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NATIONAL INSTITUTE OF RADIOLOGICAL SCIENCES

ANNUAL REPORT

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Preface

Since its initial establishment in 1957, the National Institute of Radiological Sciences (NIRS) has conducted comprehensive research in science and technology related to radiation and human health. In 2001, the NIRS reformed its structure as an independent administrative institution, and began a system to carry out activities according to a 5-year mid-term plan. The fiscal year 2009 (April 2009 - March 2010) was the 4th year of the second mid-term plan (2006 - 2011), and this Annual Report summarizes our research activities and major advances during this period.

The NIRS continues to promote the combined progress of radiation protection and the medical use of radiation. The most remarkable progress was made by designation of NIRS as a collaborating center of the International Atomic Energy Agency (IAEA). The activities as an IAEA collaborating center involve three fields : low-dose radiation effects, charged particle radiotherapy and molecular imaging. Since the NIRS aims to contribute to human health and to secure a safe society through radiological sciences, which corresponds to the main pillars of the IAEA, we would like to focus our maximum efforts towards a common mission. Charged particle therapy for cancer treatment continues to be the major topic in the medical use of radiation. The number of patients treated with this modern technology exceeds 5,000 over the past 15 years, and we celebrated this successful accomplishment in October 2009. The activities in radiation protection and preparation for possible accidents have been strengthened in collaboration with national regulatory agencies and international organizations. In order to establish an efficient system to prepare for emergency radiation accidents, we started the Radiation Emergency Medical Assistant Team (REMAT) in which we send our experts to the site of radiation emergency, particularly in Asian regions, where the number of nuclear power plants is expected to increase rapidly.

The NIRS continues its efforts to establish a solid base as a core institution promoting comprehensive scientific research in a wide range of radiological sciences, and we ask your support to accomplish our mission.

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

President

Annual Report 2009 - 2010
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1. Outline of Research Activities

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

The National Institute of Radiological Sciences (NIRS) was reformed as an Independent Administrative Institution in April 2001, when the first Mid-term Plan was started. In the second Mid-term Plan, which started in April 2006, NIRS research consisted of five fields including heavy charged particle therapy, molecular imaging, radiation protection, radiation emergency medicine and radiation technology. Both plans have been carried out by four research centers and one fundamental technology center. In this report, the achievements obtained by these centers during the four year (FY 2009 : April 2009 to March 2010) of the second Mid-term Plan are presented.

Judging from the outcome in FY 2009, including publications, presentations at scientific meetings, and collaborations with other institutes/groups, etc., it can be summarized that substantial, high level achievements had been obtained. The number of original papers published reached 294, and many of them were published in international journals with high reputation. Furthermore, more than 149 proceedings were presented at international and domestic scientific meetings, 504 oral presentations, and 58 patent applications. Collaborative studies and exchanges of researchers were also active : 112 collaborative studies were carried out, 1502 researchers worked as visiting staff, and 399 students were accepted as trainees.

The International Open Laboratory (IOL) began last year, for which 3 units were approved, including the "Particle therapy model research unit", the "Particle radiation molecular biology unit", and the "Space radiation research unit". The purpose of IOL was to create and maintain favorable environments in which young scientists can engage in advanced research at an international level. Despite the limited period since its inception, young researchers from abroad stayed in NIRS with outstanding achievements together with the NIRS staff. This success was reviewed and evaluated externally by invited world-renowned scientists.

The Research Center for Charged Particle Therapy, using HIMAC, has continuously conducted clinical studies on carbon ion radiotherapy and its related biological and physical effects. In FY 2009, a total of 692 patients (748 lesions) were treated, and the overall number of patients has reached 5,196 since June1994. This year we completed the construction of a new treatment research building as an extension of the HIMAC facility. For the new facility, we developed a new type of irradiation technique, including the spot-scanning method for treatment of moving targets. Basic fundamental studies were also conducted to obtain biological evidence useful for the development of clinical protocols of carbon ion radiotherapy. We have been supporting the charged particle project at Gunma University, which successfully completed construction of the new facility and started carbon ion therapy in March 2010.

In the Molecular Imaging Research Center consisting of four groups, an understanding of the mechanism of brain function and cancer pathology has progressed and a study on its clinical application has been carried out using PET and MRI. An example of the achievements included the tumor PET imaging of the anti-c-kit antibody with 111In-IgG and 111In-Fab as well as the possibility of immuno-radiotherapy. In a molecular neuro-imaging study on PET, the binding potential (%) of a norepinephrine transporter was evaluated against the effectiveness of the drug used for depression. One of the highly evaluated studies combined the use of fMRI and PET imaging to closely correlate emotions like fear and anxiety to the D1 binding dopamine receptor in amygdala. This could lead to the development of a new drug for psychiatric diseases. In an effort to develop OpenPET, the activity was extended to the stage of a conceptual design of a prototype machine.

Research on radiation protection and radiation emergency medicine, an important mission of our institute since its establishment, has been carried out primarily in two centers. These centers played a role as a national hub in collaboration with international organizations including the IAEA, ICRP, UNSCEAR, WHO, etc. This year we have organized REMAT. This is a medical team, which will be sent to support medical care when an accident occurs due to radioactive contamination and radiation exposure in foreign countries.

The Research Center for Radiation Protection has been providing a scientific basis for establishing regulations with global standards for radiation protection, security and safety, focusing on low-dose radiation effects derived from human-made and environmental radiation. For this purpose, fundamental radiobiological research has been carried out to promote public understanding of radiation effects and to encourage enactment of more reasonable regulations for the safe and secure use of radiation in our lives. This year, interesting findings were obtained regarding life-threatening effects of radiation on fetuses and children and the mechanism of radiation-induced cancer. The Center has renewed its designation by the IAEA as a " Collaborating Centre for Biological Effects of Low Dose Radiation".

The NIRS has been positioned as a national center for radiation emergency medical preparedness in the nuclear disaster prevention system established by the Japanese Government. The Research Center for Radiation Emergency Medicine is responsible for providing unexpectedly exposed victims (patients) of the advanced radiation emergency medicine in

cooperation with the hospital in NIRS. The Center also carried out activities to maintain and strengthen the emergency preparedness system fulfilling its role by establishing three nation-wide network councils for medicine, bio-dosimetry with chromosome analysis, and physical dosimetry. Furthermore, the Center conducted fundamental studies and investigations on radiation protection and treatment in the case of radiation exposure.

The Fundamental Technology Center, which was established to support various studies performed in the NIRS with advanced fundamental technology, has been carrying out maintenance and quality control of accelerators including SPICE, PASTA, NASBEE, etc., as well as radiation measurement apparatus for cosmic rays. Regarding this research, the world's first discovery was made, namely that plastic bottles (PET bottles) could be used as scintillator material for PET examination. Efforts were also extended to establish and support experimental animal laboratories for internal and external researchers.

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

In this report you will be able to observe substantial research that was performed in the fourth year of the second Mid-term Plan. I would like to conclude with a heartfelt thanks for cooperation and advice provided to us by all parties concerned.

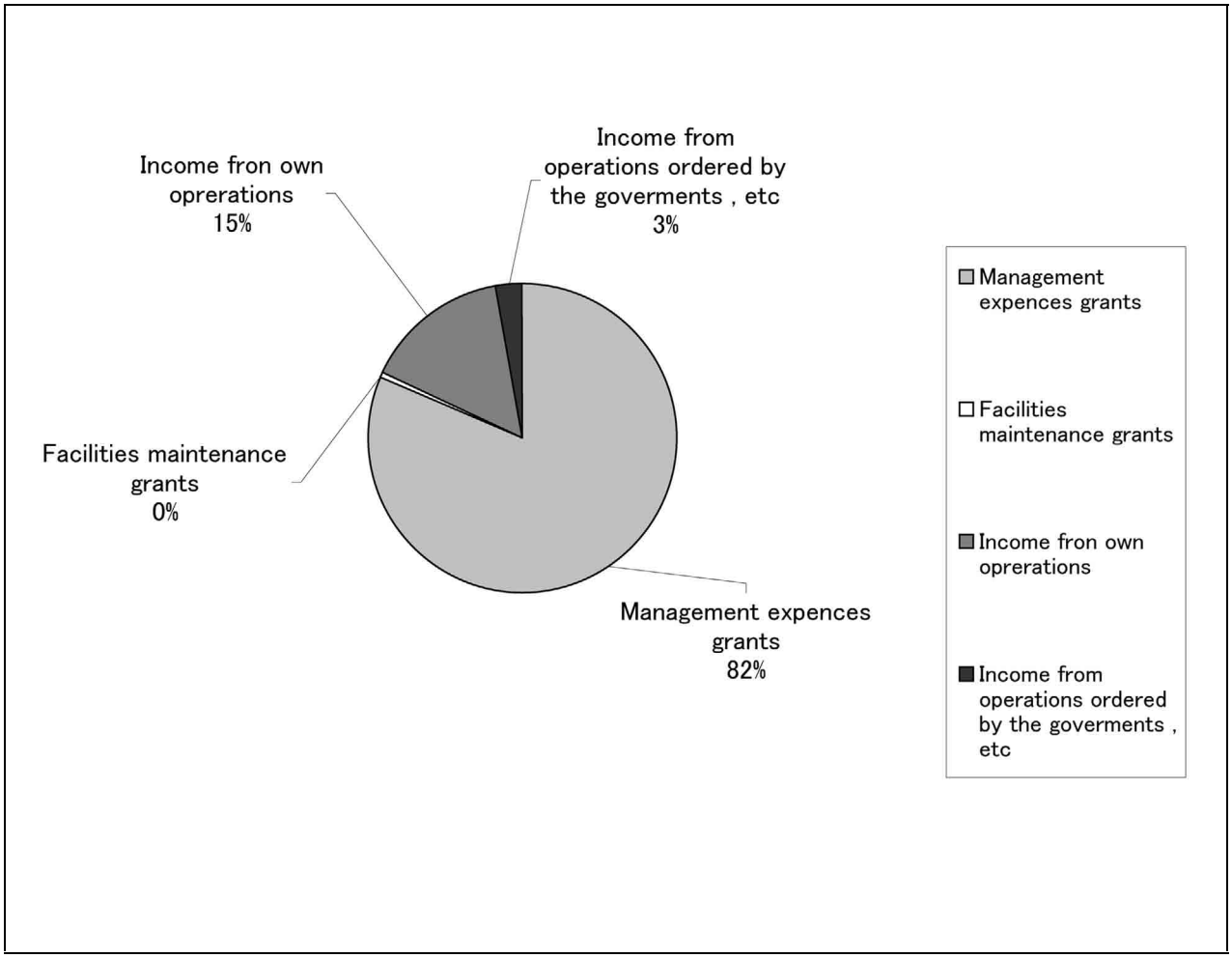
2. Organization Chart and Budget

(1) Organization

- Board of Executive Directors : President, Executive Directors, Auditors
  - Department of Planning and Management
  - Department of General Affairs
  - Department of Information Technology
  - Fundamental Technology Center
    - Planning and Promotion Office
    - Department of Technical Support and Development
    - Department of Safety and Facility Management
  - Research Center for Charged Particle Therapy
    - Planning and Promotion Office
    - Hospital
    - Department of Accelerator and Medical Physics
    - Quality Control Section
    - Radiological Protection Section
    - Promotion of Carbon Therapy Section
    - Particle Therapy Research Group
    - Medical Physics Research Group
    - Diagnosis and Treatment Advancement Research Group
    - Radgenomics Research Group
    - Heavy-Ion Radiobiology Research Group
    - Transcriptome Research Group
  - Molecular Imaging Center
    - Planning and Promotion Unit
    - Diagnostic Imaging Group
    - Molecular Neuroimaging Group
    - Molecular Probe Group
    - Biophysics Group
  - Research Center for Radiation Protection
    - Planning and Promotion Office
    - Department of Advanced Technologies for Radiation Protection Research
    - Regulatory Sciences Research Group
    - Experimental Radiobiology for Children's Health Research Group
    - Radiation Effect Mechanisms Research Group
    - Environmental Radiation Effects Research Group
    - Nakaminato Laboratory for Marine Radioecology
  - Research Center for Radiation Emergency Medicine
    - Planning and Promotion Unit
    - Department of Radiation Emergency Medicine
    - Department of Radiation Dosimetry
  - Director of Special Research
  - Audit Office
  - Compliance and Integrity Office
  - International Open Laboratory

(2) Budget (2009.4～2010.3)

Total	14,374 million yen	%
Management expences grants	11,712 million yen	81.5%
Facilities maintenance grants	64 million yen	0.4%
Income fron own oprerations	2,201 million yen	15.3%
Income from operations ordered by the goverments , etc	397 million yen	2.8%



3. Research Center for Charged Particle Therapy

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

Outline of Research Career

Dr. Kamada received a Ph.D. from Hokkaido University in 1996 for his study on radiotherapy of bile duct cancer. He has had 30 years of experience in clinical research on radiation oncology, including 14 years experience in carbon ion radiotherapy at the 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 the Director of Research Center for Charged Particle Therapy, NIRS since 2008.

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Objectives

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

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

Overview

The Center is organized into 6 research groups for two major topics (A and B) and one invited research project (C). Progress of research for each topic is summarized next.

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 carried out by the Particle Therapy Research Group (GL ; H. Tsuji) consisting of 3 teams : the Clinical Trial Research Team, the Clinical Database Research Team, and the 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 2009 as well as in previous years.

The Clinical Trial Research Team has succeeded in maintaining a large number of patients per year. Specifically, 692 patients, the maximum number ever, underwent carbon ion radiotherapy (C-ion RT) in FY 2009. So far, a total of 5196 patients were enrolled in clinical trials of C-ion RT. 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 revealed that C-ion RT provided definite local control and offered a survival advantage without unacceptable morbidity in a variety of tumors that were hard to cure with other modalities. In addition, it was possible to implement hypofractionated radiotherapy by using carbon ion beams, mainly in the treatment of common cancers, scu as lung cancer (single fraction), liver cancer (two fractions), and prostate cancer. New clinical trials of combined treatment of C-ion RT and chemotherapy were started to obtain even better survival outcomes in intractable tumors, such as pancreatic cancer, brain tumors, and malignant melanoma of head and neck regions. Survival benefits in malignant melanoma by combined treatment has been already observed.

Improvement of efficiency in C-ion RT is also an important subject in the effective use of a limited capacity of the facility. A new method for manufacturing range compensators, which eases prearation of the treatment, has been developed and used in actual treatments. Furthermore, the setup procedure could become easier and faster with a new field localization system using a flat panel detector (FPD), which was also began to be used this year.

The Clinical Database Research Team has improved the coordination among severaldatabase systems (Hospital Information System, Therapy Plan Database, Therapy Schedule Management System, two PACSs and Radiology Information System for Radiation Therapy). The developed information systems, conforming to the Integrating the 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 improved efficiency of patient registration and resulted in an increase in the number of patients. In addition, the processing speed and ease of operation of the clinical database system have been improved. By using this system physicians can analysis patients by the heavy particle radiation therapy protocol and generate survival curves in a few seconds.

The Radiation Effect Research Team has aggressively performed experiments and analyses as well.

