phase, was decreased only in the group with a combination of carbon ions and DCs. These data suggest that this combination therapy has clinical implications for enhancing patient survival after carbon ion radiotherapy.

Major Publications

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2.5. Biological Research Concerning the Improvement of Radiation Therapy

Ryuichi Okayasu, Ph.D.

Director, Heavy Ion Radiobiology Research Group.

Outline of Research Career

Dr. Okayasu received his Ph.D. in radiation biology from Colorado State University, USA in 1987. After working as research scientist at Thomas Jefferson University, MD Anderson Cancer Center, and Columbia University, he became an Assistant Professor at the University of Texas Medical Branch at Galveston in 1995, and then returned to Colorado State University as a faculty member. 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 the ISRL. In 2006, he was transferred to the Research Center for Charged Particle Therapy and became Director of the Heavy Ion Radiobiology Research Group.

Contact point: rokayasu@nirs.go.jp

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 patients' dose distributions 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 radio-sensitizers 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: Biophysics Team; Experimental Therapy Team; Cellular and Molecular Biology Team; and Radiation Modifier Team. Each team has different objectives, however, cooperation among four teams is sought in order to accomplish the goals of the research group.

Progress of Research

1) Biophysics Team and Experimental Therapy Team

Our cell survival data showed the obvious dependence of RBE on photon energy. The RBE value for 200 kV X-rays was approximately 10% greater than those for high-energy photons such as produced by a linac. Energy distributions of photons are altered by target geometry because of scatterings. To evaluate the increase in RBE, the method of deriving RBE using the MKM (Microdosimetric Kinetic Model) was proposed. The MKM has two parameters: tissue-specific parameters and the dose-mean lineal energy derived from the lineal energy (y) distributions. The y distributions with the same geometries of cell irradiations with 200 kV X-rays, ^{60}Co gamma-rays or 6 MV X-rays could be obtained with the TEPC and GEANT4 code; the averaged y values were 4.51, 2.34 or 2.36 keV/μm, respectively. The tissue-specific parameters in the MKM were determined. The RBE of photon beams in arbitrary conditions can be derived from the measurements only or from the calculations only of the dose-averaged y.

We also studied a method to calculate the RBE in mixed radiation fields of therapeutic ion beams based on the modified MKM. In addition, we showed the procedure for integrating the modified MKM into a treatment planning system (TPS) for scanning carbon beams. With this procedure, the model is fully integrated into our research version of the TPS. To account for the change in the sensitivity of cells, we measured MKM parameters from survival curves of the cells and used the parameter in biological optimization. Irradiation of HSG cells was performed with a scanning carbon beam, and the measured depth-survival distribution was compared with the modified MKM-predicted survival curve. Good agreement between the two curves proves that the proposed method is a good candidate for calculating the biological effects in treatment planning for ion irradiation.

The effect of carbon ion beams on metastatic potential of melanoma *in vitro* and *in vivo* was investigated. Carbon ions showed higher cytotoxic effects on B16/BL6 cells *in vitro* as compared with X-rays. Both migration and

invasion potential of cells were enhanced by photon beams at low dose points, but they were suppressed by carbon ions at all dose points tested. The RBE values obtained from a migration and invasion test on cells *in vivo* were higher than that from cell killing. Carbon ions were more effective in reducing lung metastasis than photon beams. These studies suggest that carbon ions significantly inhibit the metastatic process much more than low-LET photons.

Another critical study was related to the control of cancer stem-like cells by heavy ions. Using a mouse tumor model, we found that high LET carbon ion irradiation was able to control stem cell markers more effectively than X-irradiation. This kind of study may help explain the successful clinical outcome of heavy ion treatment.

2) Cellular and Molecular Biology Team

Chordoma is one of the tumors most successfully treated by carbon ion particle therapy. Last year, we developed a useful chordoma cell line, U-CH1-N out of the only one chordoma cell line available in the world, and determined its radio-sensitivity and chemo-sensitivity. Our data provide the first chronological cell survival information using the cells of chordoma origin and also help explain the successful chordoma treatment by heavy ions.

Using HiCEP, a novel comprehensive gene expression technique, we searched for various transcripts which respond to X-rays and carbon ions. A group of early responsive IR-induced genes (ATF3, BTG2, TP53INP1) remained activated for a longer period in human cells irradiated with carbon ions when compared with X-rays, suggesting that heavy ion particles could generate certain types of DNA lesions which need a longer time to be processed. In the course of screening studies, we found that the expression of ASPM, a microcephaly gene was significantly downregulated by IR in human and murine cells. Furthermore, *ASPM* siRNA significantly increased the radio-sensitivity of several tumor cell lines. Additional studies have indicated that the enhanced radio-sensitivity was due to less efficient repair of DNA double-strand breaks involving non-homologous end joining systems.

We have generated a mouse model whose *Aspm* orthologous gene (*calbpm*1) was conditionally disrupted. *Aspm null* deficient mice show "microcephaly (small head)" and additional defects in the development of gonads. As for clinical applications, *ASPM* could be a novel target for combination therapy with radiation as well as a useful biomarker for tumor prognosis.

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3) Radiation Modifier Team

The reaction mechanism of a radio-protective bio-factor, melatonin, was studied. The results showed that melatonin eliminated free radicals by an electron transfer reaction. Protective effects of γ-TDMG on radiation-induced dermatitis were investigated, however, significant protective effects could not be established from our limited experiments and this study is continuing.

Distribution and density of hydroxyl radicals caused by ionizing radiation were investigated. The total amount of hydroxyl radicals generated by carbon ions was lower than that by X-ray irradiation at the same dose, while the density of hydroxyl radicals caused by carbon beams was higher than that by X-rays. The redox mechanism of the nitroxyl radical was investigated. The glutathione-dependent reduction of nitroxyl radicals depends on pH of the reaction mixture, and this reaction can be accelerated by another kind of free radicals coexisting in the reaction mixture.

In order to find a potential clinical radio-protector, the radio-protective effect of the herbal drug "Daikenchuto" was tested. When administered orally (2% concentration in a mouse diet), Daikenchuto reduced some intestinal and/or colonal inflammation indexes which were increased by X-ray irradiation to the mouse abdomen.

Major Publications

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2.6. Transcriptome Research for Radiobiology

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

Objectives

The Transcriptome Research Group consists of three teams: Stem Cell Research Team, Model Organism Research Team and Gene Expression Profiling Team. Their objectives have been: 1) developing a new method of transcriptome analysis (HiCEP) especially for medical uses and stem cell biology; 2) developing an application of the HiCEP method for diagnosis using blood; and 3) understanding the mechanism controlling stem cells

Progress of Research

1) Gene Expression Profiling Team

This team has developed an ideal transcriptome analysis procedure called High coverage gene expression profiling (HiCEP) that is based on a different principle than that of hybridization-based methods such as micro-array analysis.

The HiCEP method was improved to allow analysis using even a small amount of starting materials. When development of the method was first started, approximately 1 μg of poly(A) RNA was needed for the analysis; however, currently the standard analysis requires only 0.1 μg of total RNA that is ~1/1,000 of the amount needed at the beginning of the development. Furthermore, a new protocol was developed allowing HiCEP analysis to be conducted using less than 100 pg of total RNA, corresponding to less than 10 cells.

Meanwhile, the team has developed a high throughput machine for the HiCEP reaction that can carry out analysis of more than 15,000 samples per year. This machine, called HiCEPer, was marketed by a collaborative company this year. A precision PCR (polymerase chain reaction) machine, in which the temperature difference among 96 wells in a sample plate can be controlled to less than 0.2 degree, was also developed and marketed; this is a valuable device as the HiCEP reaction requires an extremely high level of temperature control. In addition, a HiCEP reaction kit was developed that requires just 1 μg of starting materials, and it allows persons even without expertise in molecular biology to perform HiCEP analysis easily.

Using these new measures based on HiCEP technology, the team developed a good application for blood analysis. With only 1 mL of blood, more than three analyses of the entire transcriptome can be conducted. This application allows analysis using peripheral whole blood to be carried out; no fractionation steps are needed beforehand. Furthermore, importantly, the application demonstrated the possibility to detect any type of solid tumors using only peripheral blood with high sensitivity.

2) Stem Cell Research Team and Model Organism Research Team

This team has focused on pluripotent stem cells with the final research goal being to understand the effects of radiation at an individual level not at a cellular level.

Recently, 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 c-Myc, which are designated as induced pluripotent stem (iPS) cells. The objective of this program is to understand the molecular mechanism of the conversion from somatic cells to stem cells. However, this is a hard objective to meet, because these cells emerge at a low frequency, about 0.1% in the case of fibroblasts, and in a stochastic manner. Therefore, the team attempted to directly observe the emergence of iPS cells from somatic cells. A new investigation system was developed by improving an existing time-lapse system that allows precise investigation of iPS generation at short intervals of about 2 weeks that are needed for iPS cells generation from mouse fibroblasts. With the system, directly observation of the conversion process of a somatic cell into stem cell was successfully made (Fig.2.11). These results provide a critical new insight during the first three days of the iPS cell generation.

In addition, the team made another contribution to the iPS field, the first successful generation of genome integration-free iPS cells without oncogene, c-Myc, transduction using an inbred mouse strain (C57BL/6). This inbred mouse-derived iPS cell line library is unique and enables a precise comparison to be made among iPS cells. Some cell lines in the library were utilized for examining the immunogenicity of iPS cells and their progenitor cells. The team also was the first to demonstrate a clear

difference between iPSCs generated with Oct3/4, Sox2, Klf4 and c-Myc, and iPSCs with three factors excluding c-Myc. A crucial role of c-Myc for iPS cell generation was revealed. The results are quite important, because it had been considered that c-Myc is not essential for iPS cell generation and in addition reactivation of oncogene c-Myc frequently occurs in the mice developed from iPSs and causes various tumors in them. Finally, the role of c-Myc in iPS cell generation was demonstrated to be involved in the histone acethylation regulation mechanism.

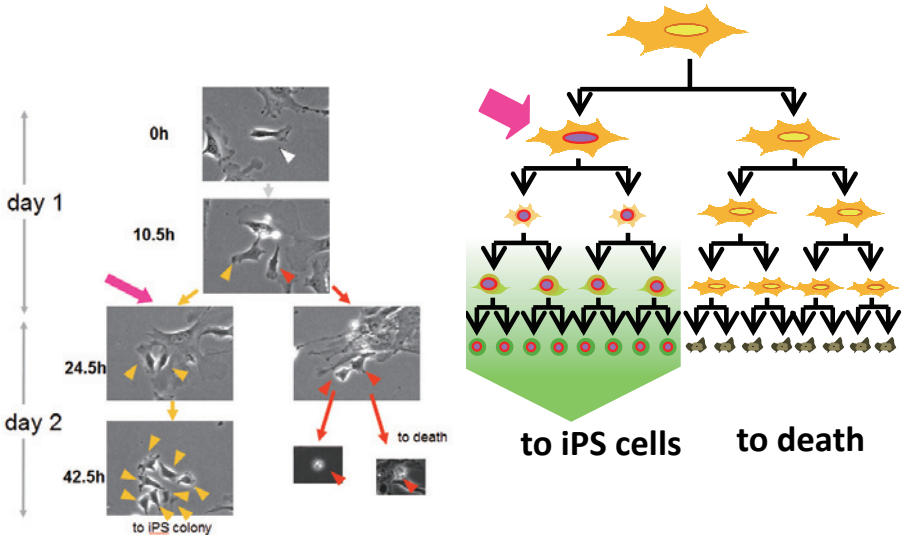

Fig.2.11 Emergence of induced pluripotent stem (iPS) cells from fibroblasts.

3. Molecular Imaging Center

Yasuhisa Fujibayashi, Ph.D., D.Med.Sci.

Director, Molecular Imaging Center

Outline of Research Career

Yasuhisa Fujibayashi graduated from the Department of Radiopharmaceutical Chemistry, Graduate School of Pharmaceutical Sciences, Kyoto University, then started his professional career in 1983 at Kyoto University Hospital as an assistant professor of the Radioisotope Research Laboratory. Ten years later, he moved to the Graduate School of Pharmaceutical Sciences, Kyoto University, as an associate professor of Genetic Biochemistry. In 1999, he became Professor of Molecular Imaging at the Biomedical Imaging Research Center, University of Fukui (former Fukui Medical University), and then Director of the Center. In 2010, he joined NIRS in his present position and he continues his research career.

Objectives

The question "What is Life?" has been a universal issue. One of the most famous attempts to answer the question is in the book entitled *What is Life?* by Erzin Schrodinger (1944), in which he argues that life is based on the interactions between molecules. Recent progress in molecular and cellular biology has in principle clarified this point. However, it is still difficult to observe the behavior and role of a single molecule in living systems.

Molecular imaging (MI) is a relatively new research field created to investigate and visualize molecular and cellular processes in biological systems. The field is based around various imaging technologies such as positron emission tomography (PET), magnetic resonance imaging (MRI), and optical imaging. It is anticipated that combining these technologies will bring new insights into what life is, because each modality has different characteristics in terms of sensitivity, time and spatial resolution and what type of subjects it can be applied to.

The Molecular Imaging Center at the National Institute of Radiological Sciences (MIC-NIRS) is funded by the Japanese Government as the "Japan Advanced MI Research Program (J-AMP). We are working on a wide range of projects from basic to clinical research, and our main target is to become a core center promoting translational research in the MI community and related areas.

Overview

At MIC-NIRS, there are four research groups, namely the Diagnostic Imaging Group, Molecular Neuroimaging Group, Molecular Probe Group, and Biophysics Group. Under the supervision of the Board of Executive Directors, the Planning and Promotion Unit works to support these groups.

The Diagnostic Imaging Group focuses on research of cancer imaging using functional imaging modalities such as PET. The aim is to develop and establish molecular probes to clarify the pathophysiological processes in cancers and other diseases, and evaluate their clinical usefulness. This group is developing probes which can detect the expression of various molecular targets in cancer cells and probes which have multiple functionalities. In this group, clinical research on the diagnosis of tumor proliferation has been performed using F-18-fluoro-deoxythymidine (FLT) and C-11-thio-thymidine (4DST). The former visualized thymidine kinase activity but not DNA synthesis itself, whereas the latter was incorporated into DNA and retained. It was clarified that FLT accumulation in cancer is a plausible prognosis marker for radiation therapy, but its accumulation in radiation-associated pneumonitis might hamper the correct evaluation. In heavy-ion radiation therapy, FLT accumulation in bone marrow is considered to be a useful indicator of change in its activity. Comparative clinical studies using FLT and 4DST are in progress. For hypoxia imaging, it was clarified that the retention mechanisms of Cu-62-ATSM and F-18-FAZA were different and these two tracers might lead to different clinical information. The FAZA study is being done in collaboration with the Cancer Institute Hospital of the Japanese Foundation for Cancer Research and the Department of Radiology of the Chiba University Hospital. For basic research, amino acid transporter, epidermal growth factor (EGF), c-kit, HER2 and integrin-$\alpha v\beta 3$ were selected as targets for imaging, and tumors could be successfully visualized using radiolabeled AIB, antibodies and RGD derivatives, respectively. In addition, the possibility of hypoxia-sensitive NIS-reporter gene imaging and Mn-enhanced MR imaging of mesothelioma were also reported.

The Molecular Neuroimaging Group is directed toward understanding the neurobiology of neuropsychiatric disorders such as schizophrenia, depression and Alzheimer's diseases, and identifying optimal treatments of these disorders. Clinical and basic approaches are integrated using in vivo and in vitro imaging technologies. This program aims to identify diagnostic molecular markers for neuropsychiatric disorders, leading to drug discovery and novel therapeutic treatments.

To quantify the neurotransmission function, optimal quantification methods and the PET scanning protocol for various PET ligands in the human brain were established Based on them, the normal database of neurotransmission function and higher brain function was constructed. Using these data, focuses of emotion in the brain could be visualized in combination with PET and MRI. It was also clarified that schizophrenia patients showed increased dopamine synthesis in the striatum and activation of microglias in the brain.

In basis studies, comparative PET and autoradiographic imaging of mice and humans indicated the importance of disease animal models for understanding molecular pathophysiology of neuropsychiatric disorders. Using similar techniques, the mechanism of motivation and its dysfunction were studied in primates as well as rats. These results are applied for screening and evaluation methods for therapeutics such as anxiolytic drugs, anti-schizophrenia drugs and so on.

Main tasks of the Molecular Probe Group are the development and routine production of useful PET probes for clinical diagnosis and bio-functional analysis. To achieve these tasks, a versatile automated synthesis system to produce safe PET probes with less radiation exposure to personnel has been developed. Using this system, new labeling techniques are applied to the synthesis of novel PET probes which can quantitatively visualize biological functions. The standard production method for clinical application of molecular PET probes is being established and related technology transfer to other international as well as domestic PET facilities is underway.

In biomarker research, basic structures of radio-labeled probes for the multi-drug resistance protein MRP4, organic anion transporter OAT1, and metabolic glutamate receptor mGluR was clarified. Also the glutathione/GST redox function was visualized in monkey brain using a newly developed F-18-ligand. A new imidazoline-2 receptor probe, 11-C-FTIMD with ultra-high specific radioactivity was successfully synthesized and its improved accumulation in the brain was confirmed. Development and application of new synthesis procedures for C-11-carbamate, urea and other compounds were achieved. As for radionuclide production, targets and an automation system for Zr-89, Br-76 and Tc-99m production were developed.

The Biophysics Group aims at developing instruments and methodologies for quantitative measurements of in vivo molecular functions using PET, MRI and optical imaging. This group consists of four teams, namely the Imaging Physics Team, Image Analysis Team, Biosignal Physiology Team, and Magnetic Resonance Molecular Imaging Team.

PET is a promising methodology for molecular medicine. The Imaging Physics Team proposed Open-PET, a new concept for the design of PET with higher resolution at reasonable sensitivity and cost, and X'tal-Cube, a next-generation DOI (depth of interaction) detector, and developed their prototypes as proof-of-concept. The Image Analysis Team developed algorithms for the compartment model estimation for quantitative PET imaging. Combination of anatomical MRI images with PET images realized quantitative PET image construction with lower noise. An automatic blood sampling system for small animals was developed and commercialized, which allows precise evaluation of pharmacokinetics and pharmacodynamics. The Biosignal Physiology Team has developed new MRI methods for the evaluation of water diffusion, tissue elasticity, tissue oxygen tension, and so on. Among them, the team found that the water diffusion method allowed evaluation of the degenerative brain damages. Using an Alzheimer model mice brain, it was clarified that amyloid deposition decreased blood vessel response. The Magnetic Resonance Molecular Imaging Team developed nano-probes as theragnostic DDSs based on thermo-sensitive liposome. Redox imaging with nitroxide probes using a combination of MRI and ESR was performed. As well, noninvasive evaluation of radiation therapy using Mn-enhanced MRI and high-speed quantitative MRI was successfully performed.

In the Planning and Promotion Unit, the Research Promotion and Administration Section performs fund-raising, mounts public relations activities, is responsible for external affairs of collaborative research, and coordinates arrangements associated with intellectual property. The Clinical Research Support Section has clinical research coordinators (CRCs) and doctors at the core and it maintains the support system for clinical research. Each section has experts whose professional backgrounds lie in a variety of fields and they support the activities of the Center.

3.1. Research on Molecular Imaging of Cancer

Tsuneo Saga, M.D., 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 basic and clinical research on molecular imaging of cancers.

Contact Point: saga@nirs.go.jp

Objectives

The Diagnostic Imaging Group is conducting research on functional cancer imaging by PET and other modalities to clarify the characteristics of an individual cancer such as its malignancy grade and responsiveness to treatment. Although several PET probes are available for clinical studies to characterize cancers, 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 PET for the contribution to the management of cancer patients including those considered for carbon-ion radiotherapy (CIRT) conducted at NIRS. In addition to FDG and ^{11}C-methionine, we are evaluating newly developed cancer-imaging probes, such as ^{18}F-FLT, ^{62}Cu-ATSM and ^{18}F-FAZA, to determine their clinical usefulness.

The Molecular Diagnosis Team conducts basic molecular imaging research focusing on designing and evaluating imaging probes that capture the changes of biomolecules specifically associated with cancers and other diseases to realize effective non-invasive diagnoses. We also are developing 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 and molecular events occurring during carcinogenesis, 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 cancer targets, we are aiming for the development of novel molecular imaging methods which can depict the characters of each cancer.

Progress of Research in the 2nd Mid-term Plan

1) Clinical studies on cancer imaging using various PET probes

We conducted clinical PET research studies using ^{18}F-fluorothymidine (FLT), a marker of cellular proliferation and proved that FLT is a significant prognostic indicator of lung cancer patients receiving CIRT and a useful marker of bone marrow activity. We have also started an initial clinical study of ^{11}C-thiothymidine (4DST), a novel proliferation marker, to confirm the safety and whole body distribution. Clinical PET studies using hypoxia PET probes, ^{18}F-FAZA and ^{62}Cu-ATSM, are ongoing to evaluate whether tumor uptake of these probes can be an indicator of responsiveness to treatment.

2) Exploration of new therapeutic and diagnostic targets of mesothelioma

In the search for a specific molecular target of mesothelioma, we found that the manganese (Mn) content is increased in various mesothelioma cell lines compared to mesothelial cells, reflecting the Mn-superoxide dismutase (SOD) expression, suggesting biological significance of Mn in mesothelioma formation and/or progression. As Mn is a signal enhancer in magnetic resonance imaging (MRI), we performed Mn-enhanced MRI and succeeded in visualizing small (~1 mm) pleural tumors expressing Mn-SOD.

To identify a new therapeutic target of mesothelioma, we conducted a large-scale functional screening of mesothelioma cells using siRNAs against 8,589 human genes. Knockdown of 39 genes significantly suppressed mesothelioma cell proliferation, including 7 genes having an anti-apoptotic function, among which COPA was highly expressed in mesothelioma cell lines, but not in a normal

mesothelial cell line. COPA depletion induced apoptosis and suppressed tumor growth, indicating that COPA would be a promising therapeutic target of mesothelioma.

3) Development and application of animal models for researches on preclinical imaging and treatment

We established a subcutaneous and pleural dissemination model of epithelioid and sarcomatoid mesothelioma in mice and compared tumor uptake and PET imaging of three PET tracers, one glucose analog (FDG) and two thymidine analogs (FLT and 4DST). The two thymidine analogs were highly accumulated in epithelioid mesothelioma, while the glucose analog was highly accumulated in sarcomatoid mesothelioma, suggesting that the suitable PET tracer is different depending on the histological subclass of mesothelioma (Fig. 3.1).

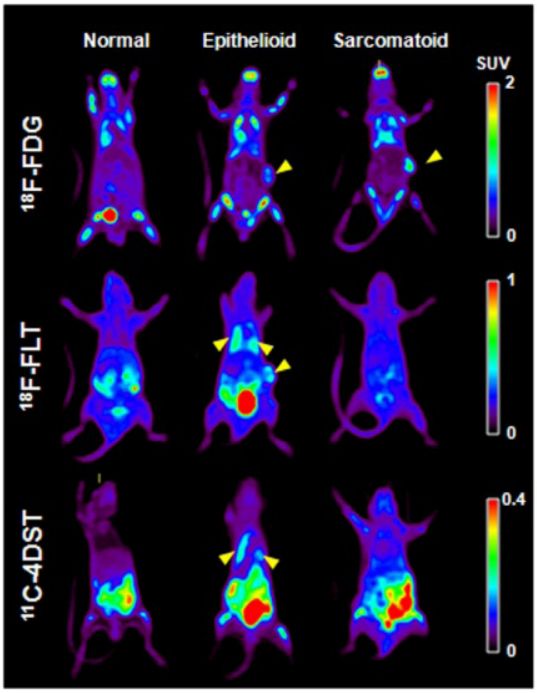

Fig. 3.1: PET images of a normal mouse and mice bearing epithelioid or sarcomatoid mesothelioma (yellow arrowhead) with three PET probes

Acute rejection remains a major complication after liver transplantation. We conducted FDG-PET in a rat liver transplantation model. FDG uptake significantly increased in liver allografts indicating acute rejection, in which high FDG signals were localized in the peri-portal area showing inflammatory cell infiltration. Furthermore, immunosuppressive treatment induced a marked decrease in hepatic ^{18}F-FDG uptake. ^{18}F-FDG-PET would be a promising imaging method for detecting acute rejection and also for monitoring immunosuppressive treatment.

4) Development of antibody and peptide probes for cancer imaging and treatment

Radiolabeled cancer-specific antibodies are powerful tools to visualize cancers. We developed antibody-based PET/SPECT imaging probes for three cancer-related antigens, ERC/mesothelin, c-kit, and EGFR, and succeeded in visualizing xenografted tumors by PET/SPECT. These antibodies can also be applied to molecular-targeted internal radiotherapy by labeling with cytotoxic radionuclides such as ^{90}Y, and we showed that ^{90}Y-labeled antibodies suppressed tumor growth in mice.

Neovascularization is important in tumor growth, invasion and metastasis. Integrin $\alpha_v\beta_3$, expressed on the surface of endothelial cells of neovasculature and on some tumor cells, can be targeted by RGD peptide. In collaboration with Dr. Dumy's group at Joseph Fourier University, we conducted small animal PET imaging of integrin $\alpha_v\beta_3$ overexpressing tumors with ^{64}Cu-labeled RAFT-c(RGD)$_4$, that has very high specificity and affinity, and succeeded in clear visualization of the tumors with the accumulation well correlated to integrin $\alpha_v\beta_3$ expression (Fig. 3.2).

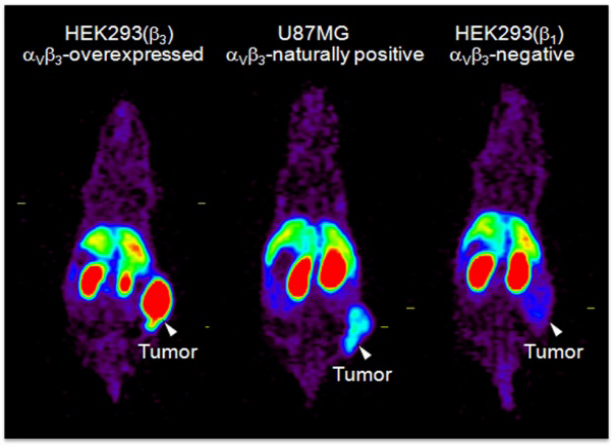

Fig. 3.2. PET imaging of tumor xenografts with ^{64}Cu-RAFT-c(RGD)$_4$

5) Preclinical studies using reporter imaging technique

By using a human Na^+/I^- symporter (hNIS) reporter gene, we evaluated therapeutic effects of a novel angiogenic gene therapy using hepatocyte growth factor (HGF) gene in a rat myocardial infarct model by reporter imaging using $^{99m}TcO_4^-$ as a reporter probe. We have also established a colon cancer cell stably expressing hNIS and succeeded in imaging spontaneous liver metastasis after orthotopic transplantation of this cell.

6) Characterization of intratumoral region of high Cu-ATSM accumulation

Cu-ATSM is a PET probe for hypoxic tissues. Studying intratumoral distribution of Cu-ATSM, we found that the regions of high Cu-ATSM accumulation had quite unique characteristics: low vessel density, low proliferation, low pimonidazol accumulation, and high ratio of cancer stem cell marker positive (CSCM+) cells. Treatment of tumor xenograft with ^{64}Cu-ATSM was more effective than X-ray treatment in decreasing the ratio of CSCM+ cells.

Major Publications

1. Koizumi M, Saga T, Inubushi M, Fukumura T, Yoshikawa K, Yamamoto N, Nakajima M, Sugane T, Baba M. Uptake decrease of proliferative PET tracer (18)FLT in bone marrow after carbon ion therapy in lung cancer, *Mol Imaging Biol*,**13**, 577-82, 2011
2. Hasegawa S, Koshikawa-Yano M, Saito S, Morokoshi Y, Furukawa T, Aoki I, Saga T. Molecular imaging of mesothelioma by detection of manganese-superoxide dismutase activity using manganese-enhanced magnetic resonance imaging, *Int J Cancer*,**128**, 2138-46, 2011
3. Sudo H, Tsuji AB, Sugyo A, Kohda M, Sogawa C, Yoshida C, Harada YN, Hino O, Saga T. Knockdown of COPA, identified by loss-of-function screen, induces apoptosis and suppresses tumor growth in mesothelioma mouse model, *Genomics*,**95**, 210-6, 2010
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5. Galibert M, Jin ZH, Furukawa T, Fukumura T, Saga T, Fujibayashi Y, Dumy P, Boturyn D. RGD-cyclam conjugate: Synthesis and potential application for positron emission tomography, *Bioorg Med Chem Lett*, **20**, 5422-5425, 2010

3.2. Research on Molecular Neuroimaging

Tetsuya Suhara, M.D., Ph.D.

Director, Neuroimaging Group

Outline of Research Career

Dr. Suhara received the Ph.D. from the 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 serves as a visiting professor at the Department of Neuropsychiatry, Nippon Medical School since 2004, at the Graduate School of Medicine, Yokohama City University since 2006 and the Graduate School of Medicine, Osaka University since 2010.

Contact Point: suhara@nirs.go.jp

Objectives

1) Clinical Neuroimaging

a) Development of methods to quantify the neurotransmission function

b) Construction of the normal database of the neurotransmission function and higher brain function

c) Clinical research for elucidation of pathophysiology of neuropsychiatric diseases

d) Estimation of drug treatment effect

2) Molecular Neurobiology

a) Application of animal models to R & D of diagnostic and therapeutic indices for dementia

b) Mechanistic elucidation of *in vivo* interactions between imaging biomarker probes and their target molecules

c) Analysis of dialogs between different neurotransmitter systems with animal models of neuropsychiatric disorders

3) System Neurochemistry

a) Brain mechanism of motivation and its dysfunction in primates

b) Research studies on an animal model of brain developmental disorders

c) Developing a multidisciplinary approach for primate brain function

Progress of Research (Achievements, Prospects) in the 2nd Mid-term Plan

1) Clinical Neuroimaging

a) Development of methods to quantify the neurotransmission function

The optimal quantification methods and PET scanning protocols were established for various radio ligands in healthy human subjects. A new graphic plot analysis was developed which could determine the total distribution volume and nondisplaceable distribution volume independently, and therefore the binding potential.

b) Construction of the normal database of the neurotransmission function and higher brain function

The normal database of the dopaminergic neural system using several radioligands for dopaminergic functions was constructed. The relation between regional densities of dopamine D1 and D2 receptors and cognitive functions were investigated. The inverted U-shaped relation between prefrontal dopamine D1 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 . Dopamine D1 receptor binding in the amygdala was positively correlated with amygdala signal change in response to fearful faces, but not in dopamine D2 receptor. Dopamine D1 receptors might play a major role in enhancing amygdala response when sensory inputs are affective .

c) Clinical research for elucidation of pathophysiology of neuropsychiatric diseases

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

d) Estimation of drug treatment effect

The measurement of dopamine D2 receptor occupancy using PET was optimized for accurate evaluation of the therapeutic effect of antipsychotics.

2) Molecular Neurobiology

a) Application of animal models to R & D of diagnostic and therapeutic indices for dementia

We provided the first demonstration that hallmark pathologies of Alzheimer's disease (AD), senile plaques and neurofibrillary tangles composed of amyloid-beta peptide (Aβ) and tau protein, respectively, in animal models can be captured by PET. Promotion of tau pathogenesis and neuronal loss by inflammatory microglia expressing 18-kDa translocator protein (TSPO) was shown by imaging of TSPO in tau transgenic mice.

b) Mechanistic elucidation of *in vivo* interactions between imaging biomarker probes and their target molecules

Our comparative PET and autoradiographic imaging of mice and humans indicated roles of N-terminally truncated and modified Aβ, AβN3pE, as a major component of AD-like plaques enriched with binding sites for amyloid PET probes. *In vivo* binding of a novel PET probe to agonistic binding sites on D2 dopamine receptor and sensitive detection of changes in synaptic dopamine release with this radiotracer were demonstrated by PET of awake rats and monkeys.

c) Analysis of dialogs between different neurotransmitter systems with animal models of neuropsychiatric disorders

A new PET probe for substance P receptor (NK-1 receptor) was developed and evaluated to visualize neurotransmissions associated with neuropsychiatric disorders. PET and autoradiographic analyses also revealed abnormalities of monoamine and glutamate receptors in mice heterozygously deficient in CaMKα, which modeled mental illnesses. Glutamate-mediated molecular mechanisms of synaptic elasticity in the amygdala potentially implicated in fear learning were clarified by our electrophysiological studies.

3) System Neurochemistry

a) Brain mechanism of motivation and its dysfunction in primates

We developed methods to evaluate a low motivational state in the monkey model of depression (hypothyroidism) through behavioral task performance (patent pending). Using the methods, we demonstrated that there were two behavioral factors for low motivation: decrease in reward sensitivity and increase in cost sensitivity. Application of SSRIs rescued the cost sensitivity, suggesting that increase of cost sensitivity is associated with low serotonin level in the brain. A PET activation study with motivational task performance revealed that the ventral striatum and ventromedial prefrontal cortex signal internal drive information. We clarified the functional dissociation in motivational valuation between lateral and orbital prefrontal cortices. Furthermore, the ability of rapid learning of visual categorization based on motivational value is reserved after bilateral ablation of the lateral prefrontal cortex.

b) Research studies on an animal model of brain developmental disorders

We have shown that synaptic dysfunction in CA1 hippocampus in juvenile rat model of maternal immune activation developed as having risk for schizophrenia in offspring. We found a decrease in dopamine D2 receptor bindings in the ACC and a loss of interneurons in the corresponding area in the model. We developed a primate model of maternal immune activation in offspring (patent pending).

c) Developing multidisciplinary approach for primate brain function

We developed the primate slice preparation for neural recording *in vivo* using marmoset monkeys. In collaboration with the Tokyo Metropolitan Institute for Neurology, the dopaminergic neuron protecting effect of vector injection against MPTP-induced dopaminergic neuronal degeneration was proofed *in vivo* by PET measurements with dopaminergic transporter ligands. We developed an evaluation system for emotion by vocalizations in marmosets. Using this system, we established screening and evaluation methods for anxiolytic drugs (patent pending).

Major publications

1. Yasuno F, Ota M, Ando K, Ando T, Maeda J, Ichimiya T, Takano A, Doronbekov T-K, Fujimura Y, Nozaki S, Suhara T: Role of ventral striatal dopamine D1 receptor in cigarette craving, *Biol Psychiatry*, **61**(11), 1252-1259, 2007
2. Maeda J, Ji B, Irie T, Maruyama M, Okauchi T, Staufenbiel M, Iwata N, Saido C. T, Suzuki K, Higuchi M, Suhara T: Longitudinal, quantitative assessment of amyloid, neuroinflammation and anti-amyloid treatment in a living mouse model of Alzheimer's disease enabled by PET, *J Neurosci*, **27**(41), 10957-10968, 2007
3. Ji B, Maeda J, Sawada M, Ono M, Okauchi T, Inaji M, Zhang M-R, Suzuki K, Ando K, Staufenbiel M, Trojanowski JQ, Lee VMY, Higuchi M, Suhara T: 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**(47), 12255-12267, 2008
4. Takahashi H, Kato M, Matsuura M, Mobbs D, Suhara T, Okubo Y: When your gain is my pain and your pain is my gain: neural correlates of envy and schadenfreude, *Science*, **323**, 937-939, 2009
5. Ito H, Takano H, Takahashi H, Arakawa R, Miyoshi M,

Kodaka F, Okumura M, Otsuka T, Suhara T: Effects of the antipsychotic risperidone on dopamine synthesis in human brain measured by positron emission tomography with L-[β-11C]DOPA: a stabilizing effect for dopaminergic neurotransmission?, *J Neurosci*, **29**(43), 13730-13734, 2009

3.3. Research on Molecular Probes and Radiopharmaceuticals

Toshimitsu Fukumura, Ph.D.

Director, Molecular Probe Group

Outline of Research Career

Toshimitsu Fukumura started his professional career in the Faculty of Pharmaceutical Sciences, Kyushu University Hospital in 1985 as an Assistant Professor of Radiopharmaceutical Chemistry and then moved in 1986 to the Department of Radiology, Kyushu University. In 1998, he joined Japan Steel Works, a major supplier of cyclotron and automated radiopharmaceutical production systems, to develop new automated synthesis apparatuses. In April 2006, he came to NIRS and in 2008, he was appointed group leader of the Molecular Probe Group.

Contact Point: t_fukumu@nirs.go.jp

Objectives

Molecular probes play essential and important roles in the rapidly developing field of molecular imaging. The purposes of the molecular probe group are: 1) to develop novel probes assessing *in vivo* biological and physiological functions; 2) to develop new labeling methods to expand the possibility of producing a wider variety of probes at high yield and high quality; 3) to develop a new integrated system for the production of safe probes considering the GMP standard, without radiation exposure to personnel by implementing automations; and 4) to establish the production methods and quality control methods of the developed probes for clinical applications.

1) The Probe Research Team
   Aims of this team are to develop novel probes for quantitative assessment of biological functions.

2) The Radiochemistry Team objectives are to develop new labeling methods and labeling precursors with PET radionuclides, to achieve ultra higher specific activity for various kinds of PET probes.

3) The Production System Team and Radiopharmaceutical Production Team not only have the above objectives but also have missions to support research activities for PET. Research by these teams is intended to establish routine production and 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 toxicity and radiation dosimetry for clinical applications.
   The research activities performed in FY 2010 are described below.

Progress in Research in the 2nd Mid-term Plan

New PET probes

1) A promising candidate compound for molecular probes for measuring the functional activity of MRP4 and organic anion transporter (OAT) was picked from the results of an examination using knock-out mouse.
2) A promising candidate for PET molecular probes which enables quantitative measurement of glutathione/GST reduction function labeled with ^{18}F was found to show excellent radioactive kinetics *in vivo*.
3) Several PET probes for mGlu1 were developed and evaluated. From this research a promising compound that has high in vivo specific binding ability was found.
4) During the past 5 years, more than 102 PET probes that are potent candidate compounds for the imaging of brain and tumor imaging were prepared and evaluated. From this activity, we developed manufacturing and quality control processes for 11 PET probes for clinical research and got approval of them.

Suitability of an ultra-high specific activity labeled [^{11}C]PET probe

A novel PET probe for I_2 imidazoline receptor of [^{11}C]FTIMD has been labeled with ultra-high specific activity greater than 100 mCi/nmol. An animal PET study demonstrated that ultra-high specific activity labeled [^{11}C]FTIMD showed a significant increase in specific binding ability in the brain compared to specific activity labeled [^{11}C]FTIMD (2 mCi/nmol) that has been achieved at other PET centers. The present study demonstrated that animal PET with ultra-high specific activity [^{11}C]FTIMD is a powerful tool for the imaging of I_2 imidazoline receptor quantitatively.

New method and labeling procedure

1) A labeling method for the [^{11}C]labeled carbamate and asymmetric [^{11}C]urea by intermolecular coupling using [^{11}C]phosgene was established.
2) Using the C-^{11}C formation reaction, a simple and effective labeling method for amino acids was established and the reaction was utilized for the synthesis of [^{11}C] AIB.
3) A synthesis apparatus for producing [^{11}C] cyanide was developed and used for the development of PET molecular probes.

Non-standard PET radio nuclide

A production system producing ^{76}Br was developed and the production method for ^{76}Br is being optimized. Using the same system, a production method for ^{89}Zr was also developed. Furthermore, a basic study for the production method of ^{99m}Tc, an important radionuclide in nuclear medicine, by proton induced nuclear reactions was carried out.

Application of the PET probe

1) Utilizing a PET probe for peripheral benzodiazepine, the probe suitability for some disease was evaluated using an animal disease model.
2) Functional imaging was successively obtained in brain astrocyte by measuring [^{11}C]benzylacetate using micro-dialysis in an animal disease model.

Contribution to the quality of clinical PET in Japan

The chemical purity tests of [^{18}F]FDG preparations produced in other PET facilities in Japan were conducted.

Major publications

1. Kato K, Kikuchi T, Nengaki N, Arai T, Zhang M-R: Tetrabutylammonium fluoride-promoted alpha-[^{11}C] methylation of alpha-arylesters: a simple and robust method for the preparation of ^{11}C-labeled ibuprofen, *Tetrahedron Letters*,**51**,45 5908-5911, 2010
2. Zhang M-R, Kumata K, Hatori A, Takai N, Toyohara J, Yanamoto K, Yamazaki T, Yui J, Kawamura K, Koike S, Ando K, Suzuki K: [^{11}C]Gefitinib ([^{11}C]Iressa): Radiosynthesis, In Vitro Uptake and In Vivo Imaging of Intact Murine Fibrosarcoma,*Molecular Imaging and Biology*, **12**(2), 181-191,2010
3. Kawamura K, Konno F, Yui J, Yamasaki T, Hatori A, Yanamoto K, Wakizaka H, Makoto Takei M, Nengaki N, Fukumura T, Zhang M-R: Synthesis and evaluation of [^{11}C]XR9576 to assess the function of drug efflux transporters using PET, *Annals of Nuclear Medicine*, **24**(5), 403-412, 2010
4. Nagatsu K, Fukada M, Minegishi K, Suzuki H, Fukumura T, Yamazaki H, Suzuki K: Fully automated production of iodine-124 using a vertical beam, *Applied Radiation and Isotopes*, **69**, 146-157, 2010
5. Yui J, Hatori A, Kawamura K, Yamasaki T, Yanamoto K, Yoshida Y, Ogawa M, Kumata K, Fujinaga M, Nengaki N, Suzuki K, Zhang M-R: Visualization of early infarction in rat brain after ischemia using a translocator protein (18 kDa) PET ligand [^{11}C]DAC with ultra-high specific activity, *NeuroImage*, **54**(1), 123-130, 2010

3.4. Research on Biophysics

Iwao Kanno, Ph.D.

Director, Biophysics Group

Outline of Research Career

Dr. Kanno graduated in Electrical Engineering from Tohoku University in 1970. He worked at the Akita Research Institute of Brain and Blood Vessels after graduation of Tohoku University. He obtained a Ph.D. (Tohoku University) in 1977. In 1978 he had a short stay at Bispebjerg Hospital in Copenhagen, Denmark, during which he developed methods to measure regional cerebral blood flow using ^{133}Xe and dynamic tomography. He then developed his first PET scanner on returning to Akita in 1979. After a short time working at Hammersmith Hospital in London in 1982, he set up a PET research laboratory in Akita in 1983. Since then he has designed and built four commercial PET scanners, developed an ^{15}O PET system for measuring brain circulation and metabolism. In 2006, he moved to the Molecular Imaging Center at NIRS as the Center Director and also as Group Leader of the Biophysics Group of the Molecular Imaging Center.

Contact Point: kanno@nirs.go.jp

Objectives

The Biophysics Group aims to develop instruments and methodologies for quantitative measurements of in vivo molecular functions using PET, MRI and optical imaging. The group consists of four teams whose progress in FY 2010 is described below.

Progress in Research in the 2nd Mid-term Plan

1) Magnetic Resonance Molecular Imaging Team

This team newly proposed and developed "Molecular Magnetic Resonance Imaging". This new concept, which consisted of functional contrast agents and hybrid nanoprobes, was tested in an animal study.

Manganese contrast agent is a useful functional probe. The team proved that manganese-enhanced MRI can provide good image contrast for studying reactive gliosis in a rat chronic stroke model, anoxic depolarization in a rat super-acute stoke model, and in a layer structure of the brain. The team also developed a multimodal therapeutic contrast agent using nitroxyl radical as a novel nonradioactive methodology. A visible anti-cancer drug "SLENU" was developed for *in vivo* noninvasive, real-time MR imaging of blood-brain barrier (BBB) permeability. The nitroxyl radical probes were tested in an *in vivo* tumor model and the results were published.

A drug delivery imaging technique using temperature-sensitive liposome was developed and applied *in vivo*. The multimodal and multifunctional liposome was synthesized as an MRI contrast agent for optical imaging and as an anti-cancer drug with tumor targeting capability. The drug kinetics, including accumulation in a tumor and drug release using thermo-triggering, and the anti-tumor effects were visualized in mice. A multimodal quantum-dot nanoprobe was developed for both MR and optical imaging. Quantum-dots have more suitable fluorescence properties than conventional organic dyes. The fluorescence properties were protected by a hydrophobic structure around the nanoparticle core, and the inclusion of MRI contrast agents was facilitated by adding a further amphiphilic silica shell structure. *In vivo* application was tested using both MRI and optical imaging.

2) Biosignal Physiology Team

This team succeeded in extracting a slowly diffusing water (SDW) signal using a new compartment model, and the SDW compartment signal showed a neural-activity correlated time course more clearly than conventional functional MRI. The results indicate that diffusion functional MRI (DfMRI) has good potential as a new brain functional imaging method. The team also clarified details of the brain diffusion property in a study with regional heterogeneity and age-related change in sub-regions of an internal capsule (IC) evaluated by diffusion tensor imaging. The results may provide important information towards understanding age-related changes and may also be useful for clinical diagnosis of a diseased IC.

The team measured brain metabolites in the medial prefrontal cortex of schizophrenic patients and healthy controls by proton magnetic resonance spectroscopy (^{1}H MRS), and obtained a significant relationship between prefrontal cortex-related neurocognitive functions and brain metabolites in the medial prefrontal cortex. These data suggest that specific metabolites of the medial prefrontal cortex are associated with the neurocognitive deficits in schizophrenia. This was a collaboration study with researchers at Chiba University.

Collaborative studies with active clinical sites have been widely performed 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. Tumor structures were visualized by diffusion tensor imaging in a collaboration study with the NIRS Hospital. Glycosaminoglycan specific MR contrast enabled evaluation of the dysfunction of cartilages around the knee joints; this was done in a collaboration study with Chiba University and Teikyo Chiba Medical Center researchers.

Experiments with a two-photon laser microscope and closely related instruments were performed in order to better understand brain microcirculation. A chronic experimental protocol was developed where the cortical microcirculation of an awake mouse can be longitudinally observed with the two-photon laser microscope through a cranial window. The system allows clarification of cellular and molecular communication between vessels, glia and neurons.

3) Image Analysis Team

PET can visualize various functionalities of living tissues such as receptor density. For fully quantitative functional imaging, the behavior of an administered radiopharmaceutical in target tissues is modeled with a compartment model, and the model parameters are estimated using a time history of radioactivity concentration in arterial plasma and tissue. This team developed algorithms for the compartment model estimation. One approach was based on MAP estimation. The Logan plot is a widely utilized algorithm for neuroreceptor imaging, but its quantitative performance suffers largely from noise in the PET data. The proposed algorithm was found to be robust for the noise and it realized fast and quantitative neuroreceptor imaging. A new algorithm for partial volume correction was also proposed. Anatomical information was acquired from MRI and wavelet transformation was applied to incorporate the brain structure into PET images. The team members also focused their interests on applying the algorithms to actual experimental data derived from both humans and small animals. A reference tissue model was evaluated to quantify the dopamine transporter. The imidazorine subtype-2 receptor was also evaluated as a new target ligand in the brain with rat experiments.