In order to analyze the mouse skin reaction in fractionated C-ion radiation, applicability of the LQ

model was investigated together with the RCR (repairable-conditionally repairable) model and the multi-target two components model. While the LQ model failed to express a decrease in response by single irradiation, RCR showed good agreement with experimental observations.

In addition to research on verification of actual radiation field, which was performed last year, the MKM (Microdosimetric Kinetic Model) was applied to estimate cell survival of hypoxic cells based on the response under oxic conditions in FY 2009. As a result, it was found that by adjusting the domain size to half that of oxic conditions, the cell survival of hypoxic cells could be correctly estimated.

② Development of a novel irradiation system for charged particle therapy

This subject has been carried out by the Medical Physics Research Group (GL ; K Noda) consisting of 4 teams : the Accelerator Development Research Team, the Irradiation System Research Team, the Therapy System Research Team, and the Compact Heavy-Ion Therapy System Research Team.

On the basis of more than 10 years of experience with HIMAC, the Medical Physics Research Group has 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. Furthermore, the new treatment research facility should accurately treat a fixed target, a moving target with breathing and/or a target near to a critical organ. For these purposes, a 3D-scanning method with a pencil beam is employed. A phase-controlled rescanning (PCR) method has been proposed and studied, especially for treating a moving target. In the new treatment facility, a rotating gantry with the PCR method will be also employed in order to reduce the patient's load, and to increase the treatment accuracy for a tumor near to a critical organ through the multi-field optimization method. After the design of beam-optics, a mechanical design has been carried out. As a result, the weight of the gantry is suppressed to 350 tons, which is almost half that of HIT gantry. For multi-field optimization, inverse-planning has been further studied. It was verified that the method can reduce the dose in OAR significantly while keeping that in the target.

Including the studies mentioned above, we have designed fixed beam-delivery, rotating-gantry, treatment-management, patient-positioning and treatment planning systems in the new treatment research facility. Related R&D work has also been carried out with HIMAC since April 2006. A building of the new treatment research facility was completed in March 2010. After installing the devices of the beam transport and beam-delivery systems, a beam commissioning and pre-clinical study are scheduled in FY 2010.

③ Standardization and improvement of therapeutic and diagnostic techniques

This research covers a wide range of research and has been performed by the Diagnosis and Treatment Advancement Research Group (GL : T. Kamada) consisting of 4 teams : the Image Diagnosis Research Team, the Image Processing Research Team, the Quality Control Research Team, and the 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 for cervical cancer was continued and metastatic lymph node imaging using C-11-Methionine (MET) was also investigated. For Cu-62-ATSM imaging for tumor hypoxia, this team found that accumulation of squamous cell carcinoma in Cu-62-ATSM PET/CT after CIRT was significantly lower than pre-therapeutic accumulation. This might imply that squamous cell carcinoma of the uterine cervix tended to hypoxic in pre-therapeutic condition and that CIRT might improve its hypoxic condition. The improvement of hypoxic condition might be associated with the therapeutic effect of CIRT. For metastatic lymph node imaging using C-11-methionine, this 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 true positive metastases 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 lymphnode metastasis from trunk cancers was higher than from head and neck cancers.

The Image processing research team analyzed intrafractional organ movement during respiration using 4D CT (256MSCT) applied to patients with pancreatic carcinoma in 2009. They evaluated intrafractional organ motion and dose validation for ungated and gated treatments. Doses to organs at risk were smaller in the gated than in the ungated treatment, although the differences were small. They suggest 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 the gated treatment. The use of an ungated treatment may shorten total treatment duty time by a factor of three compared with gated treatment in pancreatic cancer.

The quality control research team has developed a graphite calorimeter for absolute absorbed dose

measurement. The absorbed dose obtained by the calorimeter was approximately 3 to 4% higher than that by an ionization chamber for carbon beams. The disparity seems to arise from uncertainties of stopping power and the w-value for carbon beams.

This team carried out studies on dosimetry for therapeutic hadron beams.

The radiological protection research team performed dosimetric studies for secondary cancer risk after receiving carbon-ion and proton radiotherapies. Absorbed dose, quality factor and dose equivalent in water phantom outside of the irradiation field were determined by microdosimetric measurements with a commercial tissue equivalent proportional counter at passive carbon-ion and proton radiotherapy facilities : HIMAC and National Cancer Center Hospital East. They confirmed that the total secondary doses per treatment in carbon-ion and proton radiotherapies were comparable to or less than those in 3D-CRT and IMRT. They were considerably less than those in 3D-CRT and IMRT as the position became closer to the field edge. Verification of Monte-Carlo simulations, which is needed to assess the detailed distributions of dose and biological effectiveness, is in progress.

B. Research on radiation effects for improvement of radiation therapy

① RadGenomics research concerning the radiation sensitivity

This subject has been carried out by the RadGenomics Research Group (GL; T Imai) consisting of 3 teams: the Genetic Information Team, the Molecular Radio-oncology Team, and the Molecular Biostatistics Team.

Normal tissue reactions of cancer patients vary considerably after radiotherapy. A number of observations have indicated that certain genetic factors play important roles in this variability. The aim of the RadGenomics Research Group is to explore the genetic characteristics for both the patient and the bearing tumor, by which the potentially most effective radiotherapy can be delivered. From a molecular-biological standpoint, this would open a way to the development of an individual-oriented radiotherapy. This research group has focused on searching genetic predictive markers for clinical radiosensitivity of normal tissues and tumors. The clinical radiosensitivity of normal tissue is likely to be a complex trait that is dependent on the cumulative effect of many minor genetic determinants. We have searched for polymorphisms associated with radiosensitivity of patients having undergone radiotherapy.

In FY 2009, we focused on the following research subjects.

First, we investigated a novel molecular biomarker for cervical adenocarcinoma (AD) through the integration of multiple methods of genomic analysis. A difference between biopsy samples of AD and squamous cell carcinoma (SCC) was identified in the expression and genomic copy number of Villin1 (VIL1). Kaplan-Meier survival curves revealed worse disease-free survival in VIL1-positive tumors. The marker was validated by 65 newly enrolled patients, and VIL1 positive staining showed 52% sensitivity and 100% selectivity for cervical AD. This study suggests the existence of a subtype of cervical tumors which are VIL1 positive with a poor radioresponse.

Next, we extended our previous finding that fibroblast growth factor 2 (FGF2) expression levels in tumor cells (FGF2-T) may be an indicator of the efficacy of radiotherapy in cervical cancer (CC), using newly enrolled patients and further investigated stromal FGF2 expression, which was detected in tumor cells of all cases and in stromal cells in 87% of cases. Radiation causes a response in tumor cells and adjacent normal cells, and changes the extracellular matrix environment. In this study, we confirmed our previous findings showing that changes in FGF2-T expression may be used as a marker to monitor the effectiveness of radiotherapy for CC. Our findings should improve patient selection for molecular targeted therapies, such as cytokine inhibitors, following standard-of-care treatment.

Finally, to clarify how carbon-ion radiotherapy (C-ion) on primary tumors affects the characteristics of subsequently arising metastatic tumor cells, mouse squamous cell carcinomas, NR-S1, synergic C3H/HeMsNrs mice were irradiated with C-ion or gamma-rays. Irradiation doses used in this study did not suppress primary tumor growth, but inhibited lung metastasis significantly. We found no difference in the incidence and histology, and only small differences in expression profile, of distant metastasis between local C-ion and gamma-ray radiotherapy. The application of local radiotherapy per se or the type of radiotherapy applied did not influence the transcriptional changes caused by metastasis in tumor cells.

② Biological research concerning the improvement of radiation therapy

This subject has been carried out by the Heavy-Ion Radiobiology Research Group (GL ; R Okayasu) consisting of 4 teams : the Biophysics Team, the Experimental Therapy Team, the Cellular and Molecular Biology Team, and the Radiation Modifier Team.

Biophysics Team : In order to clarify the contribution of indirect and direct effects induced by heavy ions, cell survival fractions were measured for various LET values (15 to 480 KeV/μm) using Chinese hamster ovary (CHO) cells. The contribution of direct action

increased as LET increases; the contribution of indirect action was about 20% when LET was 480 keV/μm. The relative biological effectiveness (RBE) was determined for direct action (RBED) and indirect action (RBEI) separately. The maximum RBED was 9.1 at 480 keV/μm and the maximum RBEI was 2.6 at 90 keV/μm. These results indicate that the direct action induced by heavy ions results in a very high biological effectiveness.

Experimental Therapy Team : Malignant melanoma showed a good local control by heavy ion treatment despite the low overall survival of patients. The effects of carbon ions (C-ions) on metastatic potential were studied for melanoma in vitro and in vivo. Carbon-ion showed higher cytotoxic effects on B16/BL6 cells in vitro than X-rays. Both migration and invasion potential of cells were enhanced by photon beams at low doses (0.5 to 1 Gy) when compared to non-irradiated controls; however, these factors were suppressed by C-ions. The RBE values for migration and invasion in vivo were higher than that for cell killing. The number of lung metastatic nodules after tumor-irradiations decreased with each dose, and C-ions were more effective than photons. Our study suggests that C-ion significantly inhibits the metastatic process when compared with low-LET photons. This team also studied the effects of stem cells in tumors irradiated with heavy ions using a tumor xenograft model. Significant control of stem-like cells was observed after C-ion irradiation.

Cellular and Molecular Biology Team : We developed a useful chordoma cell line, U-CH1-N out of the only chordoma cell line available in the world, and determined its radio- and chemosensitivity. Our data provides the first chronological cell survival using cells of the chordoma origin and helps to explain the successful chordoma treatment by heavy ions. A group of early responsive IR-induced genes (e. g., ATF3, BTG2, TP53INP1) remained activated in human cells irradiated with carbon ions when compared with X-rays. We found that the expression of ASPM, a microcephaly gene, was significantly downregulated by IR in human and murine cells. We started to characterize the function of this gene by RNA interference ; a significant increase in radiosensitivity of several tumor cell lines was demonstrated. The other approach was to generate a mouse model whose Aspm orthologous gene (calbpm1) was conditionally disrupted.

Radiation Modifier Team : To develop a new radio-protector, we measured the redox potential of various natural antioxidants. We found a new radio-protector in an in vivo setting having nitroxyl radical and edaravone moieties. We measured the DRF value of γ-TDMG against X-irradiated bone marrow death of mice ; it was 1.2 by i. p. administration of the compound immediately after exposure. The effect of radio-protectors on tumor regulation by heavy ions was investigated using a mouse xenograft model. The effect of amifostine on tissue oxygen tension was measured by EPR oxymetry. The distribution of reactive oxygen species generated by heavy ions was also measured and analyzed. In addition, the combination of X-ray and a PI3-kinase inhibitor was found to enhance anti-tumor activity both in vitro and in vivo.

③ Transcriptome Research for Radiobiology

This subject has been carried out by the Transcriptome Research Group (GL; Abe) consisting of 3 teams : the Stem Cell Research Team, the Gene Expression Profiling team, and the Model Organism Research Team.

This year these teams obtained some notable results, especially on induced pluripotent stem (iPS) cells and on HiCEP technology as follows.

Recently, it has been demonstrated that somatic cell can be converted into pluripotent stem cells by ectopic expression of four genes, Oct3/4, Klf4, Sox2 and cMyc. Such somatic cell reprogramming suggests the possibility of generating patient-specific pluripotent stem cells. Replacement of or adding tissues prepared from patient-specific stem cells have great potential for the therapeutics of radiation-induced injuries. While needless to say, elucidating the molecular mechanisms underlying iPS generation is a key issue for efficient preparation of safe iPS cells that can be use for various medical uses, it has been quite difficult due to its unique characteristics, extremely low efficiency and stochastic manner.

The Transcriptome Research Group attempted to observe the emergence of iPS cells from somatic cells directly. Finally, they developed a new investigation system by improving a pre-existing time-lapse system that allows us to precisely investigate iPS generation at short intervals over 2 weeks. Using this system, they first succeeded in directly observing the conversion process of a somatic cell into a stem cell. Interestingly, it was revealed that the onset of the cell lineage conversion already initiated within 48 hours just after the defined gene infection in most (85.7%) iPS cell generations. In addition, unexpectedly, no morphological asymmetric cell division occurred during the conversion process from an ancestral somatic cell into an iPS cell. Namely, ancestral fibroblast cells gradually transformed into stem cells with several symmetric cell divisions. Thus, they provided critical new insight during the first three days of iPS cell generation, which was completely unknown.

This group also made another contribution in the field of iPS. They succeeded in generating genome integration-free iPS cells without an oncogene, c-Myc, for the first time, by transduction. In addition, these

iPS cells were established from somatic cells prepared from inbred mice whose genome sequence was completely determined. These materials, therefore, will serve as a valuable resource for future genetic studies of iPS cell generation.

Meanwhile, this team has developed an ideal transcriptome analysis procedure called High coverage gene expression profiling (HiCEP). The method is based on a principle different from various hybridization-based methods. This year they improved the HiCEP method to allow it to analyze even a small amount of starting materials, less than 10-20 mammalian cells. On the other hand, they also developed a new effective system for HiCEP analysis. They have developed a high throughput machine for HiCEP reaction called HiCEPer that enables us to analyze more than 15,000 samples per year, and a precision PCR (polymerase chain reaction) machine for the HiCEP reaction. This equipment was released in the H21 fiscal year. In addition, they developed a HiCEP reaction kit, for 1 μg starting material. The kit allows anyone, even without expertise in molecular biology, to achieve HiCEP analysis.

C. Research Projects with Heavy Ions at NIRS-HIMAC

131 proposals were accepted and carried out in FY2009 at HIMAC. 5490 hours of beam time was supplied in that research. 109 papers and 59 proceedings were published, while 331 papers were presented at various meetings. A total of 625 researchers participated in the project, including 85 foreign researchers for 15 international projects.

3.1. Developing Advanced Clinical Therapy with Charged Particles

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

Outline of Research Career

Dr. Tsuji received a Ph.D. from Tsukuba University in 1996 for his study on proton radiotherapy of hepatocellular carcinoma. He has had 27 years of experience in clinical reseach on radiation oncology, including 14 years experience in carbon ion radiotherapy at the NIRS. Since 2008, he has been group leader of the Particle Therapy Research Group for developing advanced clinical therapy with charged particles.

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Objectives

- 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.
- A study on optimizing irradiation methods by disease and by region, using clinical investigations of therapies in which radiation is combined with drugs and operations.
- Development of a comprehensive database on treatment, clinical course and other factors. Comparison and analysis of domestic and foreign data on particle beam therapy.
- Annual treatment of 500 patients to maximize and disseminate the therapeutic effect of charged particle technology. 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.
- Evaluation of the therapeutic effects of treatments developed by the NIRS from the viewpoint of quality of life (QOL) and therapeutic costs. 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, the Clinical Database Research Team, and the Radiation Effect Research Team. All teams are performing research and development on charged particle therapy. Progress of research in each team is summarized below.

1) Clinical Trial Research Team

From June 1994 to February 2010, a total of 5196 patients were enrolled in clinical trials using carbon ion beams generated by HIMAC. Carbon ion radiotherapy of these patients was carried out by nearly 50 different phase I/II or phase II protocols and highly advanced medical technology. Figure 3-1 lists the number of the patients for each tumor site treated with carbon ion beams.

Tumor sites in Carbon ion radiotherapy at NIRS

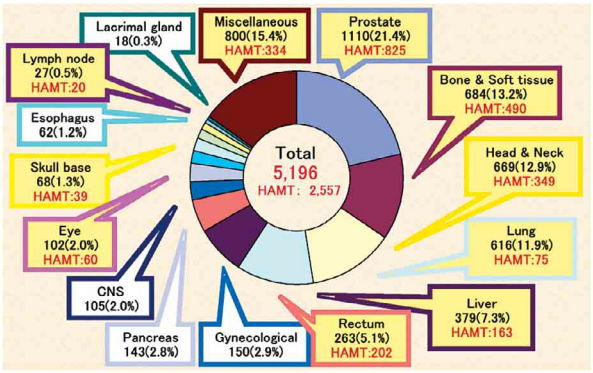

Fig. 3-1. The number of patients for each tumor site treated with carbon ion beams.

We treated 692 new patients in FY 2009. Prostate, lung, head and neck, bone and soft tissue, and liver tumors are the 5 major tumor types in the trials. A total of 4504 patients who had a follow-up period of 6 months or more were included in this report. Clinical trials revealed that carbon ion radiotherapy provided definite local control and offered a survival advantage without unacceptable morbidity in a variety of tumors that were hard to cure with other modalities. Using carbon ion beams, it was possible to implement hypofractionated radiotherapy, with application of larger doses per fraction and a reduction of overall treatment times as compared to conventional photon radiotherapy. Carbon ion radiotherapy has been approved by the Ministry of Health, Labor and Welfare of Japan as "Highly Advanced Medical Technology (HAMT)" since November 2003. Nearly 74% of the patients receiving carbon ion radiotherapy were treated by HAMT in 2009.

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 a 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. A new treatment control system has already started to be designed that would also be available for treatment in the new 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. The range compensators made with this new method has started to be used in actual treatment.

The new field localization system using a flat panel detector (FPD) was started to be used in 2009. Since localization images with FPD have higher resolution than conventional radiographs, the setup procedure could 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 patient's findings which include symptoms, tumor responses, and toxic reactions that should be estimated by a physician during a clinical interview. We improved the coordination among several database systems (Hospital Information System, Therapy Plan Database, Therapy Schedule Management System, two PACSs and Radiology Information System for Radiation Therapy). These systems are interconnected and necessary data are transmitted.

We also developed information systems that conform to the Integrating the 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 function to ease this troublesome manipulation. We developed middle-ware for the EUA and PSA functions to reduce the implementation load among the EMR, PACS-viewer, report-viewer, radiation scheduling system and radiation information system. We realized that EUA and PSA functions were essential in a multi-system environment. Our middle-ware resolved the complexities of the application implementation. The established guideline was useful to unify the user interfaces of each application. We found that the EUA and PSA functions are critical for visual integration.

We implemented a system to share medical data between hospitals and medical institutions. This system is based upon the IHE Cross-Enterprise Document Sharing (XDS) which uses SOAP, ebXML RIM and Web Service Description Language (WSDL) and HL7. We prepared the Open Source Software license for the delivery of software. We implemented the document source, document repository, document registry and document consumer that were defined by the IHE XDS. We had developed the application software. We are now designing and developing interface function that communicates between the existing system such as EMR and/or PACS and the IHE XDS system. We think that it is very important to establish a new IHE integration profile. This enables the Treatment Management System to receive and send radiotherapy orders.

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

The NIRS Hospital Information System in May 2010 is shown in Fig. 3-2.

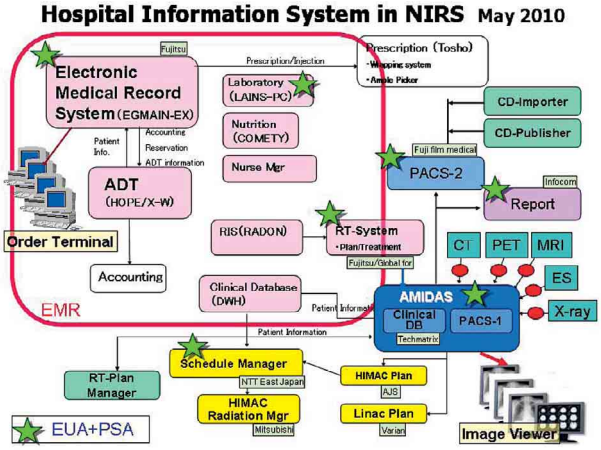

Fig. 3-2. Current configuration of Hospital Information System in NIRS.

3) Radiation Effect Research Team.

Radiosensitivity analysis based on the TCP model has been applied for the analysis of toxicity on benign tissue. Late toxicity on the genitourinary (GU) tract observed during treatment of prostate cancer with carbon ions was analyzed with the model. The analysis revealed that the α/β value of the GU was 7.7, more than 2 times larger than that against photons (3.0) in the literature. BED calculated with the α/β value for carbon-ion beam was 73.8, which was consistent with that for photons, 74.7. The information will contribute to the prospective estimation of a prescribed dose in different fractionation or further dose optimization in treatment planning.

Reaction of skin is one of the most important endpoints to be considered in radiotherapy ; however,

its analysis from clinical outcomes is not easy as radiation quality and dose given to patients significantly differs individually. From this point of view, skin reaction has been investigated through the reaction observed on mice. Through the fractionated irradiation of carbon beams to mouse leg, it was found that the effect of a single fraction irradiation differs uniquely from that by multiple fractionations : the efficacy tends to be small on single fractions. In order to analyze the response, the applicability of a commonly-used LQ model was investigated together with the RCR (repairable-conditionally repairable) model and the multi-target two components model. While the LQ model failed to express a decrease in response by single irradiation, RCR showed good agreement with experimental observations.

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 damage in order to understand clinical outcomes.

Lineal energy information measured by a tissue-equivalent proportional counter in the therapeutic irradiation field was found to be 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 the following results have been obtained.

Field effect

It was found that, in the case of a small irradiation field, the decrease in absorbed dose at the center of the irradiation field by a collimator is almost well compensated by the increase in radiation quality. The resulting isoeffective dose is regarded to be stable.

Port characteristics

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

Oxygen effect

MKM was applied for the estimation of cell survival of hypoxic cells based on the response under oxic conditions. It was found that by adjusting the domain size to half of that for oxic conditions, the cell survival of hypoxic cell was correctly estimated.

Major Publications

1. Itsuko Serizawa, Kenji Kagei, Tadashi Kamada, Reiko Imai, Shinji Sugahara, Tohru Okada, Hiroshi Tsuji, Hisao Ito*, Hirohiko Tsujii : Carbon ion radiotherapy for unresectable retroperitoneal sarcomas, International Journal of Radiation Oncology Biology Physics, 75 (4), 1105-10, 2009
2. Reiko Imai, Tadashi Kamada, Hiroshi Tsuji, Shinji Sugahara, Itsuko Serizawa, Hirohiko Tsujii, Shinichiroh Tatezaki : Effect of Carbon Ion Radiotherapy for Sacral Chordoma : Results of Phase I-II and Phase II Clinical Trials, International Journal of Radiation Oncology Biology Physics, 2009, doi : 10.1016/j-ijrobp. 2009.06.048 ()
3. Itsuko Serizawa, Reiko Imai, Tadashi Kamada, Hiroshi Tsuji, Riwa Kishimoto, Susumu Kandatsu, Hirohiko Tsujii, Shinichiroh Tatezaki : Changes in tumor volume of sacral chordoma after carbon ion radiotherapy, Journal of Computer Assisted Tomography, 33 (5), 795-798, 2009
4. Junetsu Mizoe, Azusa Hasegawa, Ryo Takagi, Hiroki Bessho, Takeshi Onda, Hirohiko Tsujii : Carbon Ion Radiotherapy for Skull Base Chordoma, Skull Base : An Interdisciplinary Approach, 19 (3), 219-224, 2009, doi : 10.1055/s-0028-1114295 (2009-01-09)
5. Takeshi Yanagi, Tadashi Kamada, Hiroshi Tsuji, Reiko Imai, Itsuko Serizawa, Hirohiko Tsujii: Dose-volume histogram and dose-surface histogram analysis for skin reactions to carbon ion radiotherapy for bone and soft tissue sarcoma, Radiotherapy and Oncology

3.2. Development of a Precise Irradiation System for Heavy-ion Therapy

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. programs there in 1981, he worked for the development of a PET cyclotron from 1981 to 1989, and he also studied the accelerator physics from 1985 to 1989 in the Institute for Nuclear Study, University of Tokyo. In 1989, he joined the HIMAC project at NIRS, and he was engaged in construction and development of the HIMAC synchrotron. He received his PhD 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.

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Photo:Noda (left)

Objectives :

On the basis of more than 10 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 should accurately treat a fixed target, a moving target with breathing and/or a target near to a critical organ. For these purposes, a 3D-scanning method with a pencil beam is employed in this project. A phase-controlled rescanning (PCR) method has been proposed and studied, especially for treating a moving target. A rotating gantry with the PCR method is also employed in order to increase the treatment accuracy for a tumor around in the vicinity of critical organ through the multi-field optimization method, while reducing the patient's load. Therefore, we have designed a fixed beam-delivery system, a rotating-gantry system, a treatment-management system, a patient-positioning system and a treatment planning system. Related R&D works have also been carried out with HIMAC since April 2006. Building of the new treatment research facility was completed in March 2010. After installing the devices of the beam transport and beam-delivery systems, a beam commissioning and pre-clinical study will be carried out in FY 2010.

Progress of Research :

1) Planning of the new treatment research facility

The new treatment facility, as shown in Fig. 3-3, 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 part. In the treatment hall, placed underground of 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 the treatment of a moving target as well as fixed target, the PCR method, which completes the irradiation on one slice during the time it takes one respiration-gate to open, has been proposed and verified through computer simulation. In order to conplete a treatment within to lerable time, the scaning speed should be faster than conventional scanning methods in order to complete a tolerable treatment time, because rescanning naturally takes more time. Therefore, we developed a fast 3D raster rescanning with gating.

By cooperating with medical staff in the HIMAC hospital, the treatment hall has been designed. Two treatment-simulation rooms are also prepared for patient positioning as a rehearsal, and for observing any change of the target size and shape during the whole treatment period with an X-ray CT. Further, six rooms are devoted to patient preparation before irradiation. The facility building was completed in March 2010, as shown in Fig. 3-3.

Specifications of the facility are summarized in Table 1.

Table 1. Specification of the new treatment facility

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

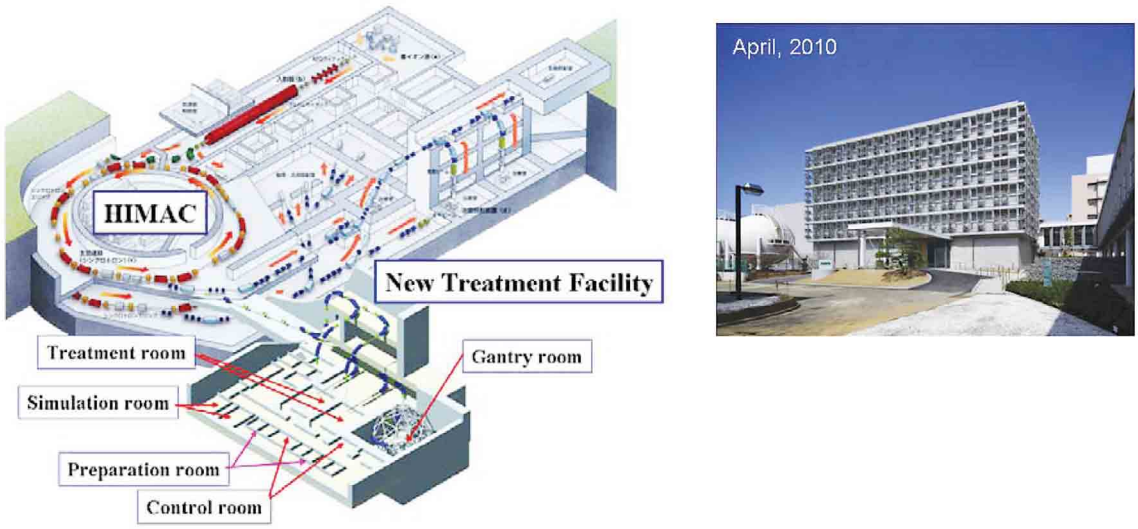


Fig. 3-3. Schematic view of the HIMAC and the new treatment facility with photograph of the new building completed (Left). The completed building of the new treatment research facility.

2) Related R&D work

a) Development of accelerator technology

An extended flattop operation of the HIMAC synchrotron was successfully developed, which can shorten the irradiation time by a factor of 2 even under rescanning. This operation method has been routinely utilized in the raster rescanning experiment. Owing to the new treatment planning, this operation mode and the high speed scanning magnet, the irradiation speed has been increased by around 100 times more than the conventional spot scanning.

In the present beam-scanning system, a range shifter, consisting of PMMA plates of various thicknesses, is used to degrade the beam energy and to control the depth dose-distribution. When using the range shifter, the setting time of the range shifter takes almost the same time as the irradiation time. Furthermore, since focused pencil beams will be used in the raster-scanning irradiation, this range shifter may broaden the spot size of the beam on the target, and also produce secondary fragments, which would adversely affect the depth dose-distribution. Therefore, it is preferable to change the beam energy directly by accelerators instead of using a range shifter. To change the beam energy, as extracted from the synchrotron ring, we propose a multiple-energy operation with the quasi-DC extension of flattops. The proposed operation enables us to provide heavy ions having variable energies within a single synchrotron-cycle ; namely, the beam energy would successively change more than 100 times within a single synchrotron-pulse by an energy step, corresponding to a water range of 2 mm. With this operation, the beam range would be controlled without using energy degraders, such as the range shifter, and hence an excellent depth dose distribution could be obtained. The scheme of the multi-energy operation and the preliminary experimental results are shown in Fig. 3-4 (a) and (b), respectively.