The team developed a new experimental apparatus to measure radioactivity concentration in the arterial plasma of mice. A permitted volume of blood sampling from mice is limited to only around three μL, and a plasma separation and volume measurement should be conducted on this small volume. The team developed a new system, in which sampled blood was dripped onto a specially designed disc with U-shaped channels etched on the surface. The blood was centrifuged, and its volume and radioactivity were measured in the apparatus. The system has been evaluated, and it is going to be commercialized.

4) Imaging Physics Team

PET is a promising method to promote molecular imaging research as well as cancer diagnosis. However there are still strong demands for higher resolution, higher sensitivity and lower cost. Therefore this team carried out basic studies on instrumentation, image reconstruction and data corrections to improve image quality and quantity in nuclear medicine.

For PET, it is essential to arrange detectors close to the object in order to increase sensitivity and avoid loss of spatial resolution due to the angular deviation effect. In practice, however, the parallax error caused by the thickness of the crystals degrades spatial resolution at the peripheral regions of the field-of-view. Therefore we invented a novel depth-of-interaction (DOI) capable detector and developed a prototype brain PET scanner, jPET-D4. Toward practical use, we developed component technologies, such as a modified design for higher resolution and an image reconstruction method to make full use of DOI information.

Based on our core technology for DOI measurement, we proposed a new equipment concept, OpenPET, which is an open-type geometry for PET to visualize a physically opened space between two detector rings. Axial spatial resolution, which was degraded with the extended gap due to the parallax error, was recovered by use of DOI detectors. OpenPET is expected to enable PET image-guided radiation therapy by letting the beams pass though the gap, and extension of an axial field-of-view with a limited number of detectors. At this stage, a small prototype has been developed to show a proof-of-concept.

On the other hand, the recent development of small semiconductor photo-detectors such as Geiger-mode avalanche photodiodes (GAPDs), that can replace conventional photomultiplier tubes, is leading researchers to make available new PET detectors. Therefore we developed a next generation DOI detector, X 'tal cube. The challenging aspect of this work is implementing effective detection of scintillation photons by optically covering all 6 faces of a segmented crystal block with GAPDs. At this stage, a prototype detector with 2 mm isotropic resolution has been developed.

Major publications

1. Zhelev Z, Bakalova R, Aoki I, Matsumoto K, Gadjeva V,

Anzai K, Kanno I. Nitroxyl radicals as low toxic spin-labels for non-invasive magnetic resonance imaging of blood–brain barrier permeability for conventional therapeutics. *Chem Commun (Camb),* **7**, 53-55, 2009

2. Kershaw J, Tomiyasu M, Kashikura K, Hirano Y, Nonaka H, Hirano M, Ikehira H, Kanno I, Obata T: A multi-compartmental SE-BOLD interpretation for stimulus-related signal changes in diffusion-weighted functional MRI. *NMR Biomed*, **22**, 770-778, 2009
3. Shidahara M, Tsoumpas C, Hammers A, Boussion N, Visvikis D, Suhara T, Kanno I, Turkheimer FE: "Functional and Structural Sunergy for Resolution Recovery and Partial Volume Correction in Brain PET", *NeuroImage*, **44**, 340-348, 2009
4. Yamaya T, Yoshida E, Inadama N, Nishikido F, Shibuya K, Higuchi M, Murayama H: A multiplex "OpenPET" geometry to extend axial FOV without increasing the number of detectors, *IEEE Trans Nucl Sci*, **56**, 2644-2650, 2009
5. Yamaya T, Inaniwa T, Minohara S, Yoshida E, Inadama N, Nishikido F, Shibuya K, Lam CF, Murayama H: A proposal of an open PET geometry, *Phy Med Biol*, **53**, 757-773, 2008

4. Research Center for Radiation Protection

Kazuo Sakai, Ph.D.

Director, Research Center for Radiation Protection

Outline of Research Career

In 1982, Dr. Sakai obtained a Ph. D. degree 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 as 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 was a research fellow in the Genetics Division of the Children's Hospital, Harvard Medical School. His research subjects there were gene amplification and cloning of genes responsible for radiosensitivity. He joined the Central Research Institute of the Electric Power Industry in 1999 to research biological effects of low dose radiation. He came to NIRS in 2006.

Contact Point: kazsakai@nirs.go.jp

Objectives

The Research Center for Radiation Protection was 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 end-points 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 activities is not limited to Japan. It has been appointed a Collaborating Center by the International Atomic Energy Agency.

Overview

The Research Center consists of 4 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 Department of Advanced Technologies for Radiation Protection Research consists of 4 sections. In the Advanced Analytical Technology Section, cooperative work with other research groups from inside and outside of NIRS has been carried out to measure trace elements and naturally occurring radionuclides in environmental and biological samples. Also, newly developed analytical techniques to determine trace elements have been compared with conventional ones to show the accuracy of these developed methods.

The Animal Pathology Section has provided technical and diagnostic histopathological support 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 at genetic, molecular and cellular levels, physiological analysis of whole animal models is inevitable for extrapolation to human health. The group supports 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 Animal Research Section also has supported research using Medaka fish by providing tumor-bearing fish, generating transgenic fish, and providing quality control of frozen sperms of qualified strains of Medaka fish.

The Environmental Radioactivity Survey Section initiated three collaborative studies with three universities in Japan. They involved "Construction of the Natural Radiation Exposure Study Network" from the Special Co-ordination Funds for Promotion of Science and Technology of the Ministry of Education, Culture, Sports, Science and Technology. In addition, several collaborative studies were conducted with domestic and foreign institutions. This section also carried out several commissioned projects, utilizing NIRS technologies and facilities.

The Research Center was designated by the International Atomic Energy Agency as a Collaborating Center for Low Dose Radiation. Annual reports for the research outcome in this area have been sent to IAEA and highly valued.

In the Research Center 49 permanent and 34 temporary members actively conducted their research during FY 2010. They produced 85 original papers and 27 reviews and proceedings. The Center held an International Workshop on Radon and Thoron (May 2010) and a symposium on "Regulatory Sciences in Radiation Protection and Their Perspective" (December 2010).

Dr. Kazuo Sakai continued to be the Director of the Research Center; Dr. Hidenori Yonehara, the Director of the Regulatory Sciences Research Group; Dr. Yoshiya Shimada, the Director of the Experimental Radiobiology for Children's Health Research Group; Dr. Mitsuru Nenoi, the Director of the Radiation Effect Mechanisms Research Group; Dr. Satoshi Yoshida, the Director of the Environmental Radiation Effects Research Group; and Dr. Kiyomi Eguchi-Kasai, the Head of the Planning and Coordination Section of the Research Center.

Summary activities in the 2nd Mid-term Plan

In addition to individual research output, one of the greatest outcomes was the establishment of a framework of an international hub function. We have, with support of the International and Research Cooperation Section reinforced connection with international organizations, including IAEA, UNSCEAR, ICRP, WHO, and OECD/NEA.

The activities as a Collaborating Center in the low dose radiation effects were highly valued by IAEA and the renewal for the second term (2010-2013) was endorsed.

For the planning of the 2nd Mid-term Plan and its execution at the early stage of this term, the contribution by Dr. Masahiro Doi (Director, Regulatory Sciences Research Group) should be specially noted, who untimely passed away in 2006.

Toward the very end of the 2nd Mid-term Plan, on 11 March, the Great East Japan Earthquake occurred, followed by the Fukushima Daiichi Nuclear Power Plant accident. The members of the Research Center have been involved in initial monitoring, screening, and other operations in the aftermath of the accident.

Nakaminato Laboratory for Marine Radioecology, only one branch laboratory of NIRS located at the seashore of Hitachinaka City, Ibaraki was closed as of March 31, 2011. Its role had been to provide data for modeling the behavior of radionuclides and radiation dose evaluations in the marine ecosystems. In this branch laboratory the distribution and behavior of artificial radionuclides in the ocean were investigated by actively utilizing external funds. The laboratory also conducted studies concerning environmental issues using natural radionuclides as tracers.

4.1. Regulatory Sciences Research for Radiation Safety and Protection

Hidenori Yonehara, Ph.D.

Director, 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 the 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 of radiation safety regulation. Since March 2007, he has been working as Director of the Regulatory Sciences Research Group.

Contact point: yonehara@nirs.go.jp

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 the information among different stakeholders to bridge the gap between science and society. The research programs of FY 2011 focused on the following four points.

1) Summarizing information on radiation protection issues

The group is summarizing 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 is also constructing 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 is constructing 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 epidemiological studies are collected for the databases. The group is carrying out epidemiological studies on health effects of the exposure to natural radiation sources for the purpose of risk assessment.

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 is developing mathematical models to estimate the risk from exposure to 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 is collecting examples in which risk information on radiation safety would be communicated to the public, and the group is analyzing methods of risk communication with sociological consideration.

Progress of Research

1) Construction of information databases for radiation risk assessment

The issue of radiation protection against exposure due to industrial use of naturally occurring radioactive materials (NORM) has become more significant with wider use of the materials in workplaces. In response to the situation, an original database for information on the exposure due to NORM use has been developed and published on the NIRS website. The database provides a search system by which users can check the level of activity concentration in more than 1000 types of materials and the dose when handling the materials (Fig.4.1).

Long term animal studies have played fundamental roles for studies on radiation effects providing important complementary data to those obtained from human epidemiological studies. NIRS has been carrying out various kinds of the long term animal experiments for many years. To carry out further biological investigations with the latest techniques and using meta-analysis of the animal data, we have been promoting the construction of animal experiment archives. The fundamental design of the

archives was decided on the basis on a previous experiment carried out in NIRS using 6400 C3H/He mice, which were gamma irradiated and grouped into 25 groups according to their doses and dose rates; the design was expanded to be able to record other sets of animal and cell experiments with related bibliographic information. Furthermore, the collaboration with the foreign archive networks has been carried out. The accumulated information and its associated researchers, radiation sources, biological results, macroscopic and microscopic observations, etc. have been registered in "STORE", the international long-term animal experiment archive which is operated within the framework of EURATOM FP7.

2) Development of mathematical models

The group aimed at developing two types of mathematical models for regulatory science. The first type of model gives simulation modeling of carcinogenesis for the main purpose of evaluating the risk of radiation at a low dose of exposure. The second type evaluates the effects of ionizing radiation on environmental biota and ecosystems.

Recently, international concerns about the framework for protection of non-human biota have been increasing and various European and North American countries have separately developed assessment frameworks and tools to evaluate the radiological impact on non-human biota. We applied the assessment tools developed by Europe and the U.S.A. to the environment of Japan and found that the assessment framework can work, although default parameters which are used in the tools were different from the Japanese environment. Therefore, we collected Japanese concentration ratio data from the literature and compared the collected data with default values of the ERICA tool (European assessment model). We also estimated the screening level with the biota-effects data obtained in Japan. To derive the screening level, we used the same method as was used in the ERICA tool. As shown in Fig.4.2, we estimated the 5% hazardous dose rate (HDR_5) was 76.4μGy/h(C.I. 16.0-595μGy/h). The predicted no effect dose rate (PNEDR) was obtained as 10μGy/h, which was the same value as obtained with the ERICA tool. Therefore, we concluded the assessment framework used in ERICA is applicable to the Japanese environment.

3) Epidemiological study

The possible effects of exposures to controllable natural radiation and medical radiation are our main research interests. We conducted a case-control study of residential radon (^{222}Rn) and thoron(^{220}Rn) levels and lung cancer among cave-dwelling residents in Gansu Province, China, in cooperation with researchers inside and outside NIRS. A total of 103 cases and 200 controls were included in the study, and 1-year measurements for radon, thoron and their decay products were made for all subjects. Data analyses are on-going, and lung cancer risk in relation to radon and thoron will be evaluated.

In order to evaluate cancer risk from medical exposures, we continued a meta-analysis of second cancer risk among childhood cancer survivors who were treated with radiotherapy. We selected 26 relevant publications by searching the PubMed database (1950 through 2009), supplemented by hand-searching reference lists of already retrieved papers. In the 26 studies, ERR estimates ranged from 0.004 to 10.2 per Gy, and the combined ERR by a random effects model was 0.61 (95% CI: 0.31, 1.20) per Gy. To examine the dependence of ERR on the age at exposure, a meta-regression including the age at exposure as a covariate was conducted, which suggested a decreasing trend in ERR with increasing age at exposure. Overall, the results of our meta-analysis were consistent with findings from other radiation epidemiological studies except for the apparent higher estimate of ERR per unit dose than that among atomic bomb survivors. Cancer risk from low dose medical exposures remains to be evaluated.

4) Investigation into justification of medical radiological procedures

We surveyed national and international guidelines for making judgments in applications of radiation diagnostic procedures. Guidelines to determine the most appropriate diagnostic imaging examinations and to reduce unnecessary exposure of patients to radiation based on the available evidence are well established in the UK and the USA. A few programs in Japanese undergraduate medical education have been started in order to train students to choose the most appropriate imaging investigation or intervention for patients. Also a few practical tools have been provided in hospitals to assist in communicating an understanding of risk among medical doctors, radiological technicians and patients for various radiodiagnostic examinations and radiation exposure. Results of a survey on risk perception done in FY 2007 were analyzed using risk ranking techniques. The survey was conducted 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 educational level, 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 the 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.

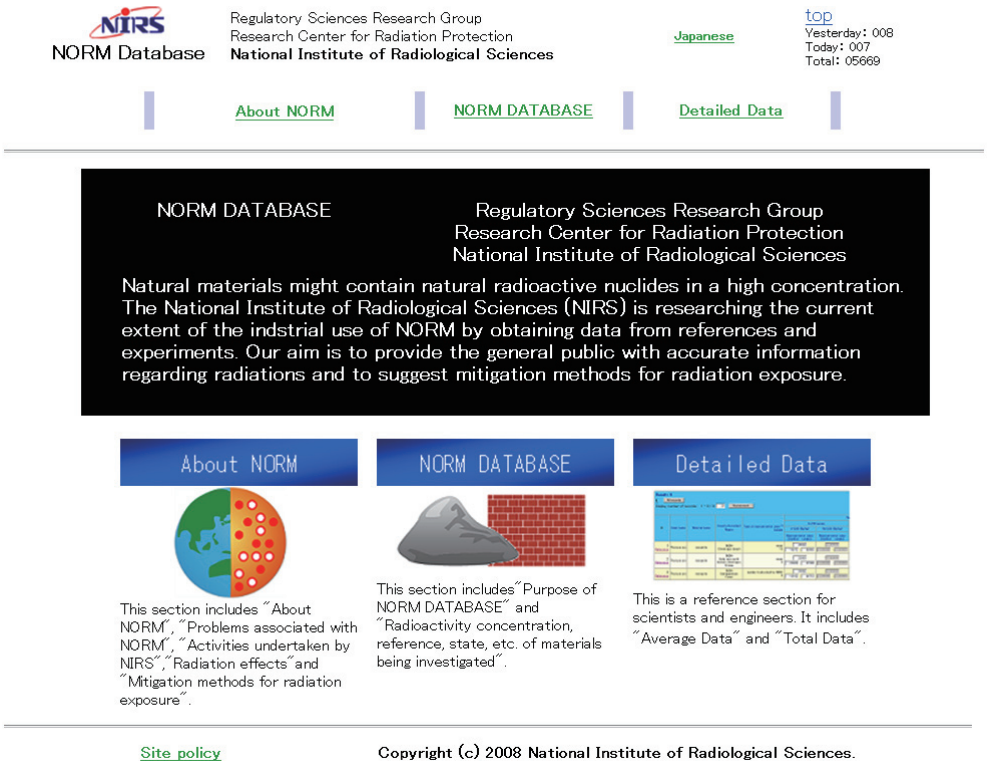

Fig. 4.1. NORM Database English version

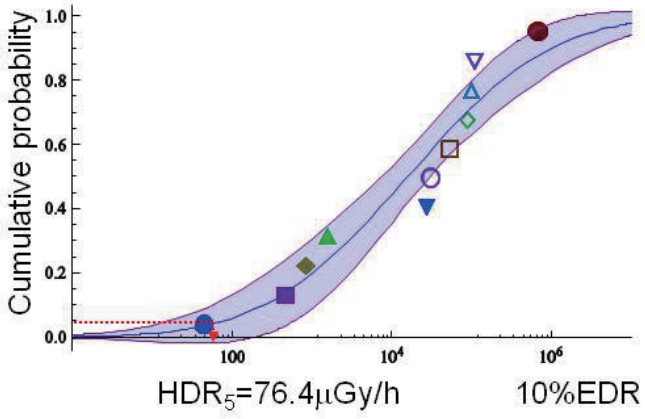

Fig. 4.2. Species sensitivity distribution using Japanese effects data

5) Risk communication on radiation exposure in medicine

A series of meetings called "Dialog Seminars" were held on various themes related to important issues of radiation protection. In the seminars regarding optimization of radiodiagnostic exposure, medical doctors, radiological technicians, experts for radioprotection, and regulators discussed international trends, the present status and experimental and epidemiological data of risk assessments, and the present regulatory status and problems in clinical fields related to protection of medical exposure. Making use of the results achieved from the seminars, materials were published to provide scientific evidence for nurses and the general public to understand the basic principles of justification of radiation exposure in medicine.

The preparation of referral guidelines for application to radiation examinations is in progress; these guidelines will helps\ medical doctors to determine the most appropriate imaging examinations, thus reducing unnecessary exposure of patients.

Major publications

1. Suzuki G, Yamaguchi I, Ogata H, Yonehara H, et al: A National-Wide Survey on Indoor Radon from 2007 to 2010 in Japan, *Journal of Radiation Research*, **51**(6), 683-689, 2010
2. Iwaoka K, Tagami K, Yonehara: H Natural radioactivities in iron and nickel ores imported to Japan and the dose assessment for workers handling these ores, *Journal of Radiological Protection*, **30**(3), 613-620, 2010
3. Ono K, Nobuhiko Ban N, Ojima M, Yoshinaga S, Akahane K, Fujii, K Akiba S, Shimada Y, Kai M, et al: Nationwide survey on pediatric CT among children of public health/school nurses for examining possibility of follow-up study on radiation effects, *Radiation Protection Dosimetry*, doi:10.1093/rpd/ncr165(2011-03-03)
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4.2 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

Dr. 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 radiation carcinogenesis from the viewpoint of a combined effect of environmental carcinogens and the age-at-exposure effect.

Contact Point: y_shimad@nirs.go.jp

Objectives

With the advent of an era of low birthrate and prolonged longevity, concern about the safety of fetuses and children has been growing. Programs to protect the health of fetuses and children from toxic agents are being instituted, particularly in the USA and Europe. The regulations are mainly directed at foodstuffs and chemicals. Recently, a 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 cancer risk of radiation exposure during fetal and childhood periods, for which there are at present insufficient data. Using animal models, we study the effects of radiation exposure on lifespan shortening and cancer induction. Final goals of this research group are to propose age-weighting factors and relative biological effectiveness (RBE) of heavy ions and neutrons for fetuses and children for radiation protection.

Progress of Research

1) Age dependence of lifespan shortening by irradiation in B6C3F1 mice

Fifty female and male B6C3F1 mice per 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 (energy, 290 MeV/u; LET, 13 keV/μm) and neutrons (energy, 2 MeV) at various ages during fetal to mature adulthood periods. The ages at exposure were pre-implantation (3 days post-conception (dpc)), major organogenesis (13 dpc), late fetal (17 dpc), neonatal (1 week after birth), pre-pubertal (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. The mice were observed until moribundity, and their lifespan and the developed cancers were analyzed. Our study indicated that female mice appeared to be more susceptible to radiation-induced lifespan shortening than male mice. The effect of gamma rays on lifespan shortening was more manifest when irradiated at the neonatal than the adult stage. Surprisingly, irradiation with gamma rays at the late fetal stage had little influence on lifespan shortening compared to infant and adulthood exposures. Dose responses of gamma rays (0.2 to 2Gy) for lifespan shortening indicated that the age weighting factor for 17-dpc, and 1 postnatal week against age-at-exposure of 7 weeks was 0.3 and 1.4 in females, and 0.9 and 2.8 in males, respectively. On the other hand, carbon ions were more potent in reducing lifespan than gamma rays especially for neonatal female mice. Fetuses were more susceptible than infants for carbon ion-induced lifespan shortening, suggesting a larger RBE of carbon ions for fetuses than postnatal stages. However, the tumor-free survival rate after carbon- ion exposure was similar to gamma rays, and RBE of 13keV/μm carbon for cancer induction was 1.0 to 1.7 irrespective of gender and age-at-exposure.

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

Radiation risks are dependent upon both the tissue types and the ageatexposure. The breast is one of the most susceptible organs to radiation-associated cancer risk. We have used the Sprague-Dawley (SD) rat mammary cancer model to investigate the age effect of ^{137}Cs gamma rays or carbon ions on breast cancer risk. In FY 2010, pathological diagnosis and autopsy were completed. The incidence of mammary carcinoma tended to increase in groups of rats

irradiated with 1 Gy of either gamma rays or carbon ions at ages between 1 and 7 postnatal weeks but not in those irradiated at fetal or mature adult stages. The dose response for irradiation with either radiation type at 1 week of age showed an irregularity at 2 Gy, which may be due to early cessation of the estrous cycle; otherwise, dose responses of gamma rays were similar among the groups of rats irradiated at 1, 3 and 7 weeks of age. The effect of heavy ions tended to increase with increasing the ageatexposure, indicating RBEs of 0, 1 and 2.5 for 1, 3 and 7 weeks of age, respectively. SD rats at 1, 3 and 7 weeks of age have been irradiated with fast neutrons at 0.05, 0.1, 0.2, 0.5 and 1 Gy for further observation.

Brain tumors (medulloblastoma) in *Ptch1*$^{+/-}$ mice developed in a dose-dependent fashion, showing considerable effects even at a low dose of 0.1 Gy. Late fetal stages were also sensitive to radiation-induced brain tumorigenesis. We confirmed that radiation-induced brain tumors in *Ptch1*$^{+/-}$ mice had interstitial chromosomal deletion, which was characteristic of radiation-induced tumors. This enabled us to distinguish radiation-induced from spontaneous tumors, and consequently led to the finding of radiation-associated brain tumors even at a low dose.

Intestinal tumors, which developed in *Apc*$^{Min/+}$ mice that had received ionizing radiation at early postnatal ages, also exhibited intrachromosomal LOH. This was rarely seen in spontaneous tumors.

The incidence of T-cell lymphomas in B6C3F1 and *Mlh1*$^{-/-}$ mice exposed at 17 dpc-, 2- or 10-week-old was also examined. Infant mice were the most susceptible to radiation-induction of T-cell lymphoma, while irradiation at 17dpc increased splenic lymphoma of T- and B-cell origin. In the thymic lymphoma, frequent frameshift mutations at mononucleotide repeat sequences in *Ikaros* were observed. On the other hand, frequent frameshift mutations at the mononucleotide repeat in *p53* were observed in the splenic lymphoma.

3) Combined effect of radiation and chemical carcinogens/ calorie restriction on tumorigenesis

The age effect of combined exposure to radiation and chemicals has been investigated on pulmonary and intestinal carcinogenesis. For lung tumors, the thoracic region of female Wistar rats was irradiated with X-rays (3 Gy) at neonatal (1 weeks of age), pubertal (5 weeks) or adult (22 weeks) stages, and then *N*-nitrosobis(2-hydroxypropyl) amine (BHP) was intraperitoneally injected one week after irradiation. Synergistic effects of the X-rays and BHP were found in rats exposed at pubertal stages, and the synergistic effect persisted for the interval of 18 months between the treatments.

We also examined the combined effect of a tumor promoter dextran sulfate sodium and radiation on intestinal tumor induction in *Apc*$^{Min/+}$ mice. The regimen gave a significant synergistic effect on colon tumor induction irrespective of the age at exposure. The synergistic effects gradually reduced with increasing intervals between the treatments. These data indicate that radiation-induced damages persist for a while, and that secondary stimuli such as inflammation and regeneration can help them get uncovered.

Calorie restriction (CR) has emerged as the most potently-acting dietary intervention for reducing cancer risk. We estimated the anti-cancer effect of CR in B6C3F1 mice on liver tumorigenesis after infant irradiation. We found that mice irradiated at 1 week of age were susceptible to radiation-induced liver tumorigenesis. CR that started from 7 weeks of age reduced both tumor incidence and lifespan shortening, suggesting that CR is unarguably the most useful remedy to prevent cancer after childhood exposure to radiation.

4) Detrimental effect of uranium on the developing kidney

The health effects on children in depleted uranium–polluted areas and uranium mining areas are of recent concern. Uranium and its compounds have the potential to cause nephrotoxicity. Uranium localization in kidney was examined in immature rats exposed to uranium acetate by microbeam-based quantitative local analysis. At 15 days after administration, the mean uranium concentration in kidney decreased to 53% of the value at day 1. Damaged tubules regenerated at the inner cortex and the outer medulla. Several tubules, however, which still contained uranium at more than 600 times the mean uranium concentration in kidney, were found in the area, indicating persistent site-selective accumulation of uranium. Experimental groups for the late effect of uranium have been set up.

Major Publications

1. Iizuka D, Imaoka T, Takabatake T, Nishimura M, Kakinuma S, Nishimura Y, Shimada Y: DNA copy number aberrations and disruption of the p16Ink4a/Rb pathway in radiation-induced and spontaneous rat mammary carcinomas, *Radiat Res*, **174**, 206-215, 2010
2. Shimada Y, Nishimura M, Amasaki Y, Shang Y, Sawai T, Hirano S, Imaoka T, Kokubo T, Ishida Y, Yamada Y, Takabatake T, Okamoto M, Kakinuma S: Interactions of low dose radiation with other factors in carcinogenesis in vivo, *Health Physics*,**100**, 278-9, 2010
3. Ishida Y, Takabatake T, Kakinuma S, Doi K, Yamauchi

K, Kaminishi M, Kito S, Oota Y, Amasaki Y, Moritake H, Kokubo T, Nishimura M, Nishikawa T, Hino O., Shimada Y: Genomic and gene expression signatures of radiation in medulloblastomas after low-dose irradiation in *Ptch1* heterozygous mice, *Carcinogenesis*, **31**, 1694-1701, 2010

4. Terada Y, Homma-Takeda S, Takeuchi A, Suzuki Y: High energy X-ray microprobe system with submicron resolution for X-ray Fluorescence analysis of uranium in biological specimens, *X-Ray Optics and Instrumentation*, 1-5,2010
5. Yamada Y, Nakata A, Yoshida M, Shimada Y, Oghiso Y, et al.: Implication of p16 inactivation in tumorigenic activity of respiratory epithelial cell lines and adenocarcinoma cell line established from plutonium-induced lung tumor in rat, *In Vitro Cellular & Developmental Biology*, **46**(5), 477-486, 2010

4.3 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.

Contact point:m_nenoi@nirs.go.jp

Objectives

Estimation of the 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 have scientific evidence to necessarily support this assumption. We do not have sufficient scientific data on the effects of low-dose radiation on developmental and differentiational anomalies either. Because it is now considered to be difficult to assess the risk of low-dose radiation from empirical studies with animals or in epidemiological data, this research group conducts mechanistic studies on 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 that can be used as a basis for the development of an appropriate regulatory framework. The following study items are 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 anomalies 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 effect to radiation-induced cancer risk has not been evaluated. We have established a thymus transplantation system for assessing the effect of a microenvironmental change on thymic lymphomagenesis. When thymuses of nonirradiated new-born wild type mice were transplanted in thymectomized, irradiated *scid* mice, T-cell lymphomas of transplanted thymus origin were induced at 0.1 or 0.2 Gy. The results indicate that low doses of γ-rays cause lymphoma induction through a microenvironmental change under a *Prkdc*-deficient condition. Bone marrow transplantation prevented this radiation effect on carcinogenesis by supplying progenitor T cells into transplanted atrophic thymuses and relieving them from radiation-induced thymic hypoplasia, which demonstrated a relationship between induction of lymphomagenesis due to a microenvironmental change and thymic hypoplasia.

To clarify cellular changes due to a microenvironmental change and their involvement in lymphomagenesis, the characteristics of thymocytes in C57BL/6 mice irradiated 4 times with 1.8Gy γ-rays were examined. Reactive oxygen species were generated in irradiated thymocytes at the stage

of radiation-induced thymic atrophy. Concomitantly, DNA double-strand breaks, chromosomal instability, aneuploidy with trisomy 15, and bystander effects on chromosomal aberration induction in co-cultured DNA repair-deficient mutant cells occurred, suggesting that reactive oxygen species were involved in the nontargeted effects. The emergence of thymic lymphomas from the thymocyte population containing abnormal cell clones indicated that clones with trisomy 15 and altered karyotypes were prelymphoma cells with the potential to develop into thymic lymphomas. Thus, delayed nontargeted radiation effects drive thymic lymphomagenesis through the induction of characteristic changes in T-cell precursor/progenitor cells and the generation of prelymphoma cells.

2) DNA Repair Gene Research Team

DNA double strand breaks (DSBs) are highly cytotoxic lesions that are generated by ionizing radiation (IR), various DNA-damaging chemicals and DNA replication itself. Failure to repair DSBs, or their misrepair, may result in cell death or genome rearrangements, including chromosomal deletions and translocations. Resulting alterations in some genes can promote carcinogenesis and accelerate aging. The repair of DSBs is indispensable for genomic integrity. Cells, therefore, are invested in at least two pathways to repair DSBs, namely homologous recombination repair (HRR) and non-homologous end-joining (NHEJ). In higher organisms, NHEJ can function in all phases of the cell cycle and is the predominant repair pathway. 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. To define the biological roles of NHEJ-related genes on DNA damage response, we utilized three cell lines, established by another research program in our institute, having *XRCC4*, Artemis and *MDC1* (mediator of DNA damage checkpoint 1) disrupted, respectively, by a gene targeting technique in a human colon tumor cell line HCT116. Through the end of FY 2010, we have demonstrated higher sensitivities of these three knockout cell lines to IR and various chemical reagents that induce different types of DNA damages by a survival assay in comparison with parental HCT116 cells. Frequencies of chromosomal aberration induced by IR were also significantly higher in all deficient cell lines than those in the parental cells. *HPRT* gene mutation frequency was significantly increased in a dose-dependent manner in *MDC1*$^{-/-}$ cells after exposure to X-rays (0.5-2 Gy). We also demonstrated that MDC1 closely correlates with regulation of the phosphorylation, at least, of ATM and DNA-PKcs after IR. In addition, we showed that enhanced expression levels of genes coding for factors related to DNA replication, cell cycle and DNA repair were exhibited in *MDC1*$^{-/-}$ cells in compared with parental HCT116 cells under the normal culture condition by use of a DNA micro-array analysis, while the expression levels of genes related to translation and protein folding were suppressed. Interestingly, we found that MDC1 is associated with the expression of genes coding for factors which function in pathways of aging and circadian rhythms.

In our most recent study, we determined the frequency of random DNA integration in *MDC1*$^{-/-}$ cells to clarify whether MDC1 makes an impact on NHEJ function, since it has long been postulated that most random integration events result from NHEJ. The frequencies of random integration of plasmid-DNA significantly declined in *MDC1*$^{-/-}$, *XRCC4*$^{-/-}$ and *Artemis*$^{-/-}$ cells to 44%, 19% and 46% of parental HCT116 cells, respectively. This suggests that MDC1 clearly participates in NHEJ function through interactions with some NHEJ components. To attest the authenticity of the outcomes from the DNA micro-arrays, quantitative real-time RT-PCR was performed on 10 genes of interest (CDC6, CHAF1A, CHAF1B, TREX1, UBE2C, WEE1, DDIT3, KLF4, PER1, PPARG) which significantly altered the expression levels in *MDC1*$^{-/-}$ cells in the micro-array analyses. Expression ratios of genes except for TREX1 were consistent with the profiles obtained in DNA micro-array analyses. This suggests that these genes might be modification factors under MDC1 governance for the risk of IR. In any event, MDC1 may regulate many aspects of DNA damage response pathways, and is likely closely associated with the recruitment, activation and retention of the DNA damage signaling and repair components. Subsequently, MDC1 may play a crucial role in the mammalian DNA damage responses.

Meanwhile, since Ku70 plays a key role as a sensor of DSBs induced following exposure to IR, we established *Ku70*-deficient epithelial cell lines from murine lungs lacking Ku70 to elucidate whether Ku70 plays a role in the low-dose radioresistance of lung epithelial cells. *Ku70*$^{-/-}$ lung epithelial cells exhibited a reduced Ku80 expression and were more sensitive than controls (*Ku70*$^{+/-}$ lung epithelial cells) to low-dose X-irradiation (<0.5 Gy). We also found that consistent with the Ku70 function as a sensor of DSBs, Ku70 mainly localized in the nuclei of murine lung epithelial cells. These findings clearly indicate that Ku70 plays a key role in the regulation of the Ku80 expression level in, and the radioresistance of, lung epithelial cells. Finally, our experimental systems utilizing human and murine cell lines deficient in NHEJ related genes could be useful for studying the molecular mechanisms of response to DNA damage induced by

radiation and a variety of chemotherapeutic drugs.

3) Developmental Anomalies Research Team

The effects of low-dose γ-rays on the embryonic development of animal cells are not well studied. Melanocytes, neural crest-derived cells, are a good model to study the effects of low-dose γ-rays on the proliferation and differentiation of animal cells, since they possess a high proliferation rate in the embryonic stage and visible pigment (melanin) as a differentiation marker. To elucidate the mechanism of the effects of low-dose radiations on the proliferation and differentiation of melanocytes in the epidermis and hair bulbs at the cellular level, pregnant females of C57BL/10J mice at 9 days of gestation were whole-body irradiated with a single acute dose of γ-rays (0.1, 0.25, 0.5, and 0.75 Gy) at a dose rate of 0.3 Gy/min. The effects of γ-rays were studied by scoring changes in the development of epidermal melanoblasts and melanocytes, hair follicles, and hair bulb melanocytes at 18 days in gestation. The number of epidermal melanoblasts and melanocytes, hair follicles, and hair bulb melanocytes in the dorsal and ventral skins was markedly decreased even in 0.1 Gy-treated embryos ($P < 0.001$), and the number gradually decreased as dose was increased from 0.1 Gy. The effects on the ventral skin were greater than those on the dorsal skin. A dramatic reduction in the number of melanocytes compared to melanoblasts was observed in the ventral skin, but not in the dorsal skin. These results suggest that the low-dose γ-rays elicit the death of melanoblasts and melanocytes, or inhibit the proliferation and differentiation of melanoblasts and melanocytes with greater effects on the ventral skin, even at the low dose (Fig.4.3).

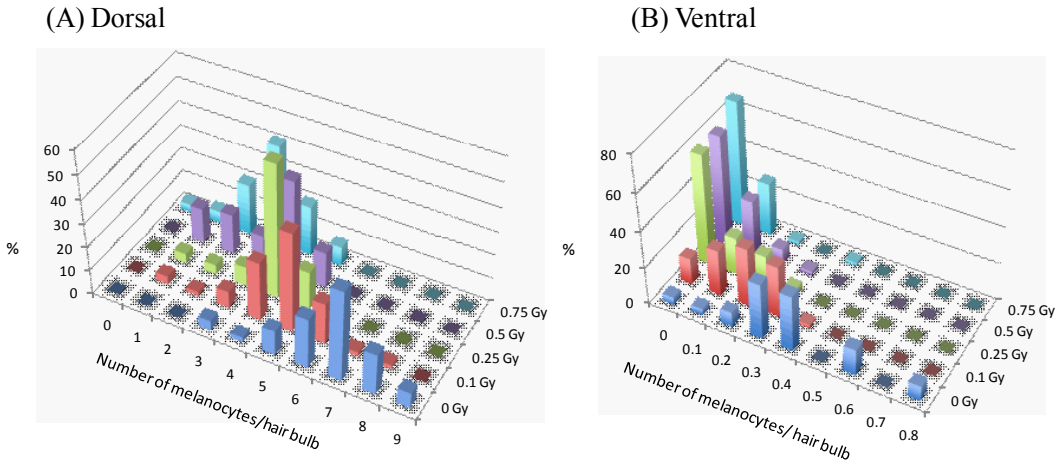

Fig.4.3. Histogram of the number of hair bulb melanocytes in the dorsal and ventral skins exposed to γ-rays. The number of hair bulb melanocytes in the control and irradiated embryos exhibits the normal distribution both in the dorsal (A) and ventral (B) skins. The distribution of hair bulb melanocytes is gradually shifted from higher to lower level after exposure to increasing doses of γ-rays in both the skins.

4) Radioadaptive response research team

We have described the existence of adaptive response (AR) in mouse embryos exposed to X-rays *in utero*. AR was described as a reduction in prenatal deaths and congenital malformations in animals pre-exposed to low doses of X-rays. On the postu-lation that priming exposure activates genes involved in the protection against ionizing radiation (IR), we analyzed transcriptome modulations in mouse embryos exposed to different low doses of priming IR, which were or were not efficient in inducing AR in this model. Gene modulations resulting from AR-inducing and non-AR-inducing priming exposure were compared and AR-specific gene regulations were identified. AR-specific genes were involved in various molecular functions and pathways (including DNA repair, cell signaling, developmental growth factors or tumor pro¬tein p53-related pathways). Identification of the molecular pathways underlying AR in mouse embryos required the use of an experimental model, which would overcome the technical difficulties inherent to *in utero* studies. We developed a model consisting of micromass cultures of limb bud cells, which gave us the opportunity to reproduce *in vitro* biological properties of our *in utero* model. We showed that the teratogenic effects of IR in mouse embryos result from radiation-induced apo¬ptosis; decreased apoptosis was observed in the limb buds of adapted embryos and in adapted cultured limb bud cells. In this study, we evaluated the role of three candidate genes in the apoptotic AR in the micromass cultures of limb bud cells: Csf1, Cacna1a and Tead3. Gene silencing of these three genes abrogated AR. Knowing that TEAD3 protein levels are significantly higher in adapted cells and

that YAP/TAZ/TEAD are involved in the control of cell proliferation and apoptosis, we suggest that modulation of Tead3 could play a role in the induction of AR in our model, seen as a reduction of radiation-induced apoptosis and a stimulation of proliferation and differentiation in limb bud cells.

Major Publications

1. Hirobe T, Eguchi-Kasai K, Sugaya K, Murakami M: Effects of Low-dose Heavy Ions on the Postnatal Development of Mice and the Yield of White Spots in the Mid-ventrum and Tail-tips, *Journal of Radiation Research*, **52**(3), 278-286, 2011
2. Hirobe T, Eguchi-Kasai K, Sugaya K, Murakami M: Effects of Low-dose g-rays on the Embryonic Development of Mouse Melanoblasts and Melanocytes in the Epidermis and Hair Bulbs, *Zoological Science*, **28**(6), 389-396, 2011
3. Koike M, Yutoku Y, Koike A: Establishment of Ku70-Deficient Lung Epithelial Cell Lines and Their Hypersensitivity to Low-Dose X-Irradiation. *Journal of Veterinary Medical Science*,**73**(5),549-554, 2011
4. Bing W, Tanaka K, Vares G, Shang Y, Fujita K, Ninomiya Y, Nakajima T, Eguchi-Kasai K, Nenoi M: X-rays-induced radioresistance against high-LET radiations from accelerated heavy ions in mice, *Radiation Research*, **174**(4), 532-536, 2010
5. Varès G, Wang B, Tanaka K, Shang Y, Taki K, Nakajima T, Nenoi M: Gene silencing of Tead3 abrogates radiation-induced adaptive response in cultured mouse limb bud cells. *Journal of Radiation Research*, **52**(1), 39-46, 2011

4.4. Studies on Environmental Radiation Effects

Satoshi Yoshida, Ph.D.

Director, Environmental Radiation Effects Research Group

Outline of Research Career

Dr. Yoshida received a B.E. in safety engineering from Yokohama National University in 1983 and a M.E. and 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.

Contact point: s_yoshid@nirs.go.jp

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 investigates three subjects related to environmental radiation and radioactivity: i.e. 1) effects of radiation on organisms and ecosystems; 2) exposure of the 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 2006 - 2010.

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 conducted studies to evaluate the effects of radiation on representative terrestrial and aquatic organisms as well as studied to estimate radiation doses on those environmental organisms. In addition, the group developed 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, plant and animal terrestrial organisms, particularly cedar trees, fungi, earthworms and collembolans, were selected due to their high radio-sensitivity or their important roles in the maintenance of the terrestrial ecosystem. At first the relationships between dose and classical effects such as those on the survival, growth or reproduction for radiation were investigated. As a number of studies have shown that gene expression analysis is a promising sensitive biomarker, a novel technology, high-coverage expression profiling (HiCEP), developed by researchers in NIRS, was applied in order to detect the radiation responsive genes in these organisms that had no genome information. The HiCEP analysis showed that several transcript-derived fragments (TDFs) were up-regulated by irradiation, and sequencing the TDFs revealed that a few of them were similar to genes relating to DNA repair and response to oxidative stress. Particularly, poly (ADP-ribose) polymerase I gene was identified as a sensitive radiation responsive gene in several animals and plants, springtail (*Folsomia candida*), a model plant (*Arabidopsis thaliana*) and an earthworm (*Enchytraeus japonensis*).

The biological effect of long-term irradiation has more relevance to study in radiation ecotoxicology. Therefore, the effects of chronic exposure were studied. The model plant *A. thaliana* was exposed to gamma rays for 2 weeks at a dose rate of 20 Gy/day and then was assessed for gene expression and metabolic analyses.

The effects of high LET radiation on terrestrial ecosystems must be considered because many radiation sources in the environment could be alpha and beta emitters as well as gamma emitters. Based on the idea that an exposure study of environmental organisms to heavy ions at NIRS-HIMAC might provide valuable information to judge whether or not the radiation weighting factors

defined in human radiation protection could be applied to the other environmental organisms, the effects of heavy ions were studied in *E. japonensis* using HIMAC. Heavy ions clearly showed stronger effects than gamma rays with respect to the growth inhibition of the earthworm.

Aquatic Radiation Ecotoxicology Research Team

Radiation effects were investigated in some selected organisms such as phytoplankton, duckweeds, daphnia and medaka (*Oryzias latipes*). Mortality, reduced ingestion rates, brain apoptosis, and thymic involution were adopted as endpoints to obtain dose-effect relationships and 50 % lethal or effect doses (LD_{50} or ED_{50}). Some of these results are cited in the ICRP Publication 108 and contributed to updating the FREDERICA radiation effects database through IAEA EMRAS II.

Radiation effects at the community or ecosystem level were also investigated in several types of experimental ecosystem models, i.e., microcosms. Interesting results were observed in the flooded paddy soil microcosms. A bacterial community structure detected by denaturant gradient gel electrophoresis (DGGE) of 16S rDNA was affected after chronic gamma-irradiation at a dose rate of as low as 1 Gy/d for 5 days. Some of the observed effects were increases in the relative abundance in specific species of the genera *Clostridium* and *Massilia*. This positive effect is unexpected from a conventional single-species approach. Additionally, the concentrations of sulfate ion increased in the liquid phase of the irradiated microcosm, while concentrations of Na^+, Ca^{2+}, F^- and soluble iron decreased. This suggests that the low dose of irradiation affected material cycles, i.e., ecosystem functioning. These effects may have been caused by the bacterial community structure change.

2) Exposure to natural radiation

Since natural radioactive substances and cosmic radiation at high altitudes 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 investigated the concentration and exposure doses of radon (^{222}Rn), thoron (^{220}Rn), and related radionuclides, mainly in areas with high natural radiation, and analyzed the results together with epidemiological data. The group also collected scientific information on dose and effects of cosmic radiation in aircraft and is working to provide them in an intelligible and easily accessible 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). We have conducted an epidemiological study (case-control study) in China, in cooperation with the Radiation Epidemiology Team of the Regulatory Sciences Research Group. Passive radon detectors developed by NIRS were used for this study. Measurements with passive detectors was conducted as follows: (1) a large number of passive detectors were assembled at NIRS; (2) these detectors were sent to China by post; (3) Chinese collaborators placed them in dwellings selected in studied areas; (4) they were retrieved after six months of exposure; (5) the exposed detectors were sent back to NIRS; and (6) they were processed at NIRS and radon concentration for each dwelling was estimated. This work has been conducted since 2007. The last series of measurements was finished in 2010 and we have now obtained residential radon concentration data for around 100 lung cancer cases and 200 controls.

We also investigated potential exposure due to natural radionuclides contained in building materials used in Japan. Building material samples were collected for this purpose and radon exhalation rates were measured for these samples. A simulation program was developed to estimate exposure due to radon exhaled from building materials. the program includes a room model and calculates indoor radon concentration and its changes with time by inputting radon exhalation rate for a building material used, together with related environmental parameters.

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 aircraft crew of Japanese airline companies. At aviation altitudes, they are exposed to enhanced cosmic radiation of which the annual personal dose generally exceeds 1 mSv. However, the situation and health effects of cosmic radiation exposure are still uncertain. The team therefore made efforts to collect scientific information on doses and effects of cosmic radiation and also to provide them to the general public. Major tasks were: (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 tool named "Japanese Internet System for Calculation of Aviation Route Doses (JISCARD)" available on the NIRS home page. In FY 2010, we carried out in-flight measurements onboard a commercial jet aircraft from New York to Seoul using a moderator-type neutron detector for verification of the calculation code. Satisfactory agreement was found between the estimated and observed results. A real-time, continuous monitoring system of cosmic-ray

neutrons in the upper atmosphere has been constructed at the summit of Mt. Fuji. Also, we continue to cooperate with airline companies in Japan, regarding management of cosmic 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 focused on the development of highly sensitive analytical methods for important radionuclides (e.g., plutonium, americium, iodine, etc.) for which data are scarce, and provided data on their activities and isotopic ratios to understand their environmental behavior in marine ecosystems.

Marine Radioecology Research Team

Anthropogenic radionuclides have been released into the environment as the result of atmospheric nuclear weapons testing, nuclear fuel reprocessing, disposal of nuclear waste, and accidental releases from nuclear power plants. To understand their environmental behavior and make dose assessments, development of a highly sensitive analytical method is required. We established a highly sensitive mass spectrometric method for precise and accurate determination of activity and isotopic ratios for isotopes of U and Pu, and ^{241}Am by the combination of a high-efficiency sample introduction system with sector-field ICP-MS. The obtained detection limits for Pu isotopes and ^{241}Am were among the best obtained by any system in the world. These newly developed methods have been applied to sample determinations for seawater, settling particles, sediment and soil . In addition, we also developed a sensitive hyphenation technique, HPLC-ICP-MS for the speciation of stable iodine in seawater, considering the fact that the chemical form of radionuclides is one of the most important factors controlling their environmental behavior in the ocean.