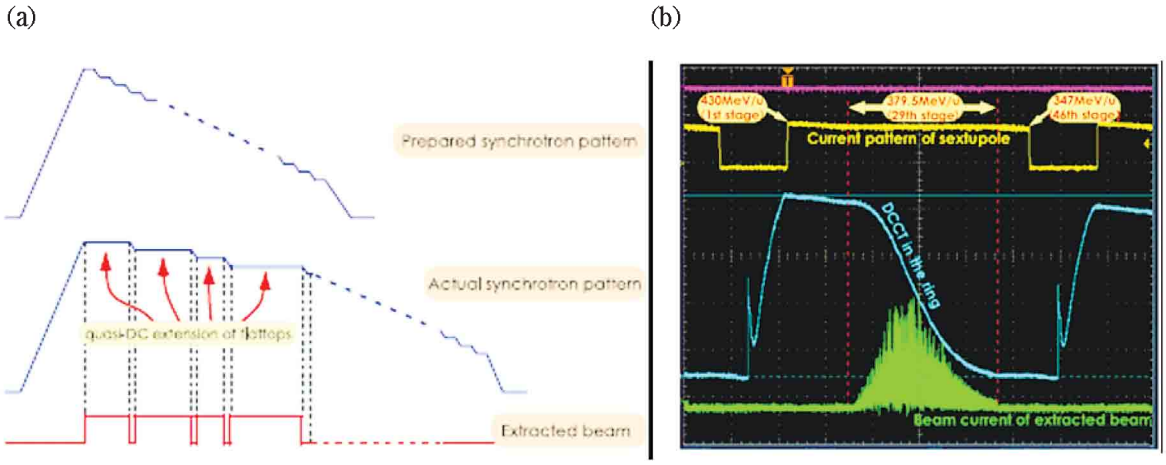


Fig. 3-4 (a) A schematic drawing of an operation pattern for the synchrotron ring. The operation pattern has a stepwise flattop, each of which can be extended, and the beam can be extracted from the synchrotron ring during any of these flattops.
(b) A current pattern for the sextupole magnets (yellow), the DCCT in the ring (blue), and the measured beam current of the extracted beam (green). The beam energy of the extracted beam is 379.5 MeV/u.

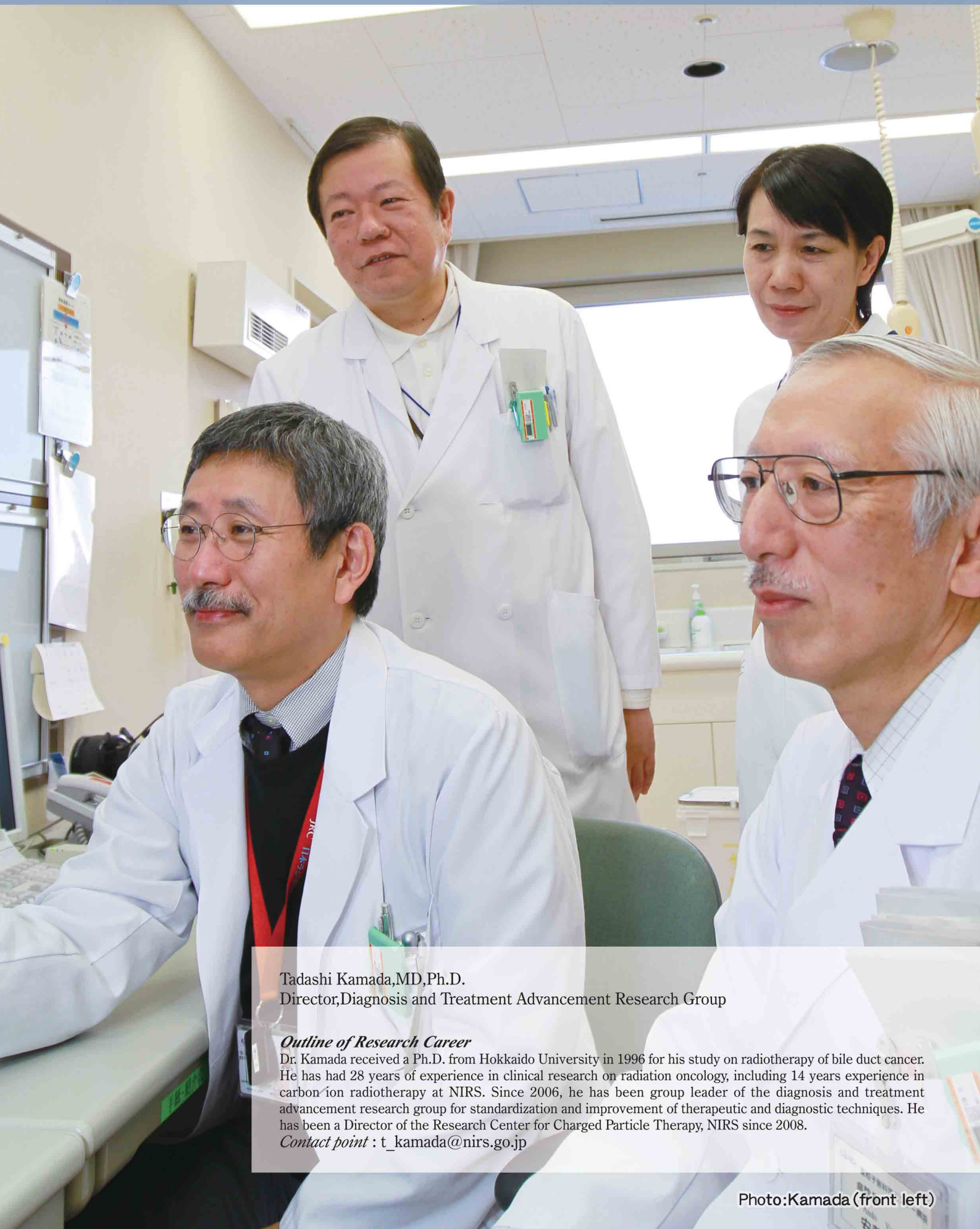
b) Experiment of fast 3D raster scanning

A test irradiation port was designed and installed to a HIMAC physics-experimental line in order to experimentally verify the fast 3D raster-scanning and the PCR method. This test port has the same configuration as the fixed beam-delivery system in the new treatment facility, as shown in Table 1 and Fig. 3-3. The scanning experiment has been being carried out since December 2008. In the experiment, the extended flattop operation has been routinely utilized. As a result of the experiment, it was verified that the scanning speed with the designated value was achieved without disturbing the dose distribution. Using a moving phantom we carried out an irradiation experiment on the moving target. As the result, we obtained and verified a uniform dose distribution with the fast 3D rescanning.

Major publications :

1) T. Inaniwa, T. Furukawa, A. Nagano, S. Sato, N. Saotome, K. Noda, T. Kanai: Field-size effect of physical doses in carbon-ion scanning using range shifter plates, Medical Physics, 36 (7), 2889-2897, 2008.
2) K. Mizushima, T. Shirai, T. Furukawa, S. Sato, Y. Iwata, K. Noda, H. Uchiyama : Reduction of uncontrollable spilled beam in RF-knockout slow extraction, Nuclear Instruments & Methods in Physics Research Section A, 606 (3), 325-329, 2009.
3) M. Kumagai, S. Mori, S. Gregory, H. Asakura, S. Kandatsu, M. Endo, M. Baba : Dosimetric Variation Due to CT Inter-Slice Spacing in Four-Dimensional Carbon Beam Lung Therapy, Physics in Medicine and Biology, 54 (10), 3231-3246, 2009.
4) N. Kanematsu : Semi-empirical formulation of multiple scattering for the Gaussian beam model of heavy charged particles stopping in tissue-like matter, Physics in Medicine and Biology, 54 (5), N67-N73, 2009.
5) N. Kanematsu, M. Komori, S. Yonai, A. Ishizaki : Dynamic splitting of Gaussian pencil beams in heterogeneity-correction algorithms for radiotherapy with heavy charged particles, Physics in Medicine and Biology, 54 (7), 2015-2027, 2009.
6) A. Kitagawa, T. Fujita, M. Muramatsu, S. Biri, A. G. Drentje : Review on heavy ion radiotherapy facilities and related ion sources, Review of Scientific Instruments, 81 (2), 02B909-1-02B909-7, 2010.

3.3. Standardization and improvement of therapeutic and diagnostic techniques



Tadashi Kamada,MD,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.

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Photo:Kamada (front left)

Objectives

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

Progress of Research

The diagnosis and treatment advancement research group for standardization and improvement of therapeutic and diagnostic techniques consists of the image diagnosis research team, the image processing research team, the quality control research team and the radiological protection research team, and performs research into the advancement and standardization of radiation therapy and diagnostic methods. The progress of research in each team is summarized.

1) Image diagnosis research team

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

We have been assessing whether Cu-62 labeled diacetyl-bis (N (4) -methylthiosemicarbazone) (Cu-62-ATSM) imaging of tumor hypoxia is associated with C-11-methionine imaging of amino acid metabolism in cervical cancer. Our data showed that cervical cancer had a greater tendency to incorporate C-11-Methionine than Cu-62-ATSM before any treatment. Pre-therapeutic accumulation of both Cu-62-ATSM and C-11-Methionine showed a significant difference between squamous cell carcinoma and other tumor groups. But post-therapeutic accumulation of either Cu-62-ATSM or C-11-Methionine showed no significant difference between squamous cell carcinoma and other tumor groups. Accumulation of squamous cell carcinoma in Cu-62-ATSM PET/CT after CIRT was significantly lower than pre-therapeutic accumulation. It might imply that squamous cell carcinoma of uterine cervix tended to be hypoxic in pre-therapeutic conditions and CIRT might improve its hypoxic condition. Improvement of the hypoxic condition might be associated with the therapeutic effect of CIRT. Cervical cancer had a greater tendency to incorporate C-11-Methionine than Cu-62-ATSM before any treatment.

Studies using C-11 methionine with PET have been undertaken for some study subjects. We performed a study about the diagnostic capability of C-11 methionine PET/CT for neck lymphnode metastasis from head and neck cancers versus trunk cancers. In this study, we evaluated the detectability of MET-PET/CT for neck lymphnode metastasis from head and neck tumors or from the other primary origin trunk tumors. We reviewed MET-PET/CT images of 1749 studies, from June 2006 to February 2007, searching for any nodular accumulation in the neck area. We selected patients with any nodular accumulation in the neck area as suspicious candidates for lymphnode metastasis and we evaluated diagnostic indexes and made ROC curve analyses. We concluded that MET-PET/CT was useful for diagnosis of neck lymphnode metastasis ; specificity in particular was relatively high. There were very few true positive metastases in neck lymphnode accumulation in the MET-PET/CT study from trunk cancers compared to head and neck cancers. But the diagnostic capability for neck lymphnode metastasis from trunk cancers was higher than from head and neck cancers.

We examined the usefulness of C-11 methionine PET/CT for predicting recurrence, metastasis and prognosis of patients with lung cancer treated by carbon ion radiotherapy. PET/CT was performed before and after CIRT for each patient. Post therapeutic PET/CT was performed at 1 month or 3 months after CIRT completion. The tumor to normal tissue ratio (TNR) before and after CIRT, the result of recurrence, the result of systemic metastasis and the result of prognosis were entered into the Kaplan-Meire analysis. Our data showed that patients with high TNR before CIRT had a significantly higher recurrence rate and poorer prognosis than patients with low TNR. Patient with high TNR at 3 months after CIRT had a significant poorer prognosis than patients with low TNR. TNR at 1 month after CIRT did not show any statistically significant relation to recurrence, metastasis or prognosis. There was no significant relation between TNR and incidence of metastasis. We concluded that MET uptake in lung cancer was a successful predictor of recurrence and survival. TNR at 3 months after CIRT is a better predictor for prognosis than TNR at 1 month after CIRT.

Regarding the usefulness of methionine, PET was also used to evaluate the response evaluation and predicting prognosis of uterine cervical cancer treated by carbon-ion beam radiotherapy. We evaluated the relationship between C-11 methionine (MET) uptake and clinical outcome such as local recurrence, systemic

metastasis and prognosis. ECAT EXACT HR+ and ECAT EXACT 47 PET scanner (Siemens CTI, Knoxville, TN) were used for PET imaging in this study. Pre- and post-therapeutic tumor TNR, its change after CIRT, the rate of local recurrence, the rate of systemic metastasis and prognosis were entered into the Kaplan-Meire analysis. Our data showed that the intensity of uptake of squamous cell carcinoma had a higher tendency than that of adenocarcinoma, although there was no significant difference between them. Pre-therapeutic TNR had a statistically significant relationship with local recurrence, systemic metastasis and prognosis. Post-therapeutic TNR was significantly related to recurrence and prognosis, and TNR residual ratio after CIRT was significantly related to metastasis and prognosis. In the squamous cell carcinoma group, pre-therapeutic TNR had a statistically significant relationship to metastasis and prognosis. In the adenocarcinoma group, pre-therapeutic TNR was significantly related only to recurrence. We concluded that MET-PET was a successful predictor for local recurrence, systemic metastasis and prognosis in patients with uterine cervical cancer treated by CIRT. But the relationship depended on the histological type of cervical cancer.

2) Image processing research team

We quantified pancreatic tumor motions due to respiration by using the 256 multi-slice CT. Patients were immobilized on a bed with, as routinely performed in treatment. CT scans were performed under free breathing, with patient respiration monitored by the respiratory sensing system. Scan conditions were slice collimation of 128 x 1.0 mm, 0.5 s in a single rotation and a scan time of less than 6 s to obtain one respiratory cycle without patient couch movement. The respiratory cycle was subdivided into 10 phases, with T0 as peak inhalation and T50 as peak exhalation. Gross tumor volume (GTV) and clinical target volume (CTV) was manually contoured on the CT data set at peak exhalation by a certified radiation oncologist. GTV contours at other phases were calculated by deformable registration, following which the oncologist checked the contour curves at each phase. Center of mass (COM) was calculated by using the GTV contours. The GTVs are displayed as a function of time in Figure 3-5.

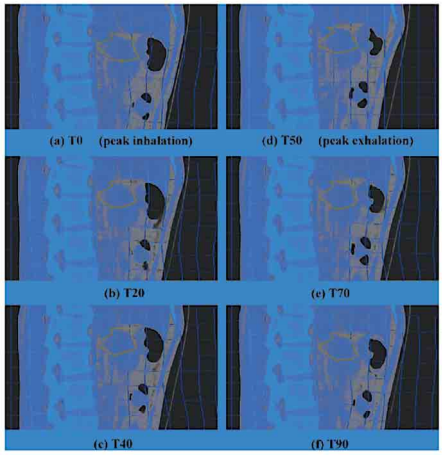

Figure 3-5 Four-dimensional sagittal CT images. (a) T0 (peak inhalation), (b) T20, (c) T40, (d) T50 (peak exhalation), (e) T70 and (f) T90. The yellow line and blue mesh grid show the GTV contours and deformed space from peak exhalation, respectively.

To compare respiratory-gated and respiratory-ungated treatment strategies using 4DCT datasets, we evaluated 4D scattered carbon ion beam distribution in the pancreatic region. Two types of compensating bolus were designed for respective CTVs to cover the whole and periexhalation CTV moving regions, which defined the 30% duty cycle around exhalation. The carbon ion beam dose distribution was calculated as a function of the respiratory phase by applying the compensating bolus to 4DCT at the respective phase. The accumulated dose distribution was calculated by registering the carbon ion beam distribution at the respective phases to that at peak exhalation (T50) by applying deformable registration, which creates transformation maps.

Figure 3-6 shows accumulated carbon ion dose distribution for the ungated and gated treatments. We calculated the difference in accumulated dose distribution between the gated and ungated treatment by subtracting the accumulated dose distribution for the gated treatment from that for the ungated treatment (Fig. 3-6c). Large positive dose differences (over 10%) were observed mainly on the inferior aspect, resulting from the fact that gated treatment irradiates only during exhalation phases. Doses to organs at risk were smaller in the gated than the ungated treatment, although the differences were small.

Given that our results for ungated and gated pancreatic treatment were closely similar with regard to tolerance doses to normal tissues, and that doses were less than the tolerance dose in both ungated and gated treatments, and taking into account the above problem, we suggest 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 an ungated treatment may shorten total treatment duty time by a factor of three compared with the gated treatment.

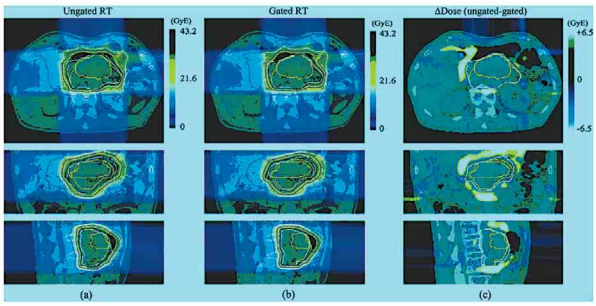

Figure 3-6 Accumulated carbon ion beam dose distribution for (a) ungated treatment, (b) gated treatment, and (c) accumulated dose distribution differences (ungated minus gated) (Patient 1). Axial (upper row), coronal (middle row), and sagittal (lower row) sections. White areas, yellow areas, and dark green lines show the planning target volume (PTV), clinical target volume (CTV), and gross tumor volume (GTV) contours, respectively. Red, green, pink, light blue, and blue lines show 95%, 80%, 70%, 50%, and 30% of total doses, respectively.

We evaluated intrafractional organ motion and dose validation for ungated and gated treatments. Our approached described here are necessary to quantify uncertainties for each treatment planning process and provide solutions for increasing treatment accuracy. We are convinced, however, that our approach to moving targets in charged particle therapy will be a decisive factor in overcoming these problems and in improving treatment.

3) Quality control research team

Due to frequent radiotherapy accidents, the importance of quality control in radiotherapy has been increasingly recognized. The quality control research team of NIRS 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 the last fiscal year. The team is preparing to establish the standard field of absorbed dose to water and has calibrated the NIRS standard chambers in terms of absorbed dose to water, in collaboration with the International Atomic Energy Agency (IAEA).

To establish a nation-wide dosimetry audit system in radiotherapy, the team carried out comparative studies between the glass dosimeters and TLD which had been used as a postal dosimeter. The results showed that the glass dosimeters were appropriate for the postal dose audit with their features. The team carried out a pilot study in which postal glass dosimeters were sent to approximately 100 hospitals in Japan. The pilot study showed 1.3% standard deviation of dose among the 100 hospitals. Since November 2007, a regular dosimetry audit service for radiotherapy facilities has been started using a glass dosimeter with a commercial base by the Association for Nuclear Technology in Medicine, in collaboration with the National Cancer Center and NIRS. The team still continues to carry out studies with glass dosimeters for non-reference conditions in therapeutic X-rays.

In addition, the team has carried out studies on dosimetry for hadron therapy. The team conducts nation-wide dosimetry intercomparison with all hadron therapy facilities in Japan, including the Gunma University Heavy Ion Medical Center which started carbon beam therapy in March 2010. The consistency of doses has been determined with a standard deviation of 0.5%. The team has also developed a graphite calorimeter for absolute absorbed dose measurements. The absorbed dose obtained by the calorimeter was approximately 3 to 4% higher than that by an ionization chamber for carbon beams. The differences seem to arise from uncertainties of stopping power and the w-value for the carbon beams.

These research activities are expected to contribute to other radiotherapy facilities as well as the NIRS. The quality control research team also intends to contribute to the field of radiotherapy internationally in cooperation with organizations such as the Forum for Nuclear Cooperation in Asia (FNCA), the IAEA, the World Health Organization (WHO), the International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC).

4) Radiological protection research team

a) Dose estimation and protection against medical radiation

An increase in the frequency of CT examinations over the past decade has raised concerns about radiation doses and the possible detriment to the health of children. The estimation of accurate dose levels and radiation risks requires organ doses for pediatric patients in CT examinations. We have evaluated organ doses in head CT, chest CT and abdomino-pelvic CT scan conditions routinely used at 23 hospitals with TLDs or photodiode dosimeters implanted at various

tissue and organ positions within a 6-year-old child anthropomorphic phantom. In head CT scans, organ doses for brain were 20-49 mGy except for one case. In chest CT and abdominopelvic CT scans, organ doses within scan ranges were 2-21 mGy and 3-21 mGy, respectively, which were on average approximately 20-50% lower than in adult chest CT and abdominopelvic CT. Organ doses varied among CT protocols mainly due to differences in the types of CT scanners and effective mAs. The setting of proper effective mAs and a strict scan length could reduce the doses in pediatric CT examinations. The dose data evaluated in this study would be useful for the evaluation of dose levels and radiation risks for children and would also lead to the optimization of pediatric CT scan protocols.

The secondary cancer risk after receiving carbon-ion and proton radiotherapies has become a great concern because of positive outcomes of the radiotherapies. Such exposure is considerably lower than that near the treatment volume, but it is not negligible for estimating the risk, especially for young patients. Organ-specific dosimetric data in the patient is essential for assessing the risk, but experimental data are scarce. Therefore, absorbed dose, quality factor and dose equivalent in water phantom outside of the irradiation field were determined by microdosimetric measurements with a commercial tissue equivalent proportional counter at passive carbon-ion and proton radiotherapy facilities : HIMAC and the National Cancer Center Hospital East. We confirmed that the total secondary doses per treatment in carbon-ion and proton radiotherapies were comparable to or less than those in 3D-CRT and IMRT, and especially, they were considerably less than those in 3D-CRT and IMRT as the position became closer to the field edge. Verification using Monte-Carlo simulations, which are needed to assess the detailed distributions of dose and biological effectiveness, is in progress.

Major Publications

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2) Shunsuke Yonai, Naruhiro Matsufuji, Tatsuaki Kanai : Monte Carlo study on secondary neutrons in passive carbon-ion radiotherapy : Identification of the main source and reduction in the secondary neutron dose, Medical Physics, 36 (10), 4830-4839, 2009,
3) Keisuke Fujii, Takahiko Aoyama*, Chiyo Kawaura*, Shuji Koyama*, Masato Yamauchi*, Susumu Ko*, Keiichi Akahane, Kanae Nishizawa : Radiation dose evaluation in 64-slice CT examinations with adult and paediatric anthropomorphic phantoms, British Journal of Radiology 82 (984), 1010-1018 2009
4) A. Fukumura ; H. Tsujii ; T. Kamada ; M. Baba ; H. Tsuji ; H. Kato ; S. Kato ; S. Yamada ; S. Yasuda ; T. Yanagi ; H. Kato ; R. Hara ; N. Yamamoto ; J. Mizoe ; K. Akahane ; S. Fukuda ; Y. Furusawa; Y. Iwata; T. Kanai; N. Kanematsu; A. Kitagawa ; N. Matsufuji ; S. Minohara ; N. Miyahara; H. Mizuno; T. Murakami; K. Nishizawa; K. Noda ; E. Takada ; S. Yonai. CARBON-ION RADIOTHERAPY: CLINICAL ASPECTS AND RELATED DOSIMETRY, Radiation Protection Dosimetry 137, 149-155. 2009
5) M. Ohkubo, S Wada, Satoshi Ida, M Kunii and A Kayugawa, T Matsumoto and K Nishizawa : Determination of point spread function in computed tomography accompanied with verification, Medical Physics 36 : 2089-2079, 2009

3.4. RadGenomics Project for Radiotherapy

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

Outline of Research Career

Dr. Imai received a Ph.D. from the University of Tsukuba in 1986. Following a fellowship from the Japan Society for the Promotion of Science for Japanese Junior Scientists at the Institute of Applied Biochemistry, University of Tsukuba, he joined the Tsukuba Life Science Center, Institute of Physical and Chemical Research (RIKEN). From 1988 to 1989, he worked in the Department of Genetics, Washington University Medical School (St. Louis, Missouri, USA) as a visiting research associate. Here Professor Maynard Olson sparked his interest in the human genome project. After joining The Cancer Institute (Japanese Foundation for Cancer Research) in 1991, Dr. Imai worked on cancer and population genomics. He moved to NIRS at 1994. From 2001 to 2006, he worked as the project leader of the RadGenomics Project. Since 2006 he has been the director of the RadGenomics Research Group.

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Photo:Imai(right)

Objectives

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

Progress of Research

1) Study population

Between October 2001 and March 2010, 2782 patients were registered including 775 breast cancer patients, 409 cervical cancer patients, 896 prostate cancer patients, and 310 head and neck cancer patients. Normal tissue reactions until the 3rd month after completion of the treatment were graded according to the National Cancer Institute-Common Toxicity Criteria (NCI/CTC). Late effects on normal tissues were graded according to the Radiation Therapy Oncology Group/ the European Organization for Research and Treatment of Cancer (RTOG/EORTC) scoring system and the Late Effects of Normal Tissues-Subjective, Objective, Management and Analytic (LENT-SOMA) scoring system. Patients were divided into two groups (radiosensitive and radioresistant) according to the grades determined by the above scoring systems.

2) Application of carbon-ion beams or gamma-rays on primary tumors does not change the expression profiles of metastatic tumors in an in vivo murine model.

Objective : To clarify how carbon-ion radiotherapy (C-ion) on primary tumors affects the characteristics of subsequently arising metastatic tumor cells.

Methods and Materials : Mouse squamous cell carcinomas, NR-S1, in synergic C3H/HeMsNrs mice were irradiated with a single dose of 5-50 Gy of C-ion (290 MeV per nucleon, 6-cm spread-out Bragg peak) or γ-rays (^{137}Cs source) as a reference beam. The volume of the primary tumors and the number of metastatic nodules in lung were studied, and histologic analysis and microarray analysis of laser-microdissected tumor cells were also performed.

Results : Including 5 Gy of C-ion and 8 Gy of γ-rays, which did not inhibit the primary tumor growth, all doses used in this study inhibited lung metastasis significantly. Pathologic findings showed no difference among the metastatic tumor nodules in the nonirradiated, C-ion-irradiated, and γ-ray-irradiated groups. Clustering analysis of expression profiles among metastatic tumors and primary tumors revealed a single cluster consisting of metastatic tumors different from their original primary tumors, indicating that the expression profiles of the metastatic tumor cells were not affected by the local application of C-ion or γ-ray radiotherapy.

Conclusion : We found no difference in the incidence and histology, and only small differences in the expression profile, of distant metastasis between local C-ion and γ-ray radiotherapy. The application of local radiotherapy per se or the type of radiotherapy applied did not influence the transcriptional changes caused by metastasis in tumor cells.

3) Villin1, a novel diagnostic marker for cervical adenocarcinoma.

Objective : The number of new cervical adenocarcinoma (AD) cases has risen slowly; however, its histological similarity to other tumor types and the difficulty of identifying the site of the original tumor makes the diagnosis of cervical AD particularly challenging. We investigated a novel molecular biomarker for cervical AD through the integration of multiple methods of genomic analysis.

Methods : Tumor samples in discovery set were obtained from 87 patients who underwent radiotherapy, including 31 cervical AD. Microarray analysis and quantitative polymerase chain reaction analysis were performed to screen a candidate diagnostic molecule for cervical AD, and its clinical significance was investigated by immunohistochemical analysis (IHC).

Results : We found a difference between biopsy samples of AD and squamous cell carcinoma (SCC) in the expression and genomic copy number of Villin1 (VIL1), which maps to 2q35. IHC revealed 14 VIL1-positive tumors ; 13 cervical AD and 1 small cell carcinoma of the cervix, while no SCCs or endometrial ADs were VIL1-positive. Kaplan-Meier survival curves revealed worse disease-free survival in VIL1-positive tumors. The marker was validated by 65 newly enrolled patients, and VIL1 positive staining showed 52% sensitivity and 100% selectivity for cervical AD.

Conclusion : We have identified VIL1 as a novel biomarker of cervical AD. Our study suggests the existence of a subtype of cervical tumors which are VIL1 positive with a poor radioresponse.

4) Change in fibroblast growth factor 2 expression as an early-phase radiotherapy responsive marker in sequential biopsy samples from cervical cancer patients during fractionated radiotherapy.

Objective : We previously showed that fibroblast

growth factor 2 (FGF2) expression levels in tumor cells (FGF2-T) may be an indicator of the efficacy of radiotherapy in cervical cancer (CC). Here, we extended this finding using newly enrolled patients and further investigated the stromal FGF2 expression.

Methods and materials : Sixty-nine patients with CC were recruited as a validation set for the immunohistochemical detection of FGF2-T from biopsy samples taken before (pretreatment) or one week after initiation of radiotherapy (midtreatment). We also investigated the expression of FGF2 in tumor stroma (FGF2-S), and vascular endothelial growth factor (VEGF), and CD31 in these patients plus 35 patients from a previous study.

Results : FGF2 expression was detected in tumor cells of all cases and in stromal cells in 87% of cases. FGF2-T was significantly higher in midtreatment samples (P =0.0002), and a high ratio of midtreatment/ pretreatment FGF2-T was significantly related to a better prognosis (P =0.025). Increased VEGF expression after initiation of radiotherapy was significantly related to a positive FGF2-S in pretreatment samples (P =0.035), although it was not related to prognosis or microvessel density detected by CD31 expression.

Conclusion : Radiation causes a response in tumor cells and adjacent normal cells, and changes the extracellular matrix environment. In this study, we confirmed our previous findings showing that changes in FGF2-T expression may be used as a marker to monitor the effectiveness of radiotherapy for CC. Our findings should improve patient selection for molecular targeted therapies, such as cytokine inhibitors, following standard-of-care treatment.

5) Vascular homeostasis regulators, Edn1 and Agpt2, are upregulated as a protective effect of heat-treated zinc yeast in irradiated murine bone marrow (Cooperative project with Dr. Anzai, Radiation Modifier Team, Heavy-Ion Radiobiology Research Group).

Objective : To elucidate the mechanism underlying the *in vivo* radioprotection activity by Zn-containing, heat-treated *Saccharomyces cerevisiae* yeast (Zn-yeast).

Methods and materials : A Zn-yeast suspension was administered into C3H/He mice immediately after WBI at 7.5 Gy. Bone marrow was extracted from the mice 6 hours after irradiation and analyzed on a microarray. Expression changes in the candidate responsive genes differentially expressed in treated mice were re-examined by qRT-PCR. The bone marrow was also examined pathologically at 6 h, 3, 7, and 14 days postirradiation.

Results: Thirty-six genes, including Edn1 and Agpt2, were identified as candidate responsive genes in irradiated mouse bone marrow treated with Zn-yeast by showing a greater than three-fold change compared with control (no irradiation and no Zn-yeast) mice. The expressions of *Cdkn1a, Bax*, and *Ccng*, which are well known radioresponsive genes, were upregulated in WBI mice and Zn-yeast treated whole body irradiation (WBI) mice. Pathological examination showed the newly formed microvessels lined with endothelial cells, and small round hematopoietic cells around vessels in the bone marrow matrix of mice administered with Zn-yeast after WBI, while whole-body irradiated mice developed fatty bone marrow within 2 weeks after irradiation.