To deal with the problem of global warming, rapid growth in nuclear power generation is expected in East Asia. For the purpose of rapid source identification and risk assessment for any future radioactive contamination in the marine environment, we made particular efforts to investigate the distribution of the Pu isotope ratio (^{240}Pu/^{239}Pu) and the mechanism controlling the transport of Pu in the Pacific Ocean and its marginal seas. The atom ratio of ^{240}Pu/^{239}Pu in surface water from Sagami Bay was found to be 0.224 ± 0.014 and showed no notable variation from the surface to the bottom with the mean atom ratio being 0.234 ± 0.004. The atom ratios for the Pacific coast, near the Rokkasho Nuclear Fuel Reprocessing Plant, were approximately the same as 0.224 obtained in Sagami Bay. The mean ^{240}Pu/^{239}Pu atom ratio in water columns in the Japan Sea was ~ 0.240 and there was no spatial variation of this ratio in the Yamato and Tsushima Basins. For the sediments collected from the Japan Sea, the East China Sea, and coastal areas in the North West Pacific, for example, in Sagami Bay and Hiroshima Bay, the ^{240}Pu/^{239}Pu atom ratios ranged from 0.20 to 0.30, while in most surface sediments, a mean of 0.24 was observed. The distribution of Pu with the ^{240}Pu/^{239}Pu atom ratio significantly higher than the mean global fallout ratio of 0.18 in the marine environment in the North West Pacific and its marginal seas was attributed to the transport and scavenging of close-in fallout Pu originating from the Pacific Proving Grounds and carried by the North Equatorial Current and Kuroshio Current. The ^{240}Pu/^{239}Pu atom ratios in seawater and marine sediments obtained in the past years in the North West Pacific will provide useful baseline data for the identification and estimating the extent of radioactive contamination from the accident at the Fukushima Dai-ichi Nuclear Power Plant.

Major Publications

1. Yoshida S, Watanabe M, Suzuki A: Distribution of radiocesium and stable elements within a pine tree, *Radiation Protection Dosimetry*, **146**,326-329, 2011
2. Ishii N, Fuma S, Tagami K, Honma-Takeda S, Shikano S: Responses of the bacterial community to chronic gamma radiation in a rice paddy ecosystem, *International Journal of Radiation Biology*, **87**, 663-672, 2011
3. Hassan NM, Ishikawa T, Hosoda M, Iwaoka K, Sorimachi A, Sahoo SK, Janik M, Kranrod C, Yonehara H, Fukushi M, Tokonami S: The effect of water content on the radon emanation coefficient for some building materials used in Japan, *Radiat. Meas*., **46**, 232-237, 2011
4. Yasuda H, Sato T, Yonehara H, Kosako T, Fujitaka K, Sasak Yi: Management of Cosmic Radiation Exposure for Aircraft Crew in Japan, *Radiat. Prot. Dosim*., **146**, 123-125, 2011
5. Liu ZY, Zheng J, Pan SM, Dong M, Yamada M, Aono T, Guo QJ: Pu and ^{137}Cs in the Yangtze River Estuary sediments: distribution and source identification, *Environmental Science & Technology*, **45**, 1805-1811, 2011

4.5. 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 30 years' experience in the fields of radioecology and environmental radiochemistry, with special 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, and U. He has improved models and parameters for radionuclides in soil-to-crop systems. Most recently, he has been working on a project to collect and estimate environmental transfer parameters of radionuclides in relation to radioactive waste management.

Contact Point: s_uchida@nirs.go.jp

Objectives

It is necessary to provide environmental transfer parameters for radiation dose assessments from radionuclides released from radioactive waste disposal sites. To obtain suitable parameters for the Japanese biosphere, this team has been studying four topics: (1) behavior of radionuclides in Japanese estuarine areas; (2) prediction of the behavior of the key radionuclides (^{14}C and ^{129}I) in transuranic waste (TRU); (3) transfer of radon from soil to the air; and (4) development of estimation methods for environmental parameters.

Progress of Research

1) Behavior of radionuclides in Japanese estuarine areas

More than 40 elements in water samples were analyzed for the estimation of the behavior of stable elements and radionuclides in selected Japanese estuarine areas. Estuarine water to biota concentration ratios (C_Rs) of various elements were also obtained as analogues of radionuclides for algae, molluscs, and crustaceans, in eight estuarine areas around Japan (Fig. 4.4). When the obtained geometric means of C_Rs were compared with the C_Rs recommended in IAEA Technical Report Series 422 for marine organisms, no big differences between them were found. Some elements tended to be concentrated in internal organs of biota collected in the estuarine areas.

2) Prediction of the behavior of the key radionuclides (^{14}C- and ^{129}I) in transuranic waste (TRU)

Production of ^{14}C-containing gas from soil was studied using ^{14}C in sodium acetate form. These production ratios were determined by batch tests using 142 agricultural (upland and paddy) soil samples. Each of the soil samples was suspended in deionized water containing either [1-^{14}C] or [1,2-^{14}C] sodium acetate and shake-incubated for 7 days. Average production ratios were 69% for [1-^{14}C] sodium acetate and 59% for [1,2-^{14}C] sodium acetate. From the results, the ^{14}C-containing gas production ratio for [2-^{14}C] sodium acetate was calculated to be 50%. The carboxyl group of sodium acetate, therefore, is easily released as gas in Japanese agricultural soils.

3) Transfer of radon from soil to the air

A continuous measurement system, with a ventilation-type accumulation chamber, was developed for radon exhalation rate determination. A reasonable sampling flow rate was estimated to be less than 0.2 L min^{-1}. In the field, radon exhalation rates were investigated in Gunma and Kagoshima Prefectures. Radon and thoron exhalation rates ranged from 72% to 74% and from 80% to 120%, respectively.

4) Development of estimation methods for environmental parameters

Based on databases such as Database for Soil Analysis in Japan and Food Composition Database, estimation models of soil-to-plant transfer factors for six elements (Ni, As, Se, Cs, I, and Ra) were developed. Soil characteristics (clay content, pH, EC, CEC, exchangeable Ca, exchangeable K, active Fe, water content, total carbon, and total nitrogen) and elements in crops (P, Ca, Fe, K, Mg, Mn, Na, Cu, Zn) were used as explanatory variables for multiple regression models. When the Food Composition Database was used for the estimation of soil-to-plant transfer factors, a good correlation was found between estimated values and actual measured values.

Major Publications

1. Takata H, Aono T, Tagami K, Uchida S: Concentration

ratios of stable elements for selected biota in Japanese estuarine areas, *Radiation and Environmental Biophysics*, **49**(4), 591-601, 2010

2. Tagami K, Uchida S, Takeda A, Yamazaki S, Tsuchiya N: Estimation of plant unavailable iodine concentrations in agricultural fields, *Soil Science Society of America Journal*, **74**(5), 1562-1567, 2010

3. Ishii N, Koiso H, Takeda H, Uchida S: Partitioning of 14C into solid, liquid, and gas phases in various paddy soils in Japan, *Journal of Nuclear Science and Technology*, **47**(3), 238-243, 2010

4. Hosoda H, et al: Influence of soil environmental parameters on thoron exhalation rate, *Radiation Protection Dosimetry*, **141**(4), 420-423, 2010

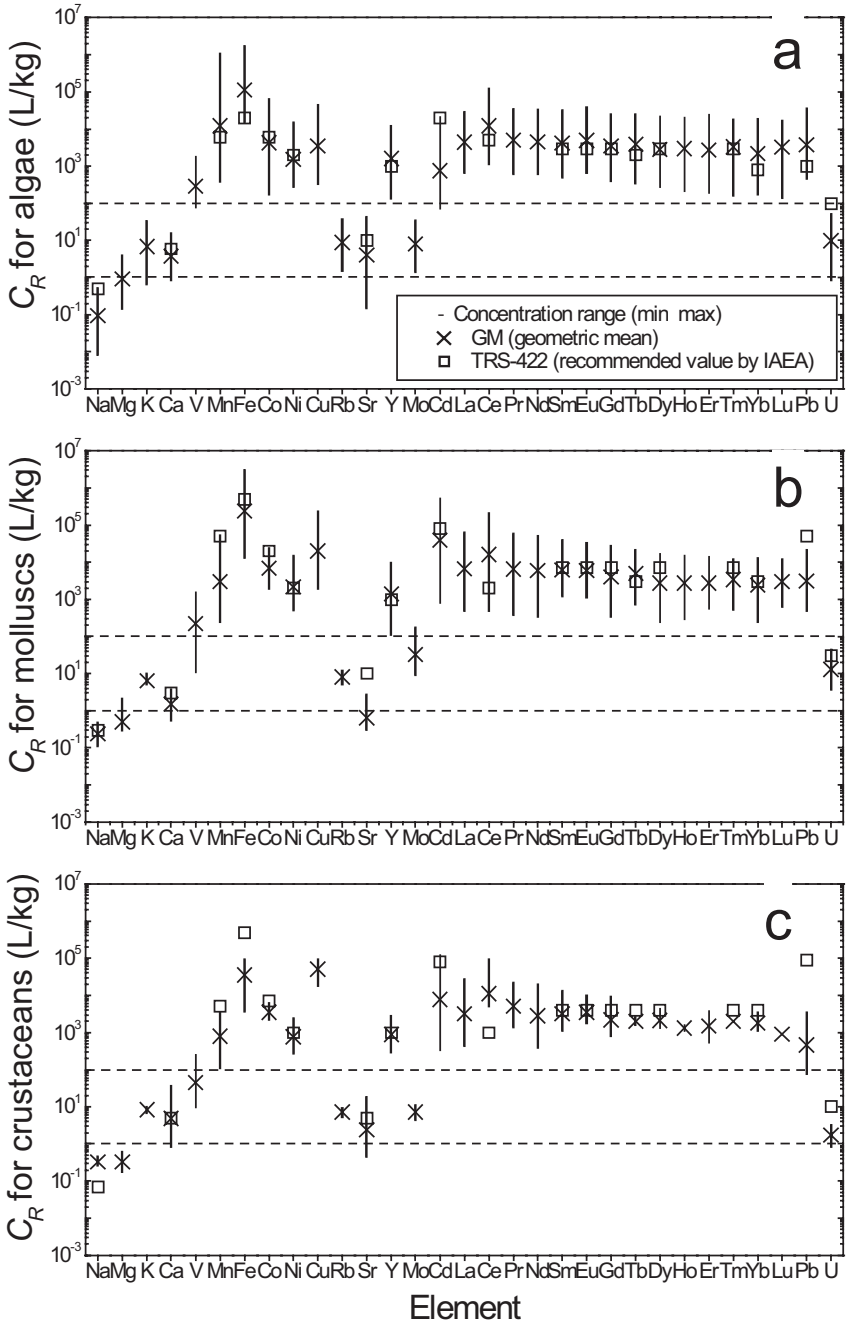

Fig. 4.4. C_Rs of the whole body for (a) algae, (b) molluscs, and (c) crustaceans collected in eight Japanese estuarine areas. Dashed lines indicate C_R values of 1 and 100 L/kg.

5. 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 the 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 Tokai-mura criticality accident. He took the lead and made great efforts when NIRS formed the Radiation Emergency Medical Assistance Team (REMAT) program which aims to support primary medical care when exposure to radiation or radioactive materials contamination incidents and accidents have occurred. These activities were initially focused on events overseas, but have been expanded to include Japan. He also has been providing advice and support as an expert regarding radiation emergency medicine for the TEPCO Fukushima Daiichi Nuclear Power Plant accident caused by the Great East Japan Earthquake of 2011.

Contact point: akashi@nirs.go.jp

Objectives

This 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. Thus, it had the unique experience of receiving three victims heavily exposed to radiation at the JCO criticality accident of Tokai-mura in September 1999. The Center is responsible for, and has established a solid system for dealing with radiation emergencies from a medical viewpoint. Our required missions 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 radiation emergencies.

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 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 nuclear power station emergencies to the Basic Plan for Disaster Prevention. This plan was reinforced in 2000 following the criticality accident at Tokai-mura in the previous year. The plan was also revised in 2008 after the Niigata-Chuetsu-Oki Earthquake of 2007 caused damage to a nuclear power plant.

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, the NSC published the guidelines 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).

Since then, the Research Center has carried out a variety of activities to maintain and enhance or strengthen the emergency preparedness system required to fulfill its role as a tertiary radiation emergency hospital.

As the latest significant activity of NIRS, we established the Radiation Emergency Medical Assistance Team (REMAT) program in January 2010. During 2010, the first activity year of the REMAT program, team members participated in not only many domestic drills but also international exercises or events such as at APEC as a comprehensive expert team dealing with radiation and nuclear accidents. Verification of the status and use of equipment and testing a communication network between the on-site team and support team at NIRS have also been performed during REMAT activities.

On 11 March 2011, a nuclear accident occurred at TEPCO Fukushima Daiichi Nuclear Power Plant of the Tokyo Electric Power Co, which was caused by a massive earthquake and accompanying tsunami. Utilizing to the fullest extent our knowledge, capabilities, experiences and REMAT's own equipment, NIRS has been coping with the accident since the first day. The responses to the accident have become a very important mission for us and an example of the intra-organizational activities of NIRS. REMAT members have played a central role in these activities. To give prompt and accurate advice from the viewpoint of radiation emergency medicine, dose assessment or radiation protection, REMAT members and many other NIRS staff have been sent to the offsite center, J-Village which became a staging area for first responders. These are ongoing activities in the present fiscal year.

1) Network System

The primary goal is to strengthen 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.

On 8 November, NIRS conducted a self-imposed exercise for accepting a contaminated victim. In order to enhance the cooperation among these network councils, NIRS organized a meeting to exchange opinions from the viewpoint of each specialism after the drill. After the drill, observers from the councils exchanged views at a meeting regarding how to improve performance when NIRS staff members accept contaminated patients.

1-1) Topics in the NIRS Radiation Emergency Medicine Network Council

This is a group of experts in radiation emergency medicine or health physics for treatment of patients in cooperation with NIRS at the time of a nuclear disaster or a radiation accident. In an emergency, the cooperation involves sending an expert to NIRS, arrangement of acceptance of patients at medical facilities affiliated with the specialized organization, and providing advice. Such collaboration is expected to reinforce the functions of NIRS. This is called 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. A communication exercise was done for members of the council as a general drill for radiation emergencies on 8 November 2010 and the council annual meeting was held on 10 February 2011.

In addition to the activities of this council, since September 2006 NIRS has had agreements on enhancement for the system of radiation emergency medical cooperation with six hospitals: The University of Tokyo Hospital; The Institute of Medical Science of The University of Tokyo; the Disaster Medical Center; the Nippon Medical School Hospital; the Nippon Medical School Chiba Hokusoh Hospital; and the Kyorin University Hospital. Some of the council's members belong to these hospitals. The first working-level meeting with these hospitals was held on 14 February 2011.

1-2) Topics in Chromosome Network Council

The Chromosome Network Council (CNC) forms a network among nearly ten experts on cytogenetic radiological dosimetry to strengthen its capability and establish technical standards of dose estimation methods using chromosomes. The members are chosen from six areas of Japan and they will cooperate with NIRS to carry out cytogenetic dosimetry when a severe radioactivity accident or terrorist attack involving radioactive materials occur in Japan. An inter-comparison study on the dose estimation by chromosome analysis is performed by the council members when the national drill for radiation emergencies is held every year.

During the 5-Year Midterm Plan, a common protocol for dicentric chromosome analysis was established by the CNC. Then, in FY 2009 and FY 2010, council members tested premature chromosome condensation (PCC) analysis for high-dose exposure (10 - 30 Gy) and it was confirmed that there were still points to be improved in sample preparation for biodosimetry using the PCC method.

In FY 2008 and FY 2010, NIRS held the "Workshop on Cytogenetic Biodosimetry" for Asian and International Science and Technology Center (ISTC) member states in cooperation with ISTC, IAEA and WHO. The CNC members presented educational lectures for participants

from about 20 countries in both the years on biodosimetry and the past serious cases of radiation exposure in Japan. In the biennial workshops, all participants agreed to share information and to facilitate cooperation, collaborations and networking among Asian countries and member states of ISTC, especially for biodosimetry in population triage in scenarios of mass casualties. This goal will be greatly facilitated by interacting with experts who are attempting to develop the infrastructure.

1-3) Topics in Physical Dosimetry Network Council

This network council is responsible for physical dose evaluation in radiological and nuclear accidents. In FY 2010, the council participated in the exercise conducted by the Japanese government assuming a nuclear disaster at the Hamaoka Nuclear Power Plants in Shizuoka Prefecture. According to the request from the REMAT (Radiation Emergency Medical Assistant Team) sent to one of the aid stations for the public, the council members in remote places far away from the disaster site gave advice on physical dose evaluation through a real-time discussion system. In the council annual meeting, the general concept of various levels for decision making in triage and limitations in practical use were discussed.

1-4) Local organizational system for radiation emergency medicine

In Japan, the medical system for radiation emergencies is currently being constructed in accordance with disaster prevention plans of local governments where nuclear facilities have been established. Within the framework of each local nuclear disaster prevention plan, establishment of a separate collaborative system by each local government with NIRS is mandatory and the plan must specify the steps to be performed in the smooth transfer of patients from an accident site to the medical facility at NIRS, including radiation protection management.

In FY 2010, as the tertiary level hospital of radiation emergency medicine in Japan, NIRS carried out a questionnaire survey of primary and secondary level hospitals dealing with radiation emergency medicine in local governments where nuclear facilities are situated in Japan. Based on the questionnaire results, NIRS was able to summarize the current situation of their equipment and personnel necessary for treating or accepting contaminated victims.

Discussions were also held with local governments in Shizuoka, Niigata, Ibaraki, Miyagi, Hokkaido, Fukushima and Aomori Prefectures to confirm the transportation route, especially use of Japan Self Defense Force (SDF) planes or helicopters, for the victims in each prefecture. Moreover, the rapid transportation of NIRS staff members and their equipment from Chiba to each destination was newly discussed. To achieve speedy transportation of contaminated victims, information on how to cover the inside of an ambulance and a helicopter was provided to the first responders who participated in the local discussions.

NIRS organized an annual general meeting on radiation emergency medicine in Tokyo in January 2011. Medical professionals and administrative officers who are responsible for radiation and nuclear accidents from 19 local governments participated in the meeting. After the presentation from the Nuclear Safety Commission (NSC) regarding the operational new guideline of the Whole Body Counter (WBC) that will soon be made public, all the participants discussed the whole concept of the WBC and how it should be managed by each local government in line with the guideline. In addition to this discussion, NIRS shared information on the results of the hospital questionnaire survey with them and introduced its readiness for dispatching a comprehensive expert team in a radiation emergency based on the request of hospitals or local governments. Personnel from the relevant ministries and agencies such as the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Ministry of Health, Labour, and Welfare (MHLW), Ministry of Defense (MOD), and Fire and Disaster Management Agency (FDMA) also attended.

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 treating victims from a nuclear disaster, first responders, and nuclear establishment employees. For that purpose, NIRS holds the following courses regularly 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. From FY 2010, response to malicious events and transport accidents of radioisotopes were newly added to the following course curriculums.

2-1) NIRS Course “Radiation emergency medicine (hospital course)”

In FY 2010, this 3-day course was designed for physicians, nurses, and radiological technologists who may receive victims exposed to radiation and/or contaminated with radionuclides. The course was held from 27-29 September with 26 participants. Some of them are working actively in primary or secondary levels of radiation emergency hospitals and playing an important

role in local radiation emergency systems.

In addition to this course, in response to a request from Hirosaki University School of Health Sciences, another the hospital course was organized for medical professionals of this university from 8-10 March 2011. There were 19 participants in the course. Aomori Prefecture has a reprocessing factory for nuclear fuel in addition to nuclear power plants. The Hirosaki University Hospital is one of the main local hospitals and it is responsible for radiation emergency medicine in Aomori Prefecture. Upon this background, NIRS and the Hirosaki University first exchanged a memorandum of understanding (MOU) in the field of radiation emergency medicine in 2008.

2-2) NIRS Course "Radiation Emergency for first responders (pre-hospital course)"

This 3-day course was primarily designed for first responders such as fire or police department personnel, paramedics, and emergency planners at nuclear facilities. The course was held from 13-15 December 2010 with 25 participants including personnel from the Japan Coast Guard and the Japan Ground Self-Defense Force.

3) Exercises for Radiation Emergency and cooperation for the Asia-Pacific Economic Cooperation (APEC)

National and local governments annually hold nuclear energy disaster prevention drills. In FY 2010, the Japanese government conducted the drill in Shizuoka Prefecture.

NIRS dispatched REMAT members and other staff to the following domestic drills to give advice from the viewpoints of medical care and radiation protection. Communication network tests between the on-site team and support team at NIRS were performed when REMAT members were dispatched to the exercises.

a) A medical doctor and a specialist on dose assessment were sent to a nuclear energy disaster prevention drill held in Ibaraki Prefecture from 29 to 30 September 2010.
b) A medical doctor and two specialists on dose assessment of REMAT were sent to a national nuclear energy disaster prevention drill held in Shizuoka Prefecture conducted by the Ministry of Economy, Trade and Industry (METI) from 20 to 21 October 2010. In addition to the team, another medical doctor was dispatched to an offsite center in the same prefecture and a specialist on radiation emergency medicine was also sent to the Emergency Operation Center (EOC) in Tokyo.
c) REMAT members were sent to a nuclear energy disaster prevention drill in Miyagi Prefecture from 4 to 5 November 2010.
d) A specialist on dose assessment was sent to a nuclear energy disaster prevention drill held in Niigata Prefecture on 5 November 2010.
e) Two medical specialists on radiation emergency medicine were sent to a nuclear energy disaster prevention drill held in Hokkaido on 17 November 2010.
f) A medical specialist on radiation emergency medicine was sent to a nuclear energy disaster prevention drill held in Fukushima Prefecture on 26 November 2010.
g) A medical doctor and a specialist on dose assessment were sent to a nuclear energy disaster prevention drill held in Osaka Prefecture conducted by Ministry of Education, Culture, Sports, Science and Technology (MEXT).

Under the Civil Protection Law, since FY 2005 the Cabinet Secretariat and other central government ministries such as the Ministry of Defense (MOD) have conducted joint exercises including field or map drills for civil protection with local governments. As the first field exercise due to a malicious event using a dirty bomb, a joint exercise was carried out in Mito City, Ibaraki Prefecture in January 2011. The Cabinet Secretariat and the local government asked for NIRS to cooperate in advising in various fields such as radiation emergency medicine, dose assessment, and radiation protection. Based on the request, some NIRS members worked on creating the scenario for the exercise from an early stage. In order to support local medical staff, two REMATs were dispatched to the Mito-Saiseikai Hospital, which normally has not been nominated as a primary or secondary hospital in this area but was newly designated to accept many contaminated victims for this exercise. One team from REMAT was transported by a Self-Defense Force's helicopter and another moved by a monitoring car. Besides these field players, a REMAT medical doctor observed the exercise and evaluated the activities conducted by both national and prefectural governments as an evaluating committee member.

From 7 to 8 February 2011, in addition to the above exercises, NIRS conducted an exercise with Hirosaki University and the Japan Nuclear Fuel Ltd. (JNFL) which has a reprocessing factory for nuclear fuel in Aomori Prefecture. In this drill, we developed the scenario and held the drill which contained some blind elements. This scenario included transportation from JNFL to Hirosaki University of a patient who had possible internal exposure. A medical doctor and two specialists on dose assessment and radiation protection were dispatched from NIRS to Hirosaki by train and a monitoring car. A TV conference between NIRS headquarters and university staff was also held as part of the exercise.

To improve our own skills, NIRS also held three self-imposed exercises for the treatment of contaminated victims in July and November 2010. Two of the exercises were focused on the treatment of internal contamination by alpha emitters.

From 12 to 15 November 2010, the Asia-Pacific Economic Cooperation Conference (APEC) summit meeting and ministerial-level meeting were held in Yokohama. The Japanese government established a local headquarters near the venue to safeguard foreign dignitaries in the case of various emergencies. On the basis of requests from the Ministry of Health, Labour and Welfare (MHLW), NIRS assembled response teams to prepare for radiation emergency medicine and created a REMAT program task force at NIRS. One team from the REMAT program that consisted of a medical doctor, two health physicists and a specialist on radiation protection were dispatched to the local headquarters. Two others were also ready to respond for the general public if a malicious event with radioactive materials release occurred at Haneda or Narita Airports.