Conclusion : This study identified a possible mechanism for the postirradiation protection conferred by Zn-yeast. The protective effect of Zn-yeast against WBI is related to maintaining the bone marrow microenvironment, including targeting endothelial cells and cytokine release.

Major publications

(1) M Ueno, K Imadome, M Iwakawa, et. al. : Vascular homeostasis regulators, Edn1 and Agpt2, are upregulated as a protective effect of heat-treated zinc yeast in irradiated murine bone marrow, J Rad Res, 51 (5) : 519-525,2010.

(2) M Nakawatari, MIwakawa, T Ohno, et. al. : Change in fibroblast growth factor 2 expression as an early-phase radiotherapy responsive marker in sequential biopsy samples from cervical cancer patients during fractionated radiotherapy, Cancer, 116 (21) : 5082-5092,2010.

(3) E Nakamura, M Iwakawa, R Furuta, et. al. : Villin1, a novel diagnostic marker for cervical adenocarcinoma, Cancer Biol Ther, 8 (12) : 1146-1153, 2009.

(4) T Tamaki, M Iwakawa, T Ohno, et. al. : The Application of Carbon Ion Beams or Gamma-Rays on Primary Tumors Does Not Change the Expression Profiles of Metastatic Tumors in an in vivo Murine Model, Int J Radiat Oncol Biol Phys, 74 (1): 210-218, 2009.

3.5. 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. In 2002, he moved back to Japan to become a team leader at the International Space Radiation Laboratory, NIRS. In 2005 he was appointed as Director of ISRL. In 2006, he was transferred to the Research Center for Charged Particle Therapy and became Director of the Heavy Ion Radiobiology Research Group.

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Photo:Okayasu (left)

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 distribution as well as experimental data on cell and animal studies ; and to propose a more efficient radiation therapy regimen by comparing heavy ion radiotherapy and other radiotherapy protocols such as the use of X-rays. Plan 3 has four goals : to explore radiosensitizers and protectors which can be used with heavy ion radiotherapy ; to elucidate the mechanism of effective heavy ion treatment for hypoxic tumor cells which show strong resistance to radiation ; to study the indirect (bystander) effects of radiation which occur in non-irradiated cells adjacent to irradiated cells ; and to integrate the proposals of Plan 2 to improve radiation therapy and accumulate biological data resources for a new cancer therapy.

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

Progress of Research

Biophysics Team

It is believed that the indirect action of radiation plays a less role for high linear energy transfer (LET) radiation when compared with low LET radiation. However, there has not been enough experimental data to support this idea. To clarify the contribution of direct and indirect action of radiation, we obtained experimental data on LET dependencies. The contribution of indirect action mediated by OH radicals in cell killing can be estimated from the maximum degree of protection by applying dimethylsulfoxide (DMSO), which suppresses indirect action without affecting direct action. Exponentially growing Chinese hamster ovary cells under hypoxic condition were exposed to different LET radiation levels from 15 to 480 keV/μm in the presence or absence of DMSO and their survival fractions were determined using a colony formation assay. The contribution of indirect action on cell killing decreased with increasing LET. The contribution was estimated to be 22% at a LET of 480 keV/μm. The relative biological effectiveness (RBE) determined at a survival level of 10%, increased with LET, reaching a maximum value of 5.06 at 200 keV/μm, and decreased thereafter. When the RBE was estimated separately for direct action (RBED) and for indirect action (RBEI), the RBED was greater than RBEI over the ion LET range tested. RBED increased with increasing LET and reached a peak value of 9.10 at 480 keV/μm. RBEI showed a peak at 90 keV/μm, but the value was 2.61. Thus the direct action of heavy-ion beams gives a remarkably higher RBE value for cell killing than the indirect action.

Experimental Therapy Team

Malignant melanoma showed a high local control at HIMAC, whereas the overall survival of patients was not extended as expected. The control of cancer metastasis is one of the most important issues in cancer treatment. The aim of our study is to clarify the effect of carbon ion beams (C-ions) on metastatic potential of melanoma in vitro and in vivo. Carbon-ion showed higher cytotoxic effects on B16/BL6 cells in vitro than X-rays. Both migration and invasion potential on cells were enhanced by photon beams at low dose points (0.50 to 1.00 Gy) than non-irradiated controls; however, they were suppressed by C-ions at all dose points tested. The RBE values obtained from migration and invasion tests on cells in vivo were higher than that from cell killing. C-ions significantly suppressed tumor growth. The number of lung metastatic nodules after tumor-irradiation decreased with dose, and C-ions were more effective for this than photon beams. The metastatic potentials of survivedcells in a tumor after irradiation was analyzed with the number of metastatic lung colonies that formed from implanted tumors and the survival of irradiated and explanted cells from a tumor. Lower metastasis was found for C-ions than photons when tumor cell survival was 10%. This study suggests that C-ion significantly inhibits metastatic processes much more than low-LET photons.

Cellular and Molecular Biology Team

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

HiCEP, a comprehensive gene expression technique developed in NIRS, was applied to normal human fibroblasts which were irradiated with X-rays and carbon ion particles at a dose of 2 Gy. A group of early responsive IR-induced genes (ATF3, BTG2, TP53INP1) remained activated for a longer period in human cells irradiated with carbon ion particles than when irradiated with conventional X-rays. Our team,

for the first time, revealed that the expression of ASPM, a microcephaly gene, was significantly downregulated by IR in human and murine cells. We have started to characterize the roles of this centrosomal protein on DNA repair mechanisms. One approach is knocking down ASPM by siRNA treatment, which demonstrated a significant increase in the radiosensitivity of several tumor cell lines. The other approach is to generate a mouse model whose Aspm orthologous gene (calbpm1) was conditionally disrupted. Targeting centrosomal proteins would be a promising strategy to augment the radiation effect and may also increase the treatability of certain types of tumors.

Radiation Modifier Team

The radiation modifier team has examined the following topics in 2009. 1) We measured redox potential for various natural antioxidants to develop a new radiation protector. 2) We found that the combination of X-ray and a PI3-kinase inhibitor effectively enhanced antitumor activity both in vitro and in vivo. 3) We discovered a new compound having nitroxyl radical and edaravone moieties, and which has radiation protection activity in 30-day survival of mice after irradiation. 4) We measured the DRF value of ?-TDMG against X-ray-induced bone marrow death of mice and obtained a value of about 1.2 by i. p. administration of the compound (100 mg/kg) immediately after exposure. 5) Effect of radiation protectors on tumor regulation by heavy ion radiation using the mouse xenograft model was measured. 6) The effect of amifostine on tissue oxygen tension was measured by EPR oxymetry using LiNc-BuO as a probe. 7) The distribution of reactive oxygen species generated by irradiation of heavy ion beams was measured and analyzed.

Major publications

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2. Megumi Ueno, Hiroshi Inano, Makoto Onoda, Hironobu Murase, Nobuo Ikota, Tsutom V. Kagiya, Kazunori Anzai Modification of mortality and tumorigenesis by tocopherol-mono-glucoside (TMG) administered after X-irradiation in mice and rats. Radiation Research 172, 519-524, 2009.
3. Dong Yu, Eimiko Sekine-Suzuki, Lian XUE, Akira Fujimori, Nobuo Kubota*, Ryuichi Okayasu : Chemopreventive Agent Sulforaphane Enhances Radiosensitivity in Human Tumor Cells, International Journal of Cancer, 125, 1205-1211, 2009.
4. Ryoichi Hirayama, Atsushi Ito, Masanori Tomita, Teruyo Tsukada, Fumio Yatagai, Miho Noguchi, Yoshitaka Matsumoto, Yuuki Kase, Koichi Ando, Ryuichi Okayasu, Yoshiya Furusawa : Contributions of Direct and Indirect Actions in Cell Killing by High-LET Radiations, Radiation Research, 171 (2), 212-218, 2009
5. Uzawa A, Ando K, Koike S, Furusawa Y, Matsumot Y, Takai N Hirayama R, Watanabe Ma, Scholz M, Elsasser T, Peshcke P : International Journal of Radiation Oncology, Biology, Physics, 73,5,1545-1551,2009.

3.6. Transcriptome Research for Radiobiology

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

Outline of Research Activities

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

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Photo: Abe (right)

Objectives

This subject has been researched by the Transcriptome Research Group consisting of 3 teams : Stem Cell Research Team, Model Organism Research Team and Gene Expression Profiling Team.

Progress of Research

1) Stem Cell Research Team and Model Organism Research Team

This year the two teams have focused on pluripotent stem cells ; their final goals are to understand the effect of radiation at an individual level - not at a cellular level only - and to obtain relevant information for their therapeutic uses.

Recently, it has been demonstrated that somatic cells can be converted into pluripotent stem cell by ectopic expression of four genes, Oct3/4, Klf4, Sox2 and cMyc, designated as induced pluripotent stem (iPS) cells. The objective of this program is to understand the molecular mechanism of the conversion from somatic to stem cells. However, it has been rather difficult because these cells emerge at a low frequency, about 0.1% in the case of fibroblasts, and in a stochastic manner. Therefore, the teams attempted to directly observe the emergence of iPS cells from somatic cells. To overcome the difficulties, team members developed a new investigation system by improving a pre-existing time-lapse system that allows us to precisely investigate the generation of iPS at short intervals over 2 weeks that are needed to generate iPS cells from mouse fibroblasts, and succeeded in directly observing the conversion process of somatic cells into stem cells. Interestingly, it was revealed that the onset of the cell lineage conversion already initiated within 48 hours just after the defined gene infection in most of the iPS cell generations, i. e. 85.7% (Figure 3-7). Furthermore, no morphological asymmetric cell division was observed during the conversion process from ancestral somatic cells into iPS cells. Namely, ancestral fibroblast cells gradually transformed into stem cells after several symmetric cell divisions (Figure 3-8). Thus these results provide a critical new insight during the first three days of iPS cell generation that has thus far been completely unknown. In addition, another contribution to the iPS field has been made: genome integration-free iPS cells without oncogene, c-Myc, transduction have been successfully generated.

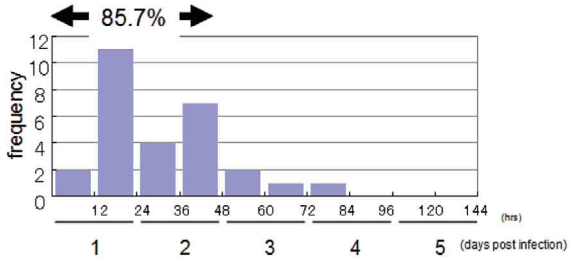

Figure 3-7

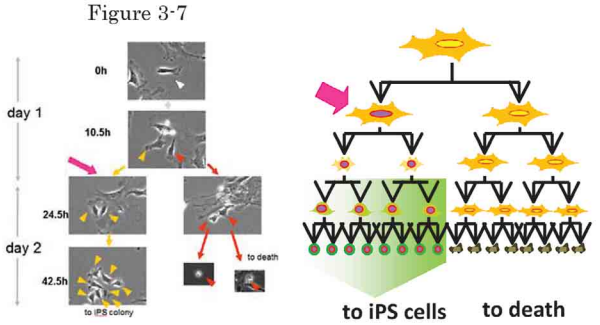

Figure 3-8

2) 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 principle different from hybridization-based methods.

This year this team attempted to improve the HiCEP method to allow it to analyze a small amount of starting material. At the beginning of HiCEP development, approximately 1 μg of polyA RNA was needed for the analysis ; however, subsequent improvement has allowed us to perform the analysis with a total RNA amount of 0.1 μg. This year team members successfully developed a new protocol using less than 100 pg of total RNA, corresponding to less than 10 cells.

Meanwhile, they developed new systems for efficient HiCEP analysis : firstly a high throughput machine for HiCEP reaction that enables more than 15,000 samples per year to be analyzed. This equipment, termed HiCEPer, will be released this year. A precision PCR (polymerase chain reaction) machine was also developed and released, because the HiCEP reaction requires an extremely high level of temperature control. The difference in temperature among 96 wells can be controlled by less than 0.2°C. In addition, a HiCEP reaction kit was developed, for 1 μg of starting material, which allows even those who do not have expertise in molecular biology to perform HiCEP analysis easily.

4. Molecular Imaging Center

Yasuhisa Fujibayashi,Ph.D.,D.Med.Sci.
Director,Molecular Imaging Center

(Outline of Research Career)

Yasuhisa Fujibayashi started his professional career at the Radioisotopes Research Laboratory, Kyoto University Hospital in 1983, where he was an Assistant Professor of Radiopharmaceutical Chemistry. Then, he was appointed as an Associate Professor of Genetic Biochemistry at the Graduate School of Pharmaceutical Sciences, Kyoto University, in 1993. In 1999, he moved to the Biomedical Imaging Research Center (BIRC), University of Fukui, as a Professor of Molecular Imaging, then was co-appointed as a Director at BIRC. In April 2010, he moved to NIRS as a Director of the Molecular Imaging Center. His major research field is development/evaluation of molecular PET/SPECT probes targeting hypoxic metabolism, fatty acid metabolism, mitochondrial electron transport, radical production, oncogene expression, and so on.

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Objectives :

The question "What is Life?" has been considered by almost every person that has ever lived. One of the most famous attempts to answer the question is in a book entitled "What is Life?" written by Erwin Schrodinger (1944), where he argued that life is based on the interactions between molecules. Recent progress in molecular and cellular biology has in principle clarified this. However, it is still difficult to observe the behavior and role of single molecules in living systems.

Molecular imaging (MI) is a relatively new research field created to investigate and visualize the 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 us 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) utilizes state-of-the-art MI research facilities and plays a major role in MI research in Japan. The people at MIC-NIRS are working on a wide range of projects ranging from basic to clinical research. The main target of MIC-NIRS is to become a major center promoting translational research in the MI community and related areas.

Overview

The Diagnostic Imaging Group has conducted intensive clinical PET studies. It included FLT, a thymidine-kinase substrate for tumor proliferation imaging, in combination with carbon-ion radiation therapy (CIRT). Cu-ATSM and FAZA are also under clinical investigation for the prognosis of CIRT. In basic research on tumor imaging/therapy, mesothelioma caused by asbestos exposure is one of the major projects in this group. In this project, "exploration of new therapeutic and diagnostic targets of mesothelioma" and "evaluation of CIRT efficacy in a mouse model of malignant mesothelioma using a PET probe" have been studied. For the development of tumor imaging and treatment, c-kit, neo-vascularization, and activated epidermal cell growth factor receptor (EGFR) have been selected as targets and their usefulness has been clarified. As applications of molecular biology in in-vivo imaging, reporter imaging for the detection of hypoxia using a combination of Tc-99m/I-124 and human Na/I symporter (hNIS) -hypoxia responsive element (HRE), and a combination of optical imaging (red fluorescence protein) and FDG-PET have been successfully performed.

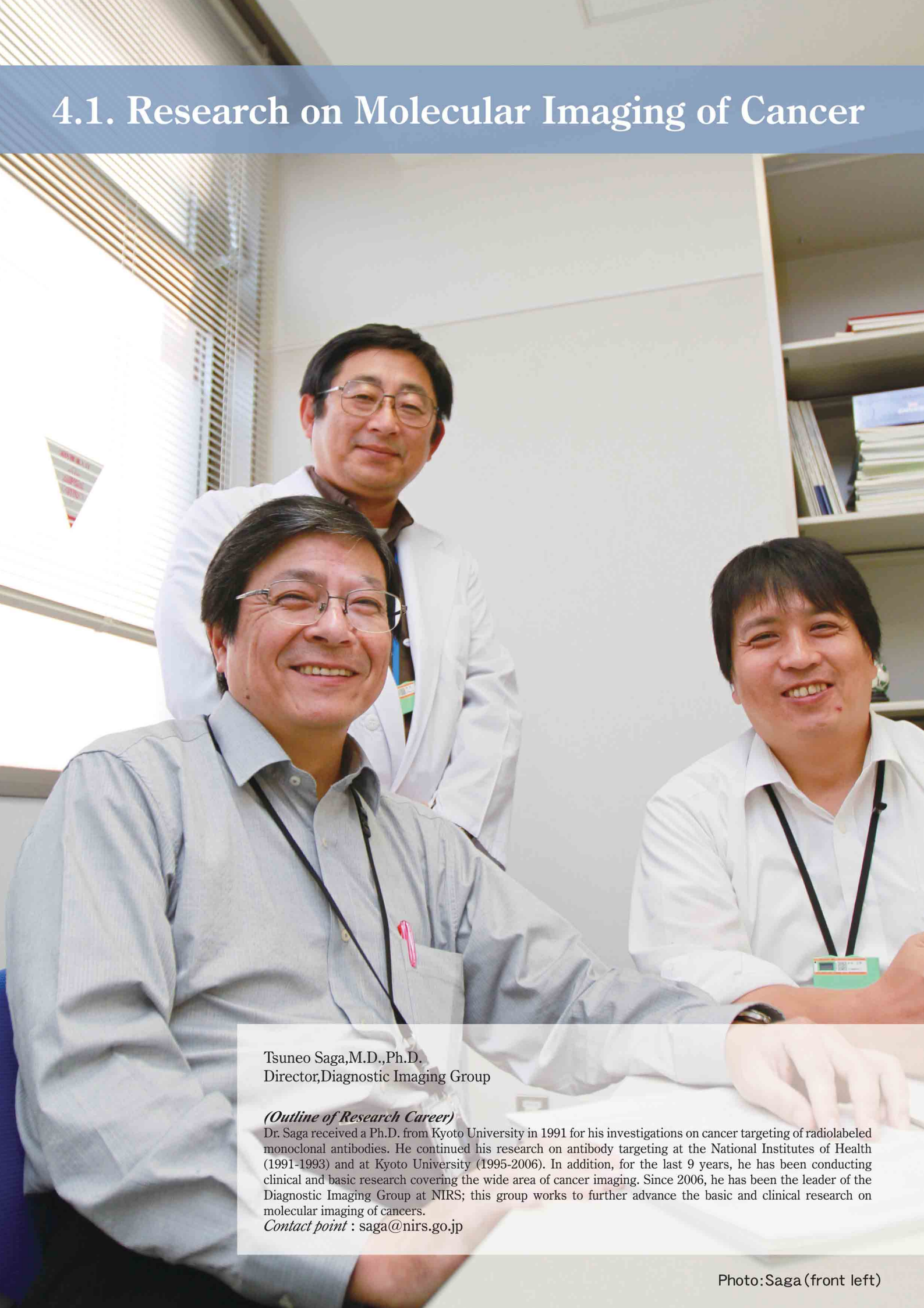
The Molecular Neuroimaging Group conducted various studies covering from basic to clinical application as well as drug development in neurological sciences, using PET, MRI and other imaging techniques. In psychiatric studies in human, the contribution of dopamine receptor subtypes to amygdale reactivity was clarified using PET and fMRI. For Alzheimer's disease research, C-11-Pittsburgh Compound-B (PIB) and related compounds have been evaluated from mouse model to human patients. This included the development of a new kinetic analysis procedure, the relationship between neuro-immune response and aggregates deposition, and so on. Drug development/evaluation research included " measurement of norepinephrine transporter occupancy by antidepressant in relation to interference of dopamine D2 receptor", "studies on the effect of antipsychotic drug on dopamine synthesis", "occupancy of serotonin transporter by a candidate antidepressant" and so on. In addition, systemic neurochemistry studies such as the development of a new method for quantification of motivation in monkeys, electrophysiological measurement using marmoset brain slices, development of a neuro-immunologically altered animal model, and so on, have been successfully performed.

The Molecular Probe Group conducts research on the whole process of the design and development of molecular PET probes, namely radionuclide production, radio-synthesis, quality control procedures and automation, then basic biological evaluation of the molecular PET probes. Provision of the established molecular PET probes to other intra-institutional groups as well as contribution for quality assurance of FDG in Japan is an important commission of this group. In new PET probe development studies, several C-11-compounds seeking MRP4, OAT3 transporters, peripheral benzodiazepine receptor, imidazoline receptor and mGlu receptor have been successfully synthesized and evaluated. In the production of C-11-compounds, specific radioactivity is crucial for quantitative detection of target proteins, and C-11-DAC and C-11-Ac-5216 with 4-6 times higher specific activity could be achieved. Also, a new radiolabeling method using C-11-acetyl chloride has been developed. A production system for non-standard radionuclides such as I-124 and Br-76 was established as a fundamental basis of PET probe design.

The Biophysics Group aims to develop instruments and methodologies for quantitative measurement of in vivo molecular functions. In imaging physics research,

a new concept named "Open-PET" has been developed and its high possibility such as in-beam usage was clarified. In addition, a new depth of interest in PET detector design, named "X'tal cube" has been proposed and its feasibility was clarified. In image analysis research, a new algorithm for partial volume correction in PET was developed. A new experimental apparatus was developed to measure the concentration of radioactivity of arterial plasma in mice, which is essential for quantification of image data. In MRI research, therapeutic drug delivery imaging using temperature-sensitive liposome and multimodal nano-probes using quantum-dots was performed. Using Mn as a MR probe, reactive gliosis could also be visualized. In human, brain metabolites in schizophrenic patients could be compared with healthy controls by proton magnetic resonance spectroscopy, and a good correlation was found between neurocognitive functions and brain metabolites. Microcirculation research was performed using a two-photon laser microscope that allows us to elucidate molecular communication between vessels, glias and neurons.

4.1. 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 the basic and clinical research on molecular imaging of cancers.

Contact point : saga@nirs.go.jp

Photo:Saga(front left)

Objectives :

The Diagnostic Imaging Group is conducting research on functional cancer imaging by PET and other modalities to clarify the characteristics of individual cancers such as malignant 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 contribution to the management of cancer patients including those considered for carbon-ion radiotherapy (CIRT) conducted in our institution. 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 the design and evaluation of imaging probes that capture the changes of biomolecules specifically associated with cancers and other diseases to realize effective non-invasive diagnoses. We also develop novel in vivo reporter gene imaging systems to facilitate the establishment of new therapies such as gene therapy and regenerative therapy.

The Biomolecule Team focuses on elucidating genetic/molecular events occurring during carcinogenesis, searching for suitable targets of molecular imaging of cancers. By using functional screening of genes, and proteome analysis of 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 in Research :

1) Clinical studies on cancer imaging using various PET probes

We continued clinical research using FLT, a cell proliferation marker, for cancer patients receiving CIRT. Investigation on lung cancer patients showed that pre-CIRT FLT uptake is a significant prognostic factor, in which patients with lower FLT uptake showed better prognosis than those with higher FLT uptake. Analysis on head-and-neck cancer patients revealed that a patient who developed local recurrence tended to show lower reduction rate of FLT uptake 1 month after CIRT, suggesting the possibility of FLT-PET for early prediction of CIRT effect (Fig. 4-1).

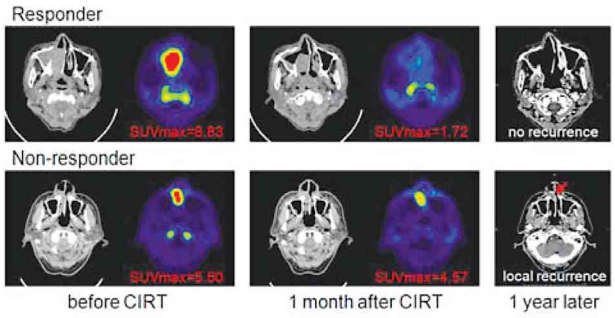


Fig. 4-1 Pre- and post-CIRT FLT-PET of responder and non-responder

We also continued a clinical study with a hypoxia tracer, ^{62}Cu-ATSM, for cancer patients receiving CIRT. At present, there is no significant difference in the outcome of CIRT between tumors with high and low ^{62}Cu-ATSM uptake. In addition, we have started a clinical study on novel hypoxia tracer, FAZA, to evaluate whether tumors showing high FAZA uptake are resistant to therapy or not, for patients with rectal and lung cancer.

2) Exploration of new therapeutic and diagnostic targets of mesothelioma

Biological analysis of mesothelioma cells has shown that the content of manganese (Mn), as well as Mn-SOD expression, in various mesothelioma cell lines, is increased compared to normal mesothelial cells. We therefore evaluated the possibility of mesothelioma imaging with Mn-enhanced MRI (MEMRI). Mesothelioma cells expressing a high level of Mn-SOD gave enhanced MRI images in vitro and the in vivo MEMRI of subcutaneous and plural tumor models gave clear tumor enhancement, indicating the possibility of detecting very small tumor masses with MEMRI.

A large-scale functional screening has shown that COPA was highly expressed in some mesothelioma cell lines, but not in a normal mesothelial cell line. Knockdown of COPA by siRNA induced apoptosis and suppressed tumor growth not only in vitro but also in vivo, suggesting COPA would be a promising therapeutic target of mesothelioma.

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

We succeeded in developing a heterotopic rat heart transplantation model, and assessed the viability and damage of cardiomyocytes using FDG-PET. This animal model will be used to investigate transplant immunity, as well as to evaluate the effectiveness of a novel preservation method of extracted heart.

In addition we have developed a fluorescent cancer model in "Medaka", which can provide a new opportunity to visualize in vivo tumor cells "as seen in a

culture dish" and is useful for in vivo tumor cell biology and facilitates the development of cancer imaging probes and therapeutics. We are now studying the relationship between X-ray irradiation and metastasis formation in this model.

4) Development of antibody probes for cancer imaging and treatment

For the PET imaging of c-kit-positive tumors, an anti-c-kit Fab was labeled with positron-emitting ^{64}Cu. ^{64}Cu-Fab highly accumulated in xenografted tumors and the tumors were clearly visualized by PET. To apply this antibody to c-kit targeted internal radiation therapy, we started to evaluate the efficacy of ^{90}Y-labeled antibody therapy in the small cell lung cancer mouse model.

5) Development of PET probes for neovascularization and tumor imaging

Tumor neovascularization is important not only in the local growth of tumors, but also in tumor invasion and metastasis. Integrin $\alpha_V\beta_3$, expressed on endothelial cells of newly formed vessels and on some tumor cells, can be targeted by RGD peptide. In collaboration with Dr. Dumy's group, RAFT-c (RGD) $_4$ conjugated with cyclam was labeled with ^{64}Cu. PET imaging of tumor-bearing mice gave clear visualization of the integrin $\alpha_V\beta_3$ expressing tumors, reflecting the levels of integrin $\alpha_V\beta_3$ expression in the tumor.

6) Development of imaging probe for activated EGFR

Activation of EGFR (epidermal growth factor receptor) is implicated in carcinogenesis and cancer progression. In order to develop imaging probes to capture the activated state of EGFR, we designed a peptide probe binding to activated EGFR based on the SH2 domain of Grb2, adding TAT for delivery into cells and tissues. After cellular uptake, this peptide probe was found to bind to activated EGFR and the cellular retention was dependent on the activated state of the receptor.

7) Evaluation of CIRT efficacy in mouse model of malignant mesothelioma

Both epithelioid and sarcomatoid tumors in mouse showed a reduction in tumor size starting 14 days after 30-Gy of carbon-ion irradiation and disappeared thereafter. To determine whether the efficacy of CIRT could be evaluated earlier than size reduction, we measured tumor uptake of FLT, a PET tracer of proliferation, after CIRT. In epithelioid tumors, early reduction in FLT uptake was observed followed by transient increase at 1 week after CIRT, reflecting the tumor proliferation activity determined by histological evaluation. In sarcomatoid tumors, however, change of FLT tumor uptake did not correlate with tumor growth. These findings suggest that FLT-PET could evaluate the efficacy of CIRT in epithelioid tumors.

8) Preclinical studies using reporter gene imaging technique.

With a human Na+/I- symporter (hNIS) reporter gene and a reporter probe of $^{99m}TcO_4$- (SPECT) or ^{124}I (PET), we evaluated therapeutic effects of a novel angiogenic gene therapy using a hepatocyte growth factor (HGF) gene in a rat myocardial infarct model. We have also developed a cancer cell line stably transfected with the hNIS reporter gene coupled with a hypoxia responsive element (HRE). A mouse xenograft model of this cell line can report hypoxia response at the genetic level, and can be used for the evaluation of various hypoxia tracers.

The use of tumor-suppressor gene p53 as an anticancer therapeutic has been widely investigated. We constructed a cell line expressing a red fluorescence protein (RFP), as a reporter, and p53 under a controllable promoter. We determined that the level of p53 expression could be monitored by RFP and also that the p53-mediated anticancer effects could be evaluated using FDG-PET.

Major Publications :

1) A. Tsuji, C. Sogawa, A. Sugyou, H. Sudou. M. J. Toyohara, Koizumi, M. Abe, O. Hino, Y. Harada, T. Furukawa, K. Suzuki, T. Saga : Comparison of conventional and novel PET tracers for imaging mesothelioma in nude mice with subcutaneous and intrapleural xenografts. Nucl Med Biol 36 : 379-88, 2009.