4) Follow-up Studies

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

4-1) Follow-up examination of the victims of the Bikini Atoll 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 a 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, were also injured from the nuclear fallout. Their medical follow-up aims at studying late radiation effects by examining the health states of these victims over a long period of time. The follow-up examinations that have been conducted for 50 years provide important information. The type of exposure was external and also internal, although internal doses were thought to be relatively small. The estimated whole body doses were 1.7 to 6.9 Gy. Among 23 victims, 14 have already died. In FY 2010, a medical check-up of survivors was conducted for 6 victims at Yaizu City Hospital. Details on the 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, 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 intravascularly for 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. There were no patients who had a medical check-up this year.

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 medical data of the victims of radiation accidents and exchanging information with countries that have developed radiation accident medicine.

6) Operation of 24/7 Radiation Emergency Call System

Since FY 2008, the NIRS has been operating the 24/7 on call radiation 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 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.

7) Other consultation for health effects of radiation

The NIRS receives consultations on health effect of radiation. From 1 April 2010 to 10 March 2011, we received consultations on 24 cases. Of those, 3 cases were consultations on radiation exposure; 18 were consultations on doubtful radiation exposure; and 3, miscellaneous.

On 11 March 2011, Northeastern Japan was struck by an incredibly strong earthquake, which was followed by the nuclear accident at the TEPCO Fukushima Daiichi Nuclear Power Plant. The NIRS has received many inquiries on radiation and radioactive materials by first responders, medical experts, and government officials since 11 March 2011. We were consulted 421 times on the 24/7 radiation emergency call system from 11 to 31 March 2011. But in addition to the calls from experts, the number of callers from the general public increased sharply, so the NIRS set up another phone service for the public to answer questions and reduce anxiety.

The NIRS disseminated information through its homepage; for example, simple methods of decontamination for radioactive materials and correction of misinformation on the internet regarding commercially available products containing iodine, that were purported to provide radiation protection. Government ministries, particularly the Ministry of Foreign Affairs of Japan (MOFA) and other public administrations introduced NIRS's website as a useful source of accurate information. Foreign embassies in Japan also introduced NIRS's website as a reliable information source to their citizens residing in Japan.

8) International Cooperation

8-1) Training courses for foreign medical professionals organized by NIRS

Upon a request from the Korea Institute of Radiological & Medical Sciences (KIRAMS), the NIRS Training Course for Korean Medical Professionals on Radiation Emergency Medical Preparedness was held from 7-10 September and from 16-18 November 2010.

8-2) International seminars/workshops

a) The NIRS-KIRAMS Joint Seminar on Radiation Emergency Medicine 2010 was held from 6-8 October 2010 by KIRAMS and NIRS.
b) NIRS-IAEA Workshop on Cytogenetic Biodosimetry for Asia 2011 & NIRS-ISTC Workshop on Cytogenetic Biodosimetry in cooperation with WHO was held from 26-27 January 2011.
c) The NSC/NIRS workshop on medical response to nuclear accidents in Asia was held from 28 February to 2 March 2011 by the Nuclear Safety Commission (NSC) and NIRS. As part of this workshop, information on internal contamination and other topics was exchanged among all 14 people (10 from 10 Asian countries, 3 from other area countries, and 1 from IAEA) attended.

8-3) Invited lectures

NIRS staff members were invited to give lectures in the following meetings and training courses.

a) IAEA Training Course on Medical Response to Radiation Emergencies held in Teheran, Iran, 20-28 May 2010.
b) IAEA National Training Workshops on Medical Response to Radiological Emergencies held in Bucharest, Romania, 22-27 June 2010.
c) IAEA National Training Course on Emergency Planning, Preparations and Response for Spent Nuclear Fuel Shipment held in Beograd, Serbia, 19-23 July 2010.
d) Invited lecture for Korean medical experts from KIRAMS held in Seoul, Korea, 7-10 September and 16-18 November 2010.
e) VAEI/JAEA Follow-up Training Course on "Nuclear and Radiological Emergency Preparedness" held in Hanoi, Viet Nam from 27 October to 2 November 2010.
f) Technical Support Working Group(TSWG)held in Florida, USA from 28 November to 3 December 2010.
g) The 13th Coordination and Planning Meeting of the WHO REMPAN Collaborating Centers and Liaison

Institutions held in Nagasaki City, Japan, 15-18 February 2011.

8-4) International meetings / conferences

NIRS staff member attended the following meeting.

a) 2nd International MELODI Workshop, Cite Internationall Universitaire de Paris, France, 18-20 October 2010.

8-5) Members of international committees

NIRS staff members participated in the following committees.

a) Planning meeting for GHSAG TABLE TOP EXERCISE held in Luxembourg, Grand Duchy of Luxembourg, 10 June 2010.
b) Global Health Security Initiative: GHSI Meeting held in Ottawa, Canada, 16 June, 2010.
c) The 2nd Planning Meeting for EXERCISE ECLIPSE held in Luxembourg, Grand Duchy of Luxembourg, 2 September 2010 (Video attendant).
d) The 2nd meeting of WHO BioDoseNet held in Mandelieu-La Napoule, France, 10 October 2010.
e) IABERD meeting held in Mandelieu-La-Napoule, France, 12 October 2010.
f) Meeting on International Organization for Standardization held in Mandelieu-La-Napoule, France, 14-15 October 2010.
g) Consultants' Meeting on Strengthening Biological Dosimetry in IAEA Member States held in Vienna, Austria, 10-12 November 2010.
h) ICRU Annual Meeting held in Essen, Germany, 14-20 November 2010.

8-6) Other overseas visitors

a) A researcher from Washington State University was invited to NIRS to give a lecture and to exchange information about the recent status of radiation emergency medicine on 27 May 2010.
b) Two researchers and an administrator from KIRAMS were visited to NIRS on 17 July 2010 to exchange information and see our facilities.
c) A medical doctor from Sri Lanka stayed to work in improving the network of radiation emergency medicine in Asia from September to December 2010.
d) A medical doctor from Germany visited NIRS on 15 February 2011 to give two lectures on radiation protection for accepting patients with internal contamination and on information regarding public response in case of radiological accidents in Germany.
e) Two cadets from a school of medicine in Germany visited and we gave guidance about radiation emergency medicine from 22-23 February 2011.

8-7) Exchange of human resources and information

a) An NIRS medical doctor worked at the IAEA Incident and Emergency Centre (IEC) to collect information from February 2010 to March 2011.
b) An NIRS member worked at the IAEA to collect information from February 2010 to March 2011.
c) An NIRS member went to the Institute de Radioprotection et de Sûreté Nucléaire (IRSN) to learn about bioassay techniques from April 2010 to March 2011.
d) Some NIRS staff and REMAT members attended an international antiterrorism tabletop exercise hosted by the Global Health Security Action Group (GHSAG) from 26-27 October 2010.
e) A medical doctor and a clerk from KIRAMS observed Ibaraki Prefecture's drill, in which NIRS participated, to protect civilians hosted by the Cabinet Secretary on 30 January 2011.

8-8) Memorandum of Understanding

As of March 2011, NIRS has signed MOUs on radiation emergency medicine with the following overseas organizations.

a) Korea Institute of Radiological & Medical Sciences (KIRAMS), Seoul, Korea, in effect since 16 November 2004.
b) National Institute for Radiological Protection (NIRP), Beijing, China, in effect since 27 November 2007.
c) Institute de Radioprotection et de Surete Nucleaire (IRSN), Fontenay-aux-Roses, France, in effect since 28 October 2008.
d) King Abdulaziz City for Science and Technology (KACST), Riyadh, Saudi Arabia, in effect since March 2010.

8-9) Activities in the REMAT (Radiation Emergency Medical Assistance Team) program

Today, radiation is widely used in our lives. Potential sources of radiation accidents include industrial radiography, therapeutic devices, sterilizers, transportation accidents, and nuclear power plants; devices used for industrial radiography and accelerators are frequent sources of external exposure accidents. However, once an accident involving radiation occurs, much anxiety and fear arise in society, based on the fact that such accidents, fortunately, are not common; but then, paradoxically, there are few chances to become knowledgeable about radiological accidents. Radiation cannot be seen by the human eye, smelled, heard, or otherwise detected by our normal senses, nor do symptoms or signs appear soon after exposure. Therefore, dose assessment is essential for taking care of patients involved in radiation accidents, providing appropriate treatment including administra-

tion of decontamination agents. Since the practice of medicine is based on science as well as past experience, the knowledge of triage, assessment, initial diagnostic methods, and general treatment protocols has to be shared among medical professionals throughout the world.

In FY 2010, the Radiation Emergency Medical Assistant Team (REMAT) program was established at the NIRS. As of March 2011, there are 42 members, including physicians, nurses, radiation protection experts, and health physicists ready to respond to radiation emergencies. As the first overseas activity, REMAT participated in an exercise program on radiation monitoring near the Chernobyl disaster area in June 2010. The program was organized by the European Centre of Technological Safety, Ukraine. And also the REMAT program dispatched the appropriate staff members to various exercises conducted against a severe accident of a nuclear power plant or terrorist attack using radiological substances. In those exercises, we reconfirmed the great importance of communication between on site staff and staff at NIRS. On 11 March 2011, the Great Northeast Japan earthquake occurred, followed by the Fukushima nuclear disaster. REMAT promptly dispatched three staff members --a physician, a health physicist and a nurse-- to the off-site center established in Fukushima, and emergency action was quickly activated.

8-10) Other topics

Staff members attended the IAEA general conference and introduced the activities of the Radiation Emergency Medical Assistance Team (REMAT) program which was established in January 2010.

9) Radiation Emergency Medicine Cooperative Research Facility

The Radiation Toxicology Building was constructed in 1985 and research using animals for internal contamination with Pu or other radioactive materials was conducted there. After completion of inhalation experiments, a future plan for the building was discussed within NIRS.

Considering the situation in Japan including the expectations of the Nuclear Safety Commission regarding research on radiation exposure to Pu and operation starting at the Rokkasho Reprocessing Plant, NIRS decided to reactivate the facility for a new research direction in 2009. The building was renamed the Radiation Emergency Medicine Cooperative Research Facility. To facilitate the project, the Promotion Section for Radiation Emergency Medicine Cooperative Research Facility was created in April 2010. The research plans include studies on kinetics of aerosol and dose assessment, dose assessment by measurements such as chemical analysis and bioassay, and acute-sub acute toxicity assessments of actinides and de-cooperation drugs. Replacement and repair of deteriorated facilities and equipment were started, including renewal of a scrubber for an incinerator. An animal raising hood with glove-box type air sealing was also replaced in 2011.

Meanwhile some researchers conducted other work during this time. Actinide safety research (mainly, U and Pu) including experimental toxicology, decontamination research, dosimetry research, and environmental dynamics and molecular carcinogenesis, have been conducted at the facility.

For internal decontamination research in radiation emergency medicine, acute toxicity of actinides, and effect of agents on removal of actinides contamination were studied. This study focused on (1) the examination of the acute toxicity of uranium in simulated wounds using rat model and (2) the decontamination effects of various agents including chelating substances in this model.

5.1 The Study of 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 the 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.

When the Tokai-mura criticality accident occurred in 1999, he treated the patients who were taken to NIRS. He also has been providing advice and support as an expert regarding radiation emergency medicine for the Fukushima Daiichi Nuclear Power Plant accident caused by the Great East Japan Earthquake of 2011.

Contact Point: akashi@nirs.go.jp

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 study 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 in a living body that can provide a guide for treatment to radiation exposure.

Progress of Research in the 2nd Mid-term Plan

1) Study on treatment for intestinal injuries due to high doses of radiation

Several members of the fibroblast growth factor (FGF) family have potential to protect the intestine against the side-effects of radiation therapy. FGF1 is capable of signaling through all subtypes of FGF receptors (FGFRs). Therefore, we compared the protective activity of FGF1 and other FGFs, and examined the profiles of FGFR expression in the jejunum of BALB/c mice given total body irradiation (TBI) with γ-rays. The results revealed that FGF1 was more potent than FGF7 or FGF10 for protection of the intestine against radiation exposure, and suggested that the profiles of FGFR expression in the intestine favored the FGF1 signaling pathway before and during the initial period after irradiation. In contrast, an FGF1:FGF2 chimera (FGFC) was created and it showed greater structural stability than FGF1. Therefore, FGFC was expected to have greater biological activity *in vivo*. We evaluated and compared the protective activity of FGFC and FGF1 against radiation-induced intestinal injuries. Consequently, we found that FGFC strongly enhanced radioprotection with the induction of epithelial proliferation without exogenous heparin after irradiation and FGFC was useful in clinical applications for both the prevention and post-treatment of radiation injuries.

2) Effect of FGFC chimeric protein in mouse survival after high-dose irradiation

FGFC shows a higher radioprotection effect on mice intestine as compared to FGF1. However, the effect of FGFC on the survival of irradiated mice is unknown. In this study, we compared the effects of FGF1 and FGFC on their survivals after irradiation using BALB/c mice. FGF or saline was administrated intraperitoneally to mice before or after whole body γ-irradiation. Administration of each FGF to mice before irradiation with 7 Gy (LD100/30) increased the survival rates significantly as compared to those of control mice. However, there was no difference between mice with FGFC and FGF1. When mice were exposed to irradiation with a higher dose, 11 Gy (LD100/10), neither bone marrow transplantation (BMT) after irradiation or administration before irradiation improved the survival rates. In contrast, combination of pre-treatment with FGFC and BMT after irradiation

significantly improved the survival rates, whereas the combination of FGF1 and BMT did not affect the rates in these mice. These results suggest that FGFC has a synergistic effect with BMT on the survivals in heavily irradiated mice.

3) A cell-permeable C-terminal PIDD fragment 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 apoptosis induced by DNA damage through the formation of a so-called PIDDosome, which contains the adaptor protein RAIDD and caspase-2. We found that transcription of PIDD was induced after exposure to ionizing radiation in rat small intestinal epithelial cell line (IEC6) cells. Yeast two-hybrid analysis indicated that the death domain of rat PIDD interacts with RAIDD. Interestingly, a rat C-terminal PIDD fragment (residues 773-917) containing the death domain interacts with RAIDD much more tightly than the longer PIDD fragment (residues 610-917). We purified a recombinant PIDD (773-917) fragment fused with a basic 11-amino acid peptide (TAT) derived from the HIV-Tat protein which facilitates uptake of the protein into mammalian cells with high efficiency. When PIDD (773-917)-TAT was added to the IEC6 cells, the protein was efficiently delivered into the cells within an hour. Furthermore, we observed that ionizing radiation-induced activation of caspase-2 and caspase-9 was inhibited when PIDD (773-917)-TAT was added to the IEC6 cells. These results suggest that PIDD (773-917)-TAT can protect gastrointestinal cells from ionizing radiation-induced cell death.

4) Cell-permeable inhibitor of apoptosis (IAP) proteins inhibits radiation-induced cell death

Gastrointestinal syndrome after high-dose radiation exposure is caused by gastrointestinal apoptosis. Inhibitor of apoptosis (IAP) proteins, such as X-linked inhibitor of apoptosis (XIAP) and cellular inhibitor of apoptosis protein 1 and 2 (cIAP1 and 2), are intrinsic cellular inhibitors of apoptosis. In order to prevent gastrointestinal syndrome, we purified cell-permeable recombinant XIAP (full-length, BIR2 domain, and BIR3-RING domain with or without mutations of autoubiquitilation sites) and cIAP2 proteins fused with a protein transduction sequence (TAT) derived from the HIV-Tat protein and examined the effects of these proteins on radiation-induced cell death in rat small intestinal epithelial cell line (IEC6) cells. When the TAT-conjugated IAP proteins were added to IEC6 cells, these proteins were delivered into the cells and inhibited apoptosis after irradiation. Furthermore, we found new protein modifications of IAP proteins. Our results suggest that the cell-permeable IAP proteins may be useful for protection of gastrointestinal cells from radiation-induced cell death. Future analysis of the protein modifications may facilitate improvement of the inhibitory efficacy of the TAT-conjugated IAP proteins.

5) Modification of radioprotective effects of heat-killed Lactobacillus casei by glucodorticoids mediated by proinflammatory cytokines in mouse

Administration of proinflammatory cytokines in experimental animals 1 day before lethal dose of irradiation leads to increased survival rate via alteration of hematopoietic progenitor cells to increase resistance against radiation, and they are recognized as radioprotectors. A single injection of bacterial constituents such as heat-killed *Lactobacillus casei* (HLC) to C3H/He mouse 24 hours before x-irradiation of the LD50 dose of 8.0Gy also show similar radioprotective action. We found that administration of HLC effectively increases the level of interleukin (IL)-1 beta as compared to *Bacillus subtilis* and *Escherichia* coli in the mouse species. Since HLC stimulates inflammation in early immune responses, effects of pharmaceutical drugs modifying the early process were compared. The increase in both blood IL-1 beta levels and survival rates by HLC were simultaneously accelerated by coadministration of mineralocorticoid and inhibited by glucocorticoids, known as anti-inflammatory drugs. In contrast, no similar modification in the IL-1 beta levels and survival rates by HLC were found by coinjection of non-steroidal anti-inflammatory or anti-rheumatoid drugs. This suggests that expected action of inflammation-related radioprotectors can be controlled by the coadministration of drugs at least in C3H/He mice, based on consideration of their pharmacological properties.

6) Radiation dose-dependent augmentation of mRNA levels for DNA damage-induced genes elicited by accurate real-time RT-PCR quantification and the evidence of the effects of circadian rhythm in mouse

We established a method to quantify mRNA levels of DNA damage-induced genes as indicators of growth-arrest (*p21* and *mdm2*) and of apoptosis (*bax* and *puma*) with high reproducibility and accuracy based on real-time RT-PCR. Messages for *p21* and *mdm2* were augmented before growth-arrest and a *puma* mRNA was increased before apoptosis in RAW264.7. Their peak levels were dependent upon x-ray irradiation doses between 0.1 to 3.0Gy. Similarly, the relative RNA levels of *p21*, *mdm2*, *bax*, and *puma* per GAPDH also increased dose-dependently in peripheral blood and bone marrow cells isolated from whole-body-irradiated mice in the ranges from 0.1 to

1.0Gy of x-ray.

Generally, quantitative study using cells isolated from the living body of humans and experimental animals is difficult, because they are altered by a physiological oscillation such as circadian rhythm. The induction levels in peripheral blood of all the above-mentioned messages were reduced by half after nighttime irradiation as compared with daytime irradiation of mouse. In marrow cells, nighttime irradiation enhanced the *p21* and *mdm2* mRNA levels more than daytime irradiation. No significant difference in *bax* or puma mRNA levels was observed between nighttime and daytime irradiation in marrow cells. This suggests that the damage in hematopoietic cells can be quantitatively analyzed using apoptosis-related genes in marrow and that modulation between diurnal and nocturnal irradiation is remarkable in peripheral blood.

7) Regeneration of mucosa in small intestine damaged by high-dose radiation is accelerated by anabolic steroids and inhibited by follicle hormone

Mucosal damage in the small intestine is a serious problem after accidental or clinical high-dose radiation exposure. To examine substances to ameliorate the damage by post-irradiation administration, we focused on the regeneration process after irradiation of the intestine. Using an in vitro experiment in IEC-6 epithelial cells of rat intestinal mucosa, the effects of various sex hormones on the growth were compared. The proliferation was stimulated by steroids with anabolic action including 19-nortestosterone (nandrolone) and androgens, and was inhibited by high concentrations of follicle hormone, such as estradiol. The significant life-saving effects of nandrolone ester by a single injection 24h after exposure was confirmed by in vivo experiments using abdominally irradiated mice at the LD50 dose of 15.7Gy of x-ray. Regeneration indicators such as microcolonies of proliferating cells visualized by bromodeoxy uridine staining at day 5 and c-*myb* mRNA expression levels at day 4 in the small intestinal mucosa were enhanced by nandrolone administration, suggesting that the drug contributes to repair of mucosa after irradiation. A similar life-saving effect was not found in native androgens *in vivo*. As in the *in vitro* experiment, treatment of abdominally irradiated mice with estradiol ester decreased these regeneration indicators and the survival rate. These results suggest the effectiveness of anabolic steroid as well as the importance of manipulation of steroid receptors in the recovery of mucosa in small intestine damaged by high-dose radiation.

Major Publications

1. Nakayama K, Hagiwara A, Umeda S, Asada M, Goto M, Oki J, Suzuki M, Imamura T, Akashi M: Post treatment with an FGF chimeric growth factor enhances epithelial cell proliferation to improve recovery from radiation-induced intestinal damage, *Intl. J. Radiation Oncology Biology Physics*, **78**(3), 860-867, 2010
2. Tanaka I, Tanaka M, Sato A, Kurematsu A, Ishiwata A, Suzuki K, Ishihara H: Alteration of radioprotective effects of heat-killed Lactobacillus casei in X-irradiated C3H/He mouse related to blood level of proinflammatory cytokines by corticoids, *J. Rad. Research*, **51**(1), 81-86, 2010
3. Ishihara H, Tanaka I, Yakumaru H, Chikamori M, Ishihara F, Tanaka M, Ishiwata A, Kurematsu A, Sato A, Ueda J, Akashi M: Circadian Transitions in Radiation Dose-Dependent Augmentation of mRNA Levels for DNA Damage-induced Genes Elicited by Accurate Real-time RT-PCR Quantification, *J. Rad. Research*, **51**(3), 265-275, 2010
4. Ishihara H, Tanaka I, Yakumaru H, Tanaka M, Sato A, Ishiwata A, Yokochi K, Kurematsu A, Ueda J, Sibata T, Hachiya M, Akashi M: Acceleration of Regeneration of Mucosa in Small Intestine Damaged by Ionizing Radiation Using Anabolic Steroid, *Rad. Research,* **175**, 367-374, 2011

5.2. Research on Radiation Dose Assessment

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 accumulated 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 the Lovelace Foundation, USA as a visiting scientist where he studied aerosol deposition within the respiratory tract.

Contact Point: yj_yamad@nirs.go.jp

Objectives

Radiation accidents can be divided into those that result in external exposure and those that result in 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, taking into account 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) Chromosome aberration analysis for dose assessment

The National Institute of Radiological Sciences (NIRS) is the national center for radiation emergency medical preparedness in the nuclear disaster prevention system of Japan. Biodosimetry is a method for accurately estimating unknown radiological doses to individuals following radiological or nuclear accidents.

Among several methods for biodosimetry, dicentric chromosome analysis (DCA) based on chromosome morphology has been used since the mid 1960s and is called the gold standard. By the end of FY 2010, we had established a practical and more rapid system based on DCA using a microscopic image analysis instrument equipped with automatic cell-finding and cell-capturing functions. We have confirmed the system accuracy, its limitations, and the time required for dose estimation.

For analyzing radiation-induced chromosome aberrations based on DNA sequences, we have introduced and developed a fluorescence *in situ* hybridization (FISH) technique. By using centromere- and telomere-specific peptide nucleic acid (PNA) probes, more accurate detection of multi-centric chromosomes as presented by dicentrics has been made possible (Fig. 5.1). By Multiplex FISH (M-FISH) using chromosome paints which identify 22 autosomes and the sex chromosomes X and Y, we detected more complex aberrations in irradiated cells and found that the actual frequency of chromosome aberration caused by radiation exposure was much higher. Since M-FISH is useful for detecting stable aberrations such as translocation, we will apply it to long-term follow-up studies and retrospective studies for past radiological accidents in Japan in the next stage.

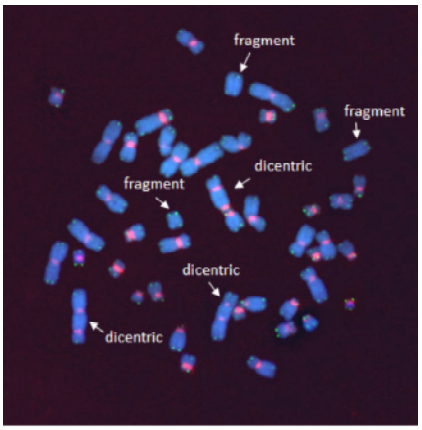

Fig.5.1. FISH using centromere- and telomere-specific PNA probes. Centomeres and telomeres were stained with red and green, respectively.

2) Development of rapid biological dose estimation method for partial body exposure

Chromosomal aberrations in the peripheral lymphocytes are the most reliable indicators for biological dose estimation of radiation exposure. The conventional method for estimating this dose uses score marker aberrations, such as dicentric and ring chromosomes in lymphocytes. However, because lymphocytes circulate in the peripheral blood, the dose estimated from these dicentric or ring values is the mean dose of whole-body cumulative radiation exposure. Therefore, in the case of partial body exposure, it is difficult to estimate the partial dose of radiation by this method. 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 positional identification in partial body exposure.

3) Development of an early detection system for unknown radiation in a radiological emergency

Two types of early detection systems concerning unknown radionuclides and unknown energies were developed aiming at prompt personal dose evaluation in a radiation emergency. One is an alpha, beta and gamma surface contamination measuring system corresponding to contamination such as due to fission products. This system consists of three detectors, i.e. the EJ-204 type plastic scintillator is inserted as a beta radiation detector through an electron shield into the CsI(Tl) scintillator used as a gamma radiation detector and ZnS(Ag) scintillator is painted on the surface of the plastic scintillator as an alpha radiation detector. All their luminescences are measured with one photomultiplier tube set on the same axis. The separate measurement of each radiation type from mixed contamination becomes possible in real time by synchronization of the time spectrum and the energy spectrum from each scintillator.

The second detection system is an external dose evaluation system for use in a mixed gamma radiation field. It is composed of a physical phantom, a phantom insertion type semi-conductor detector (Fig. 5.2), and the GUI type Monte Carlo calculation code. The Si detector (1cm in diameter) on the following amplifier substrate designed for the Compton spectrum measurement is buried into the tissue-equivalent medium. The detector which can identify radiation up to the ^{60}Co energy region is inserted into the main internal organs position in a physical phantom. It can measure the equivalent dose based on the response function in a gamma radiation field. This detector is used to get bench mark values in the Monte Carlo calculation under various conditions. The effective dose evaluation by this Monte Carlo calculation code is carried out based on the initial information about the exposure geometry in an unequal external exposure accident.

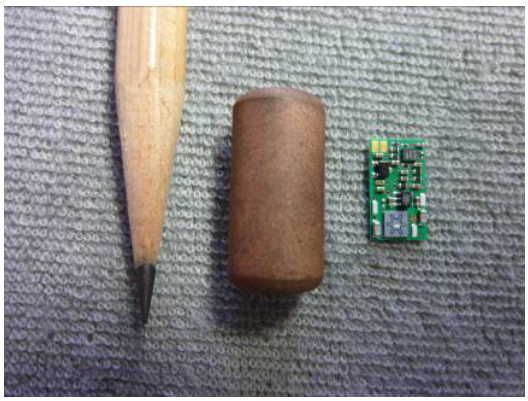

Fig.5.2. The phantom insertion type semi-conductor detector

4) Nasal swab for alpha emitters

Nasal swabs are useful to confirm the possibility of internal intake just after accidental inhalation of alpha emitters. The swabs are also expected to be a useful method for rapid dose assessment. To improve the first estimation of intake activity, the quality of a nasal swab measurement was experimentally investigated. Particle diameter is important information for dose assessment. The dose conversion factor for the ET_1 region (DCFnasal) was simulated by using a computer code, LUDEP. The DCFnasal showed a clear dependency with the aerosol size. Further, results indicated that a reference aerosol size of 5 μm for occupational exposure given in the ICRP Publication was not always a safe dose estimation for accidentally exposed patients. To get information on particle diameter from a swab sample, a $^{239}PuO_2$ particle sampling filter was

examined. An especially thick film was coated onto a filter which was exposed for 60 days. Alpha tracks were counted for each particle. Particle diameter was calculated based on the number of tracks. The calculated particle diameter was equivalent to the measured particle diameter obtained by an aerosol measuring instrument. When a simulation was done based on the result, the dose assessment for a particle diameter of 5 μm could be estimated in a 10 minute film exposure when the assumed particles were $^{239}PuO_2$. These results indicated that rapid dose estimation would be expected using the combination of the DCFnasal and track measurements.

5) Development of in vivo measurements

It is important to estimate the amounts and decide the types of radionuclides from outside the body at the time of accidental intake of radionuclide. Especially, when transuranic elements are inhaled, the low energy LX-rays must be measured; these are difficult to measure accurately with a lung monitor. The Lawrence Livermore National Laboratory phantom (LLNL phantom) is used to calibrate the lung monitor. But its size is very different from the physical size of a Japanese adult. So, we developed the phantom that fits the Japanese physical size. The formation of the lung models in the phantom agreed with MRI data for the lung of Japanese individuals as well, and the characteristics for radiation penetration also had good agreement. The distribution of the material was confirmed by X-ray tomography and cutting of the lung model. As a result, the composition was seen to be almost the same independent of the position. The radioactive lung models were made by uniformly diffusing a radio-source in the polyurethane phantom by foamed. One of them was also cut. Because the radioactivity was about 3 kBq for the whole lung model, it sections were positioned closely together on an imaging plate surrounded by a blackout curtain inside a low background room and the 59.5keV gamma rays from Am-241 were observed. Moreover, we made the mapping measurement that rolled a 1mm lead collimator in a one-inch NaI detector, too. From the results, the uniformity and the physical structure of the radiation source were proven. Finally, we compared the model with the LLNL phantom. But no big difference was observed in counting efficiency.

6) Effects of chelation therapy and new chelating agents on removal of uranium in a simulated wounds model of rats

A study on acute uranium toxicity clarified that the biochemical markers of renal function, such as N acetyl-beta-D-glucosaminidase, blood urea nitrogen and creatinine, are useful clinical indicators for renal damage, and osteocalcin is a useful indicator for bone damages in rats. A study on the removal of uranium contamination clarified that catechol-3,6-bis (methyleiminodiacetic acid) (CBMDIA), ethydronate disodium (EHBP), and lactoferrin were effective, however 1,2 dimethyl-3-hidroxypyrid-4-one (deferipron), sodium bicarbonate, diuretic agents, transfusion showed no effects. In addition, no promising compounds have been found yet among newly synthesized chelating agents.

Major Publications

1 Iwasaki T, Takashima Y, Suzuki T, Yoshida M, Hayata I: The Dose Response of Chromosome Aberrations in Human Lymphocytes Induced In Vitro by Very Low-Dose γ Rays, *Radiat Res*., **175**(2), 208-213, 2011

2. Suto Y, Akiyama M, Yamada Y: Unequivocal Detection of Radiation-induced Multicentric Chromosomes by Fluorescence in situ Hybridization using Peptide Nucleic Acid Probes, Cytologia: *International J. Cytology*, **76**(1), 1-2, 2011

3. Fukutsu K, Yamada Y, Akashi M: Numerical Simulation on Dose Estimation from Nasal Swab Data at Nuclear Accident, *Earozoru Kenkyu*, **25**(3), 257-261, 2010

4. Kurihara O, Saito F, Koarashi J, Kim E, Shiraishi K, Yamada Y, Akashi M: Emission Rates of Alpha Particles from Supports with Different Surface Conditions in Direct Deposition Sources, *Radiat. Protec. Dosim*., **145**(1), 13-20, 2011

5. Yamada Y, Fukutsu K, Akashi M: Contamination Control by Green-house for Emergency Medical Treatment of the Contaminated Patient, *Radiat. Protec. Dosim*., **146**(1-3), 50-53, 2011

6. Fundamental Technology Center

Shigeo Uchida, Ph.D.

Director, Fundamental Technology Center

Outline of Research Career

Dr. S. Uchida received his doctor al degree from Kyoto University. He has about 30 years' experience in the fields of radioecology and environmental radiochemistry; his special interests are the behaviors of long-lived radionuclides in the environment, e.g., ^{63}Ni, ^{79}Se, ^{90}Sr, ^{99}Tc, ^{129}I, ^{137}Cs, Th, and U. He has worked extensively to improve the models and parameters for radionuclides in soil-to-crop systems. He became Director of the Research, Development and Support Center, NIRS in April 2011.

Contact Point: s_uchida@nirs.go.jp

Objectives

The Fundamental Technology Center was established in 2006 to support and promote the wide variety of research activities of NIRS. This center includes two departments, that is, the Department of Technical Support and Development and the Department of Safety and Facility Management. While the Center provides technologies from basic to state-of-art to help NIRS scientists further their research studies, it also secures the safety of working environments. These two departments work in a complementary manner to each other. The Center activities and structures are outlined in the next section.

Overview

The Center consists of one office and two departments with seven sections. Figure 6.1 shows the organizational structure. The Planning and Promotion Office is responsible for planning and management of work in the Center by providing smooth research support. It also manages common use facilities. In addition, the Office sponsors a variety of meetings to facilitate the technical development of NIRS and to provide a bridge between scientists and technologists. The Department of Technical Support and Development is aimed at developing advanced technologies. It consists of the following three sections.

(1) Technical Advancement of the Radiation System Section
- Maintaining radiation generators
- Carrying out R & D of advanced irradiation technologies
- providing quality assurance of radiation fields
- Supplying and maintaining common use (basic) devices

(2) Radiation Measurement Research Section
- Carrying out R & D of radiation measurement techniques for radiation biology
- Measuring space radiation at space stations
- Constructing standard fields of α particles and other particles

(3) Laboratory Animal Science Section
- Supplying laboratory animals for biological effect studies and medical studies on radiation
- Maintaining clean rearing environments for the animals
- Controlling the hygienic condition of the animals
- Carrying out relevant R & D on hygiene and reproductive engineering

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 promoting safety assurance
- Training employees on safety issues
- Assuring safety on campus
- Protecting the public from nuclear power accidents

(2) Radiation Safety Section
- Supervising legal management of radiation and radioactive materials
- Supervising radiation exposure management
- Training employees who deal with radioactive materials and radiation
- Assuring safety with respect to radiation
- Supervising 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
Assuring safety in all work environments

(4) Facility Management Section
Supervising management of energy consumption, working environments, and general wastes
Supervising construction and maintenance of buildings

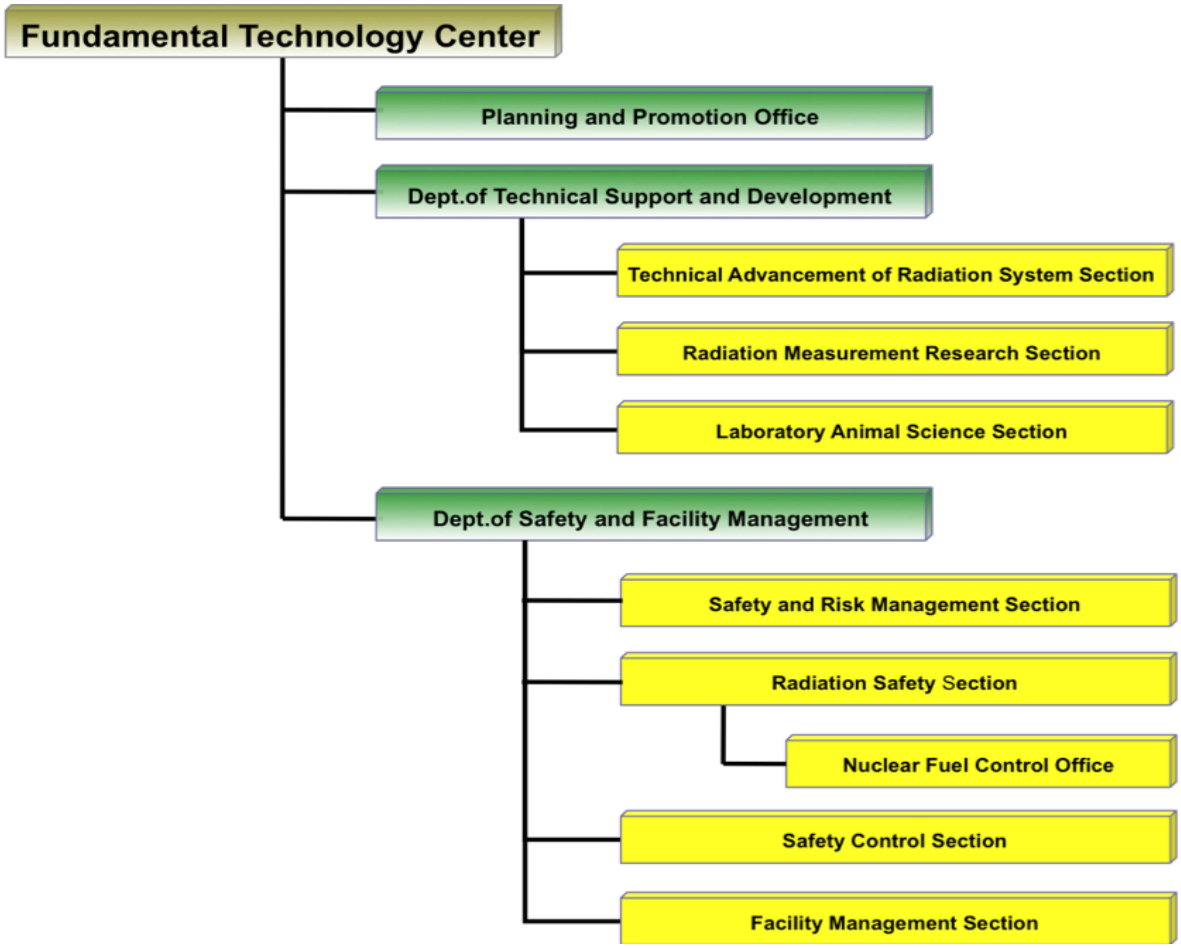

Fig. 6.1. Organization of the Fundamental Technology Center

6.1. Department of Technical Support and Development

Yoshiyuki Shirakawa, Ph.D.

Director, Department of Technical Support and Development

Outline of Research Career

Dr. Shirakawa studied electric and electronic engineering at the Tokyo Institute of Technology, and then started his professional career at Nippon Steel Corporation in 1980, where he was in charge of development for monitoring and control of huge blast furnaces for 16 years. While working there, he was dispatched to Harwell Laboratory in Oxford for two years to develop a prompt on-line elemental analysis by using neutron and gamma radiation. He joined the Faculty of Engineering of Fukui University in 1996, and then moved to NIRS in 1998. His specialty is applied radiation measurement.

Contact Point: sirakawa@nirs.go.jp

Objectives

The Department of Technical Support and Development was founded in 2006 accompanied by the establishment of the Fundamental Technology Center. Since then we have played two important roles for NIRS. One role is to carry out fundamental developments on radiation measurements, irradiation systems, and laboratory animals to promote research activities in NIRS. The other is to support researchers working in other centers using facilities, equipment, and techniques which were mostly developed and introduced by NIRS researchers.

Overview

The Department consists of three sections with 22 staff members. They are Technical Advancement of Radiation Systems Section, Radiation Measurement Research Section, and Laboratory Animal Sciences Section. Every section is proud of its own original state-of-the-art technologies and provides them to other researchers to promote studies in the field of radiological sciences. It is unique that the department consists of three sections with different technologies and has a mixture of scientists and technologists. Another feature is that our staff members, with completely different specialties, have merged into one support team which works together and contributes to the success of research activities done in NIRS and in collaborative universities and research institutes worldwide.

Here three sections of the Department are briefly introduced and the details on research and support activities are described in following pages.

1) Technical Advancement of Radiation Systems Section

This section carries out maintenance of special and original radiation generators such as PIXE (Particle Induced X-Ray Emission), PASTA (PIXE Analysis System and Tandem Accelerator), SPICE (Single Particle Irradiation System to Cell), NASBEE (Neutron Exposure Accelerator System for Biological Experiment), which were mainly designed by this section and have been constantly modified and advanced. This section also provides conventional radiation sources such as X-ray radiation generators and gamma-ray radioisotope sources, and hundreds of common devices. According to demand, we give technical support on correct use of such equipment and we advise researchers working in NIRS and other institutes. We also contribute to ensure the quality of those radiation fields, such as dose, dose rate, and uniformity.

The section performs research and development as well as maintenance. The themes are selected from the viewpoint of support and promotion of many studies in and outside NIRS. For example, we realized great improvement in the Micro Beam Scanning PIXE by installing a new radiation detector and a data acquisition system and we have gotten excellent results with SPICE on beam focusing, setting a world record of 2 μm focusing.

2) Radiation Measurement Research Section

One of the important roles of this section is to provide technical support on radiation measurement and dosimetry required for research activities in such fields as radiation biology and radiation physics.

The members in this section perform research and development pursuing the state-of-the-art radiation detection, measurement and dosimetry. For example, we are developing a new CR-39 detector for the precise measurement of high LET particles and studying a

fluorescent nuclear track detector for the measurement of heavy charged particles. We also are working to realize unique neutron detectors and plastic scintillation detectors for multi-uses such as space radiation applications and medical applications.

During the study of new plastic scintillation detectors, we found some common plastics such as used in drink bottles emitted blue light by bombardment of radiation (α particles, β particles, γ rays). This discovery shows the possibility that cheaper detectors can be designed and made in the near future.

This section is carrying out the well-known international ICCHIBAN Project, which consists of intercomparison experiments of several space radiation dosimeters on a ground base and in the Russian Service Module of the International Space Station.

3) Laboratory Animal Sciences Section

This section has developed and supplied the laboratory animals needed for biological effects and medical studies in radiological sciences, and we have kept several important animal species, for examples, mice, rats and monkeys. Our site has 11 animal facilities, and we maintain them under clean and hygienic conditions.

This section is carrying out several research programs: developing a new genetic monitoring system for the mouse, examining cannibalism of mouse-strain differences, and shortening the operation time of an isolator.

Summarizing our 5-year Mid-plan achievements (2006-2010), 71 original papers were accepted and published and 17 patent applications were made. Through conferences for the media, we have presented some of our significant results for introduction to the general public.

6.1.1. Technical Advancement of Radiation System Section

Contact Point (Dr. Y. Shirakawa): sirakawa@nirs.go.jp

Objectives

The section has a variety of radiation sources, such as X-ray, gamma-ray irradiation fields, and two tandem accelerator facilities, such as for the PIXE analysis system (PASTA) and the microbeam irradiation system (SPICE), and the low energy neutron generators (NASBEE). In addition, the section manages, and provides technical support for the joint-use facilities in NIRS. Our mission is to assure the reliability of the radiation fields for physical and biological research projects in NIRS and for collaborative research studies, and also to carry out developmental research studies related to advancement of irradiation systems, fields and applications.

Progress of Research

1) Development of Particle Induced X-ray Emission (PIXE) analysis system

The electrostatic accelerator facility of NIRS supplies protons and helium ions by a Tandetron accelerator (HVEE, High Voltage Engineering Europe Ltd.). Three horizontal beam lines were developed for PIXE analysis. The PIXE Analysis System and Tandetron Accelerator, PASTA, consists of a conventional PIXE line for analysis under vacuum conditions, an ‘‘in-air” PIXE line, and a microbeam scanning PIXE line for two-dimensional mapping of multi-elemental distributions. One of the major developments of the PIXE analysis system in these past five fiscal years was the advancement of the micro-PIXE system. A CdTe detector (XR-100T-CdTe, Amptek, active area: 25 mm^2) was installed in the micro- PIXE system, especially for detection of heavier elements than iron. The CdTe detector was mounted just behind the sample to provide a large solid angle (about 1 psr) against the X-ray emission from the sample: in this case, the distance from the detector crystal to the sample was set to be 3 mm. A glassy carbon disk (f20 mm, t=200 mm, Tokai Carbon Co. Ltd.) was attached in front of the detector window, which was used as a proton beam dumper, and also functionalized as a beam current monitor for conductivity. This advancement enabled studies to detect the distribution of anti-cancer drugs that include heavy metal elements, such Pt in cis-DDP distributed in mammalian cells, or tissues.

Another advancement in the PIXE system was the development of a technique for quantitative analysis in the conventional-PIXE system using spectrum analysis software, which derives detection efficiency of the whole system from the measurement of standard samples. As a result, quantitative analysis was enabled in the conventional-PIXE system (Fig. 6.2).

2) Development of microbeam irradiation system, SPICE for radiation biological studies

The Single Particle Irradiation system to CEll, SPICE is the fourth beam line, which diverges vertically from the micro-PIXE line. This microbeam irradiation system was developed for low dose radiation effect studies, such as for the cellular response of targeted and non-targeted effects, and now its is has become the world’s top class microbeam irradiation system. SPICE provides a 3.4 MeV proton microbeam by using a two two-slit system and a mono-block triplet Q lens so as to exclude such low-energy particle components by due to scattering seen with the collimation method. An approximately, 2 μm in a diameter beam are is routinely available. As a routine procedure, cell nuclei are fluorescentlyfluoresced, and the X-Y coordinates of the cell position in the dish are calculated automatically corresponding to the obtained fluorescent images. Each nucleus can be irradiated with the pre-set number of protons with a probability of 96.6 % accuracy, and it will be irradiated according to the calculated coordinates with a maximum speed of 400 cells per minutes by controlling the voice coil motor stage. These irradiation procedures are were developed to beas fully automated and functional. An example of irradiated WI38 human normal fibroblast cell line is shown in Fig. 6.3.

SPICE is operational and open to domestic and foreign research projects for collaborative studies, and it is now being prepared as a joint-use research microbeam facility. In the past five years, we have started seven collaborative research studies including two domestic and two foreign universities and institutes to construct new fields in microbeam applied radiation biology.

3) Development of Neutron exposure Accelerator System

for Biological Effect Experiment (NASBEE)

We developed the neutron irradiation facility NASBEE which accelerates proton and deuterons to 4MeV with the 2MV Tandem accelerator (High Voltage Engineering Europa (HVEE)) to produce a neutron irradiation field. With NASBEE, the main goal is to elucidate the differences of neutron-induced carcinogenesis between childhood and adulthood exposures, and identify other significant factors which are considered to be targets of carcinogenesis. The average irradiation field of 2MeV neutrons generated by a Be(d–n)B reaction is established. Dose uniformity in a 240 mm diameter irradiation field is producible within 72.5% with a dose rate of 0.87 Gy/h at a sample target distance of 1170mm. Two irradiation rooms, a specific pathogen-free (SPF) conditioned one and a conventional, are now available. Irradiation protocols for *in vitro* experiments have been established and demonstrated by obtaining the relative biological effectiveness (RBE) of cell inactivation of 3.54 with 10% survival dose (D10).

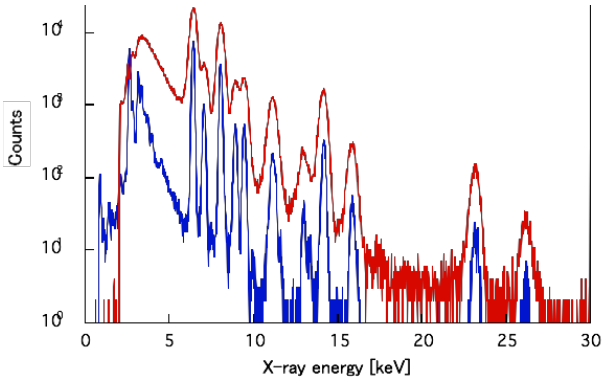

Fig.6.2 Comparison of detection efficiency by PIXE analysis of a multi-element standard sample with the existing Si(Li) detector and the new CdTe detector.

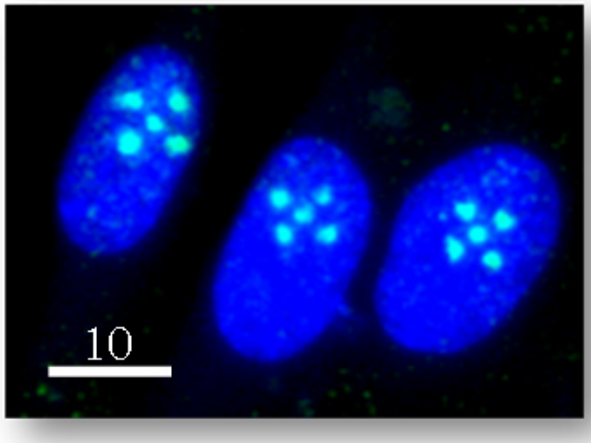

Fig 6.3. Each WI-38 cell nucleus, counter stained in blue was targeted at five different positions with 3 μm pitch. At each position, 500 protons were delivered and then cells were immune-stained against γ-H2AX (seen in aqua-blue), which is known as a marker for DNA double strand breaks.

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1. Miyahara, Honma T, Fujisawa T: Irradiation effects of a 10 MeV neutron beam on a Nd-Fe-B permanent magnet, *Nuclear Instruments & Methods in Physics Research Section B*, **268**(1), 57-61, 2010
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4. Choi VWY, Konishi T, Oikawa M, Iso H, Cheng S.H, Yu KN: Adaptive Response in Zebrafish Embryos Induced Using Microbeam Protons as Priming Dose and X-ray Photons as Challenging Dose, *Journal of Radiation Research*,**51**, 657-664, 2010
5. Suda M, Hagihara T, Suya N, Hamano T, Takada M, Konishi T, Maeda T, Ohmachi Y, Kakinuma S, et al.: Specifications of a neutron exposure accelerator system for biological effects experiments (NASBEE) in NIRS, *Radiation Physics and Chemistry*, **78**, 1216-1219, 2009

6.1.2. Radiation Measurements Research Section

Contact Point (Dr. Y. Shirakawa): sirakawa@nirs.go.jp

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 the latest radiation detectors. And, we also propose 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 codes, and electronics have been developed.

Dosimetry 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 dosimetry.

After the accident at the Fukushima Dai-ichi Nuclear Power Plant in, some members visited there and carried out a radiation survey for residents near the plant and workers; as well, radiation measurements were made in Fukushima City.

Progress of Research

Passive detectors

Development of a fluorescent nuclear track detector technique

A new optical, non-destructive method of detecting and imaging individual heavy charged particle tracks using Fluorescent Nuclear Track Detectors (FNTD) was investigated as a possible spectroscopic technology for heavy charged particles of low and high linear energy transfer (LET). The technique uses new luminescent aluminum oxide single crystals having aggregate oxygen vacancy defects and doped with Mg ($A_{12}O_3$:C,Mg) in combination with laser scanning confocal fluorescence microscopy. Spectroscopic capabilities of this new method were demonstrated for energetic heavy ions of $LET_{\infty}H_2O$ ranging from 1 to 730 keV/μm. Applications of this technology include neutron detection and dosimetry, a radiobiology study using protons and heavy ions, microdosimetry, space radiation dosimetry, and nuclear and particle physics research. [Done in collaboration with: Landauer Inc. (USA) and Nagase Landauer Inc. (Japan)]

Development of the new CR-39 technology for high LET particle measurements

High LET secondary particles produced by target fragmentation reactions may give dose contributions in proton therapy and space radiation fields. They result in a continuous LET distribution higher than about 30 keV/μm. Controlling the detector response and LET detection threshold of CR-39 detectors will allow the measurement of selectively high LET secondary particles without recording low LET particles. As one approach, we have developed a new type copolymer detector of CR-39 and DAP resin detectors. The CR-39/DAP copolymer has the unique characteristic to degrade the sensitivity to the high LET particles. As another approach, we have developed a novel etching techniques called the two-step etching method using PEW-*x* solution [17wt% KOH + *x*wt% C_2H_5OH + (83-*x*)wt% H_2O] for pre-etching and 7N NaOH solution for post-etching. This makes it easy to increase the detection threshold as shown in Fig. 6.4 and improve the charge resolution for high LET particles in CR-39 detectors. Developed technologies to control detector response and detection threshold allow selective measurement of high LET secondary particles produced by target fragmentation reactions in radiation cancer therapy fields.

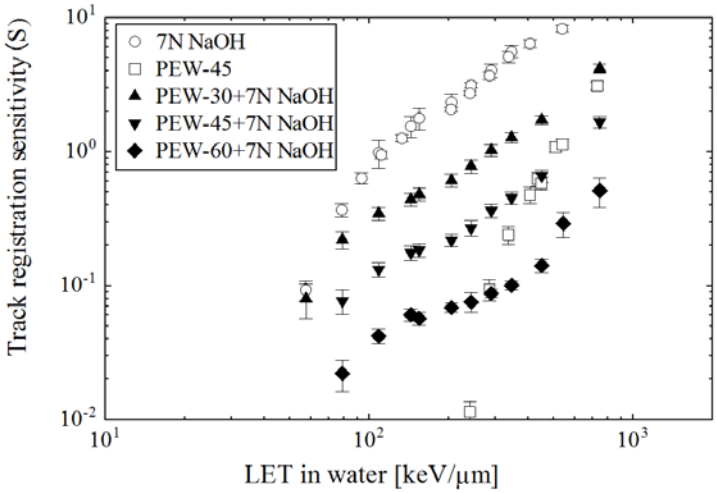

Fig.6.4. Variation of detector responses for the two-step etching method, single etching of 7N NaOH solution, and PEW-45 etching solution as a function of LET. The responses smoothly shifted to higher LET region as the ethanol concentration is increased in the PEW etching solution.

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 has been developed for the measurement of projectile fragmentation cross sections of heavy ions in matter. A high speed imaging microscope with special track analysis software was utilized to extract the charge information from multiple ion tracks belonging to a single fragmentation event. The projectile total and partial charge changing cross sections for Fe and Mg ions on several targets such as carbon, polyethylene and aluminum were obtained in the medium energy region of several hundred MeV/n. 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 the LET spectrum in particle therapies and space dosimetry.

Neutron detectors

Measurement of neutrons is one of most important tasks in radiation measurements. In order to support biology experiments in the neutron exposure facility NASBEE, characterization of the neutron field has been done for LET distribution, energy distribution, spatial distribution and other factors.

In order to measure high energy neutrons onboard an aircraft, a newly developed phoswitch-type neutron detector was used which can distinguished neutrons and protons at high altitude. This onboard study provides the first experimental neutron energy spectrum in the high-energy region (over 10 MeV) with a high energy resolution. For future use of the phoswitch detector in space environment, the detector was tested to simulate launching into space.

It was found that a silicon detector had a funnel effect for charged particles. The charge-collection lengths were 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 was introduced to calculate the charge-collection length and the deposited energy in the silicon detectors.

Scintillation detectors

Organic scintillators have lower response to gamma rays, but we found that their combination with inorganic scintillators led to much higher capabilities (high signal-to-noise (SN) ratio, high energy, time and position resolution) than each scintillator alone. In addition, because the main detector is an organic scintillator, the total cost and weight are very low.

Some prototype detectors were developed to confirm the capabilities. The CROSS-mini was developed to achieve high sensitivity. A plastic scintillator plate as an organic scintillator and two NaI(Tl) plates as an inorganic scintillator were adopted in the CROSS-mini. As the next prototype, CROSS-Zero was developed to confirm possible use as a diagnostic device for small animals (Fig. 6.5). These developments were successful and this new idea of organic scintillators will bring new applications of radiation detectors with high performance.

A new method was developed to obtain reliable calibrations using radioisotope sources. This has proven to be a powerful tool to obtain 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.

At the same time, we looked for cheaper organic scintillators and found a plastic commonly used to make drink bottles was a good candidate. We succeeded for the

first time in the world to measure radiation (α particles, β particles, γ rays, and internal conversion electrons) discharged from a radiation source using this plastic material.

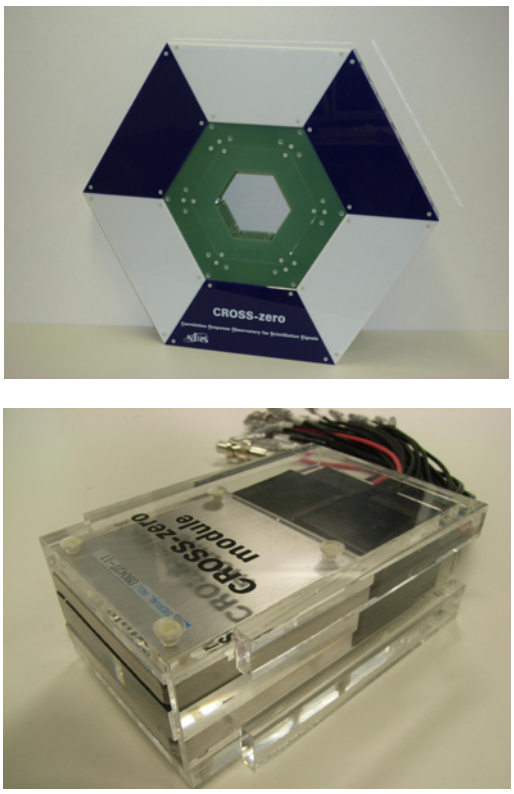

Fig.6.5 CROSS-zero detector (top), which consists of 6 modules. Mounted in each module are an organic material, two thin rectangular NaI(Tl) scintillators, and two photomultiplier tubes (R8900, Hamamatsu Photonics K. K., Japan) (bottom).

ICCHIBAN program

ICCHIBAN (InterComparison for Cosmic-ray with Heavy Ion Beams At NIRS) was started in 2002 and 13 experiments using HIMAC and other accelerator facilities worldwide have been done. Space radiation dosimeters and monitors were irradiated with beams and compared to each other in an international collaboration to understand their responses and to set a standard methodology of measurement and analysis.

From the ground base experiments, we established the standardization for heavy ion beams. However, from our recent space intercomparison experiments (Space-ICCHIBAN-1 to 3), it was recommended that an international society for space radiation be set up for monitoring requests and performing intercomparisons and calibration research in order to understand the responses of luminescence detectors (TLD, OSL, RPL and so on) in the low LET region. For this purpose, the 2nd and 3rd intercomparison experiments (Proton -ICCHIBAN-2 and -3) were performed in the cyclotron facility in NIRS (Figs. 6.6 and 6.7). For these experiments, luminescence detectors which have been used for radiation measurements in the space environment by institutes and universities worldwide, were collected and brought to NIRS and exposed to 30 to 230 MeV proton beams in 2010 and 2011. A total of 13 institutes and universities in 10 countries participated in these experiments. The intercomparison results have been discussed in some international workshops and we will prepare a new standard for space radiation monitoring in the near future.

Fig. 6.6 Photograph of the international participants in the 3rd Proton-Intercomparison experiments.

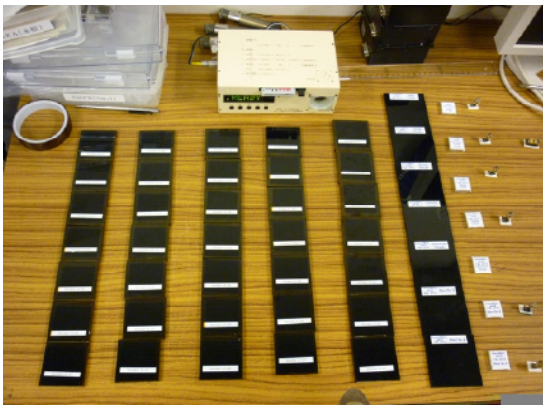

Fig.6.7 Photograph of detector packages in the 2nd Proton-Intercomparison experiments.

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tion of 370 MeV/n ^{20}Ne and 470 MeV/n ^{24}Mg in light targets, *Radiat. Meas.*, **45** (2010),856-860
4. Nakamura H, Kitamura H, Hazama R: Radiation measurements with heat-proof polyethylene terephthalate bottles, *Proceedings of the Royal Society A*., **466**, no. 2122 • p.2847-2856, 2010
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6.1.3. Laboratory Animal Science Section

Contact Point (Dr. Y. Shirakawa): sirakawa@nirs.go.jp

Objectives

In the management of laboratory animal facilities, microbiological and genetic controls are the most important items. In

NIRS, mice have been produced in- place for the past 50 years and provided to internal and external researchers. It is important to verify that a mouse colony is negative for pathogenic viruses, bacteria, endoparasites and ectoparasites. Routine bacteriological and serological examinations for phathogens are performed. For these examinations, a new cage lid for partitioning mouse cage was developed.

Genetic control is also important for standard inbred strains of mice and genetically modified strains of mice. Until now, biochemical and immunological marker genes have been used in the genetic monitoring of the mice strains. However, using these markers is complicated, so a search was made for a more convenient and precise method. The mouse micro satellite markers (MSMs) are a useful tool for genetic analysis of gene mapping, the same as biochemical and immunological loci are. It was proven that genetic monitoring could be carried out by using MSMs.

Progress of Research in the 2nd Mid-term Plan

When mice are transferred among institutions and universities, it is important to verify that the mice were raised under a specific-pathogen-free (SPF) condition.

In our laboratory bacteriological tests for 7 items and serological tests for 7 items have been preformed for the past 50 years. A new cage lid made of stainless steel wire mesh and having a screen barrier for partitioning mouse into compartments was developed (Fig.6.8). The transmissibility of Cilia-Associated Respiratory (CAR) bacillus from infected mice to uninfected sentinel mice

Fig.6.8. A new type of cage lid and mouse cage. The cage is divided into two compartments.

Table 6.1. Results of external fertilization, colliquation, implantation and frozen stored embryo at NIRS.

Strains	External fertilization			Colliquation		Implantation		Frozen Stored Embryo	Note
	Collected Egg	Fertilized Egg	2-cell Stage Embryo	Colliquative Embryo	Normal Embryo	Implantaed Embryo	Fetal Development		
A/J	577	552 (96%)	544 (99%)	54	54 (100%)	36	9 (25%)	490	
C57BL/6J	571	543 (95%)	538 (99%)	18	16 (89%)	16	10 (63%)	520	
C57BL/6J-*bg-nude*	72	71 (99%)	66 (93%)	49	48(98%)	48	24 (50%)	17	636*
C57BL/10	555	536 (97%)	486 (91%)	70	70 (100%)	51	28 (55%)	416	
B10.BR	407	396 (97%)	373 (94%)	22	22 (100%)	22	16 (73%)	351	
B10.D2	143	128 (90%)	122 (95%)	12	12 (100%)	12	6 (50%)	110	
B10.Thy1.1	395	377 (95%)	301 (78%)	32	32 (100%)	32	21 (66%)	266	
BALB/c-*nude*	877	588 (67%)	570 (97%)	70	52 (74%)	52	6 (12%)	500	
C.B.-17	857	736 (86%)	714 (97%)	27	27 (100%)	18	4 (22%)	687	
C.B.-17 *scid*	941	882 (87%)	803 (98%)	61	59 (97%)	59	8 (14%)	742	
C3H/He	568	547 (96%)	530 (97%)	32	31 (97%)	31	20 (65%)	498	
C3H/He-*scid*	478	467 (98%)	457 (98%)	127	115 (91%)	105	39 (37%)	330	409***
C3H-*Atm*	253	220 (87%)	215 (98%)	22	18 (82%)	18	8 (44%)	193	
STS	691	359 (58%)	353 (98%)	75* 21**	73 (97%) 21(100%)	73 21	49 (67%) 17 (81%)	278 296	
RFM	1169	1007 (92%)	1061 (99%)	56	56 (100%)	47	29 (62%)	1005	

*: External Fertilization **: Natural Mating ***: Separately Frozen Heterozygote

was tested to evaluate the effectiveness of this cage. The cage lid is very useful when uninfected mice are used in quarantine and in contagion experiments to prevent fighting among the mice.

The frozen embryos of 15 strains of mice maintained at NIRS were stocked at our laboratory and deposited into the Riken Bio Resource Center (Riken-BRC) and Center of Animal Reproduction and Development at Kumamoto University (Kumadai-CARD).

Table 6.1 shows the results of external fertilization, colliquation, implantation and the number of frozen stored embryo in our laboratory.

The genetic monitoring system using MSMs was originally established for15 inbred strains of mice. It was considered to be excellent regarding time, labor, economy, efficiency, validity, and accuracy, compared with biochemical and immunological markers. However, it was difficult to determine the genotype by viewing, because the DNA fragment pattern after agarose gel electrophoresis was unclear and PCR product size numerically. Although it was difficult to determine the genotype by viewing the agarose gel electrophoresis, the genotype could be examined thoroughly with MultiNA.

The optimal selection of MSMs was necessary, so a total of 101 loci MSMs of 19 mouse chromosomes were selected, and of them 60 of these loci were determined to be usable. To perform this technique more efficiently, these loci were narrowed down to 1 or 2 per chromosome, for 37 loci in total, which we will use as standard markers for genetic monitoring (Fig.6.9). The genetic monitoring by these 37 MSMs is possible on inbred strains and also congenic and outbred strains (Fig.6.10).

In the facilities which have maintained the mouse strains, this system is applicable even in everywhere.

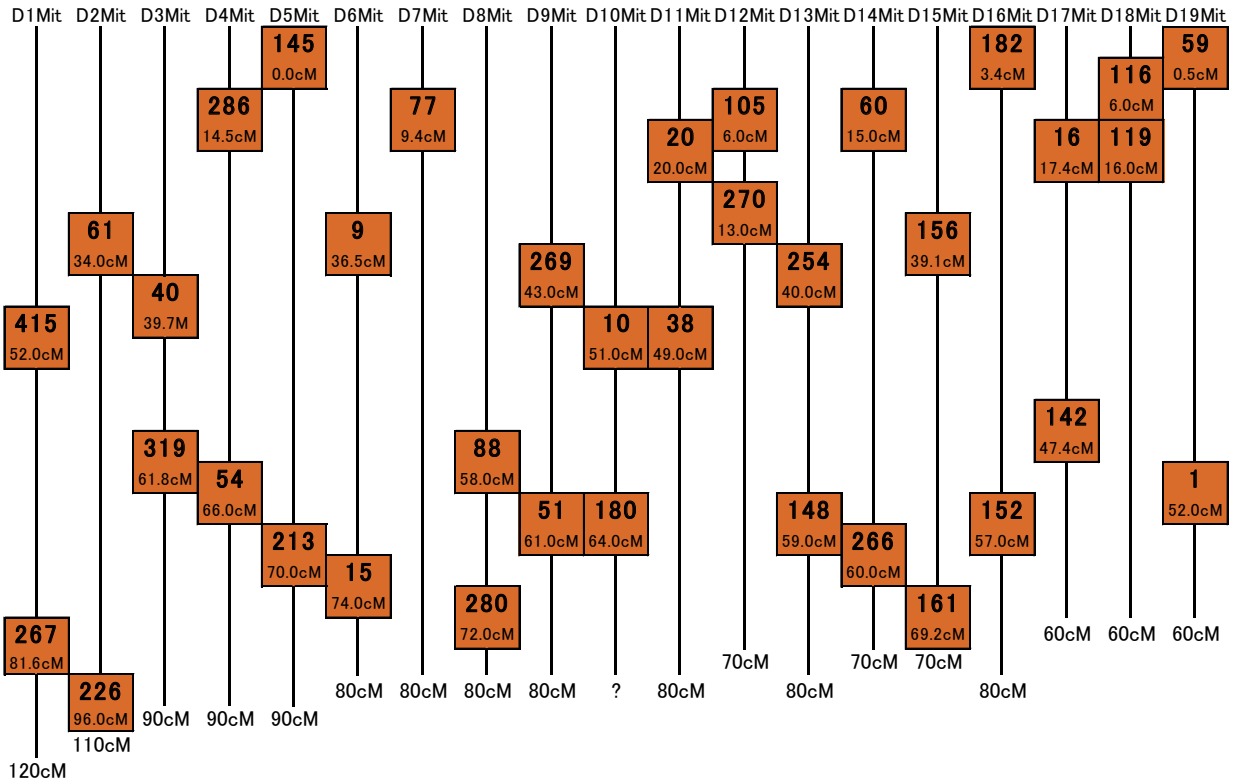

Fig.6.9. The 37 MSMs selected for genetic monitoring of mice.

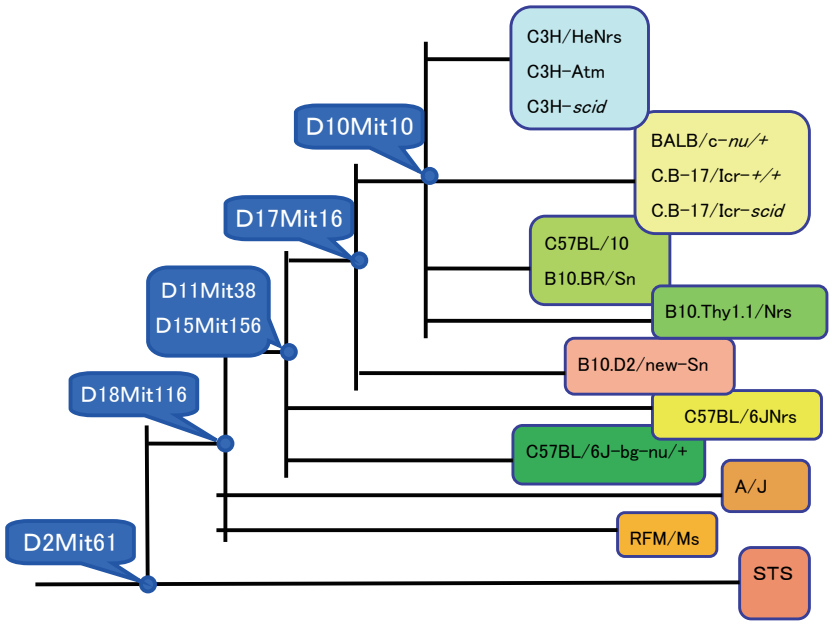

Fig.6.10. The most effective 6MSMs which are distinct in 15 strains of mice maintained at NIRS.

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1. Kokubo T, Matsushita S: Evaluation of new cage lid with partitioning barrier based on transgenic of CAR Bacillus in mice, *Exp. Anim.*, **58**(2), 189-192, 2009
2. Umino A, Ueno W, Iina M, Niizuma D, Ida H, Miyazawa M, Hayao T, Nishikawa T: Establishment of the genetic monitoring system of the mouse using microsatellite markers, *J Exp Anim Tech*, **43**(2), 47-52, 2008 (in Japanese with English summary)
3. Umino A., Iina M., Ookubo T., Niizuma D., Ishihara N., Ito M., Fujii K., Mugasa I.,Ueno W., Hayao T., Nishikawa T: The trial for the genetic monitoring system of the mouse by the microsatellite markers with MultiNA, *J Exp Anim Tech*, **45**(1), 9-14, 2010 (in Japanese with English summary)
4. Iina M, Umino A, Ookubo T, Ueno W, Hayao T, Nishikawa T: Establishment of mouse genetic monitoring system in National Institute of Radiological Sciences, *J Exp Anim Tech*,**45**(2), 65-72, 2010 (in Japanese with English summary)
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7. List of Original Papers

This list includes main publications by staff members that appeared during the period from April 1, 2010 to March 31, 2011.

Research Center for Charged Particle Therapy

Developing Advanced Clinical Therapy with Charged Particles

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Department of Technical Support and Development

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