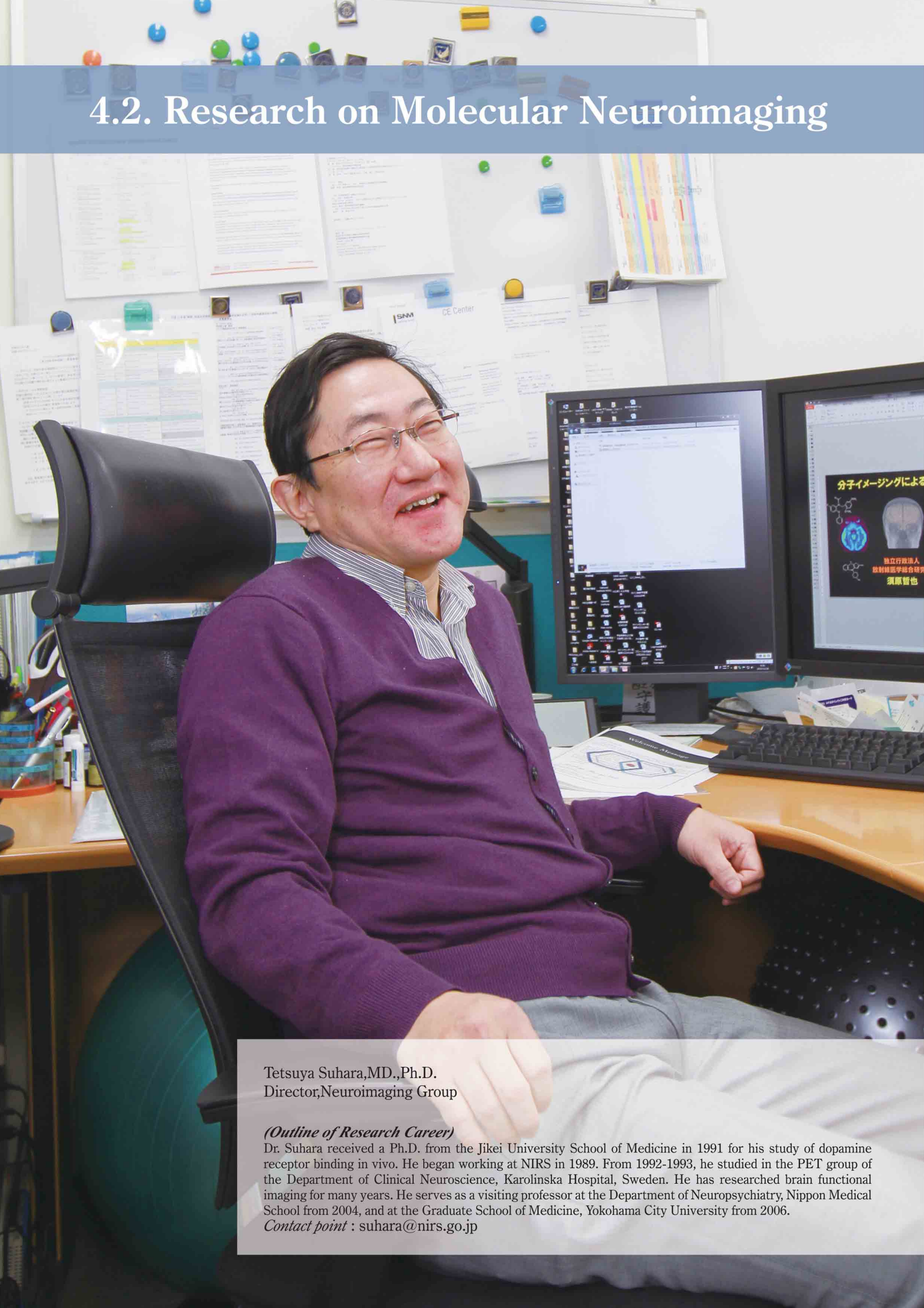
2) S. Hasegawa, K. Maruyama, H. Takenaka, T. Furukawa, T. Saga : A medaka model of cancer allowing direct observation of transplanted tumor cells in vivo at a cellular-level resolution. Proc Natl Acad Sci USA 106 : 13832-7, 2009.

3) Z. H. Jin, T. Furukawa, A. Waki, K. Akaji, J-L. Coll, T. Saga, Y. Fujibayashi : Effect of multimerization of a linear arg-gly-asp Peptide on integrin binding affinity and specificity. Biol Pharm Bull 33 : 370-8, 2010.

4) C. Yoshida, C. Sogawa, A. Tsuji, H. Sudou, A. Sugyou, T. Uehara, O. Hino, Y. Yoshii, Y. Fujibayashi, T. Fukumura, M. Koizumi, Y. Arano, T. Saga : Development of positron emission tomography imaging by 64Cu-labeled Fab for detecting ERC/mesothelin in mesothelioma mouse model. Nucl Med Commun 31 : 380-8, 2010.

5) C. Sogawa, A. Tsuji, H. Sudou, A. Sugyou, C. Yoshida, K. Okada, T. Uehara, Y. Arano, M. Koizumi, T. Saga : C-kit-targeted imaging of gastrointestinal stromal tumor using radiolabeled anti-c-kit monoclonal antibody in a mouse tumor model. Nucl Med Biol 37 : 179-87, 2010.

4.2. Research on Molecular Neuroimaging



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

(Outline of Research Career)

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

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Objectives :

1) Clinical Neuroimaging

a) Development of PET quantification methods for radioligands.

b) Exploration of the relation between regional distribution of pre- and postsynaptic dopaminergic neurotransmission functions and higher brain functions in healthy human subjects.

c) Investigation of time course of amyloid deposition in Alzheimer's disease using a new kinetic analysis method.

d) Estimation of occupancy of norepinephrine transporter by antidepressant using (S, S) - [^{18}F] FMeNER-D_2, and error analysis of measurement of dopamine D2 receptor occupancy using the agonist radioligand [^{11}C] MNPA.

e) Investigation of effects of antipsychotic drug on a function of presynaptic dopaminergic neurotransmission, dopamine synthesis rate.

2) Molecular Neurobiology

a) Promote a translational development of radioprobes for core pathologies of Alzheimer's disease and related disorders by optimizing ^{11}C- and ^{18}F-labeled radioligands for Aβ amyloid and ^{11}C-labeled ligands for tau lesions.

b) Clarify the significance of 18-kDa translocator protein (TSPO; also known as peripheral benzodiazepine receptor) as a PET-detectable biomarker for glial functions. Identify a molecular element linking amyloid deposition and neuroinflammation with the aid of small-animal PET imaging.

c) Establish a preclinical PET assay system enabling estimation of potencies of in-development drugs acting on neuroreceptors and transporters of neurotransmitters.

3) System Neurochemistry

a) Demonstrate the factors and mechanisms diminishing motivation in the depression model of monkeys using behavioral tasks that are measurable at the level of motivation.

b) Identify the changes of hippocampal function in rats born from mothers that have experienced maternal immune activation induced by mimic infection, which implies a model of the pathophysiology of schizophrenia.

c) Establish an in vivo multidirectional experimentation system to evaluate animal models, especially using transgenic common marmosets.

Progress of Research

1) Clinical Neuroimaging

a) A new graphic plot analysis has been developed which could determine the total distribution volume and nondisplaceable distribution volume independently, and therefore the binding potential (Neuroimage, 2010).

b) The contribution of dopamine receptor subtypes to amygdala reactivity was investigated using PET and fMRI. 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 (J Neurosci, 2010).

c) Time course of amyloid deposition in Alzheimer's disease was investigated by [^{11}C] PIB with a new kinetic analysis method which could determine the specific binding rate using short scan time data. The present kinetic analysis method was sensitive to determine changes in amyloid deposition with time compared to the conventional analysis method.

d) The occupancy of norepinephrine transporter by an antidepressant, nortriptyline, was measured using (S, S) - [^{18}F] FMeNER-D_2, and norepinephrine transporter occupancy corresponding to the administration dose was determined (Psychopharmacology (Berl), 2010). Errors of measurement of dopamine D2 receptor occupancy using the agonist radioligand [^{11}C] MNPA have been determined, and the measurement was optimized (J Cereb Blood Flow Metab, 2010).

e) Effects of an antipsychotic drug, risperidone on dopamine synthesis rate were measured, and risperidone could be assumed to stabilize the dopamine synthesis rate (J Neurosci, 2009).

2) Molecular Neurobiology

a) A series of ^{18}F radiotracers capable of capturing fibrillar Aβ aggregates were tested by means of microPET, in collaboration with Tohoku University. Several compounds bound to amyloid plaques in an animal model with affinities nearly comparable to that of a widely used ^{11}C ligand, [^{11}C] Pittsburgh Compound-B. We also screened β-sheet-binding chemicals for an imaging agent applicable to in vivo PET imaging of tau inclusions. A derivative of our original tracer used for near-infrared optical visualization of tau lesions was found to be suitable for PET assays, and tau fibrils in tauopathy model mice were successfully detected by PET with a ^{11}C-labeled version of this ligand.

b) PET investigations of model mice undergoing intracranial implantation of microglial clones expressing TSPO at different levels demonstrated an inverse correlation between TSPO upregulation in microglia and its ability to protect neurons against Aβ

deposition. A comprehensive assay of cytokines secreted by these clones revealed that a subset of inflammatory chemokines was overproduced in the TSPO-rich clone. In addition, glutaminyl cyclase was found to catalyze conversions of Aβ and these chemokines to more biostable and potent forms, highlighting the role of this enzyme in the synergistic induction of Aβ amyloidosis and neurotoxic microgliosis.

c) Occupancy of serotonin transporter by a candidate antidepressant was quantitatively assessed by microPET imaging of living rat brains, in a collaborative project with Mitsubishi Tanabe Pharma Corporation. The dose and plasma concentration of the drug resulting in 50% transporter occupancy were nearly equivalent to those determined by ex vivo analyses of postmortem rat brains and by clinical PET studies, proving the usefulness of this rat PET system for evaluating the potency of new drugs and predicting their effective dosages in humans (Int J Neuropsychopharmacol, 2009).

3) System Neurochemistry

a) We developed a method to quantify changes in the motivation of monkeys (in preparation for patent application). By using this method, we demonstrated that the suppression of motivation was caused by two factors (the suppression of reward sensibility and the augmentation of cost sensibility) and that SSRIs returned both factors to normal levels by facilitating serotonin function. Activation studies using $H_2{}^{15}O$ PET identified the mechanism of motivational control localized in the ventral striatum and fronto-orbital cortex.

b) The rats born from maternal immune-activated mothers showed postnatally a lowered synaptic function in the CA1 region of the hippocampus and neuroinflammation accompanied with abnormally activated glial cells (in preparation for submission).

c) We established an electrophysiological technique using slices of marmoset brain (in preparation for submission). In a collaborative project with the Tokyo Metropolitan Institute for Neuroscience, the functional effects of transfection which protects the dopaminergic neurons from neuronal degeneration by the neurotoxin MPTP were confirmed by a PET study with the positron-labeled dopamine transporter probe.

Major publications

1) H. Ito, H. Takano, H. Takahashi, R. Arakawa, M. Miyoshi, F. Kodaka, M. Okumura, T. Otsuka, T. Suhara : 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, 13730-13734, 2009

2) R. Arakawa, T. Ichimiya, H. Ito, A. Takano, M. Okumura, H. Takahashi, H. Takano, F. Yasuno, M. Kato, Y. Okubo, T. Suhara: Increase in thalamic binding of [11C] PE2I in patients with schizophrenia : A positron emission tomography study of dopamine transporter. J. Psychiatr. Res., 43, 1219-1223, 2009

3) T. Saijo, A. Takano, T. Suhara, R. Arakawa, M. Okumura, T. Ichimiya, H. Ito, Y. Okubo : Electroconvulsive therapy decreases dopamine D2 receptor binding in the anterior cingulate in patients with depression : a controlled study using positron emission tomography with radioligand [11C] FLB 457. J. Clin. Psychiat., 2009 (E-pub)

4) T. Saijo, J. Maeda, T. Okauchi, J. Maeda, Y. Morio, Y. Kuwahara, M. Suzuki, N. Goto, K. Suzuki, M. Higuchi., T. Suhara : Utility of small animal positron emission tomographic imaging of rats for preclinical development of drugs acting on serotonin transporter. Int. J. Neuropsychoph., 12, 1021-1032, 2009

5) H. Takahashi, H. Takano, F. Kodaka, R. Arakawa, M. Yamada, T. Otsuka, Y. Hirano, H. Kikyou, Y. Okubo, M. Kato, T. Obata, H. Ito, T. Suhara : Contribution of dopamine D1 and D2 receptors to amygdala activity in human. J. Neurosci., 30, 3043-3047, 2010

4.3. Research on Molecular Probes and Radiopharmaceuticals

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

(Outline of Research Career)

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

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Objectives :

Molecular probes play essentially important roles in the rapidly developing molecular imaging field. 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 automation 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 oxidative stress and/or disruption of homeostasis and brain efflux function targeting multidrug resistance-associated protein (MRP).

2) The Radiochemistry Team objectives are to develop new labeling methods and labeling precursor 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/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 2009 are described below.

Progress in Research :

New PET probes

1) We found a promising candidate for PET molecular probes which enable quantitative measurement of glutathione/GST reduction function labeled with 76Br.

2) We successfully developed a PET molecular probe for the quantitative assessment of an iodide transporter, whose physiological function is still unclear in the brain. A promising candidate for PET probe for measurement of MRP4 and OAT3 functions in the brain was found from a basic study with ^{11}C-labeled compounds.

3) Some PET probes for the imaging of peripheral benzodiazeine receptor were developed. Among them, some new 18F/11C-labeled probes were useful for imaging brain ischemia, cranial neuritis, pneumonia, and hepatitis. A new tracer for imidazoline receptor and mGlu receptor were developed and evaluated. Drug

Availability of PET probe labeled with ultra-high specific activity

A cerebral ischemia model animal was subjected to a PET imaging study using ultra-high specific activity (>3.7 TBq/μmol) labeled [^{11}C] DAC and [^{11}C] Ac-5216. PET probes labeled with an ultra-high specific activity clearly imaged mild ischemic lesions, whereas probes labeled with ordinary specific activity (maximum value achieved at ordinary PET center) hardly imaged mild ischemic lesions. Additionally, labeled probes with ultra-high specific activity had 4-6 times higher sensitivity to severe ischemic lesions than PET probes labeled with ordinary specific activity.

New method/labeling procedure

A novel reaction for introducing a [^{11}C] acetyl group on an aromatic ring via a cross-coupling reaction and a novel C-^{11}C bond formation reaction via Michael addition was developed using [^{11}C] acetyl chloride ([^{11}C] AcCl) and [^{11}C] nitromethane as a labeling precursor, respectively. Furthermore, an efficient and practical labeling method for [^{13}N] thalidomide by [^{13}N] NH_3 was developed.

Non standard PET radio nuclide

An irradiation system producing 124I and 76Br has been developed and the production method for 124I is being optimized. The system showed high thermal tolerance allowing proton beam irradiations up to 20 μA. Additionally, an automated purification system was also optimized. ^{124}I is obtained as ^{124}I solution automatically.

As a useful radionuclide for PET molecular probes, production and isolation procedures for 63Zn and ^{64}Cu were established.

New PET Probe approved for clinical research.

Four new PET probes ([^{18}F] FEtPE2I, [^{11}C] sulpiride, [^{11}C] AZD2184, 4'- [methyl-^{11}C] thiothymidine) were approved by IRB. [^{18}F] FEtPE2I would be used for assessment of dopamine transporter function. [^{11}C] Sulpiride is used to evaluate its distribution in human. [^{11}C] AZD2184 is expected to give a high contrast clear image of amyloide plaque in Alzheimer's disease. 4'-[methyl-^{11}C] thiothymidine will be useful for diagnosis of tumors.

Contribution to quality of clinical PET in Japan.

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

Major publications

1) Tatsuya Kikuchi, Toshimitsu Okamura, Ming-Rong

Zhang, Kiyoshi Fukushi, Toshiaki Irie : In vivo evaluation of N- [18F] fluoroethylpiperidin-4ylmethyl acetate in rats compared with MP4A as a probe for measuring cerebral acetylcholinesterase activity, Synapse, 64 (3), 209-215, 2010

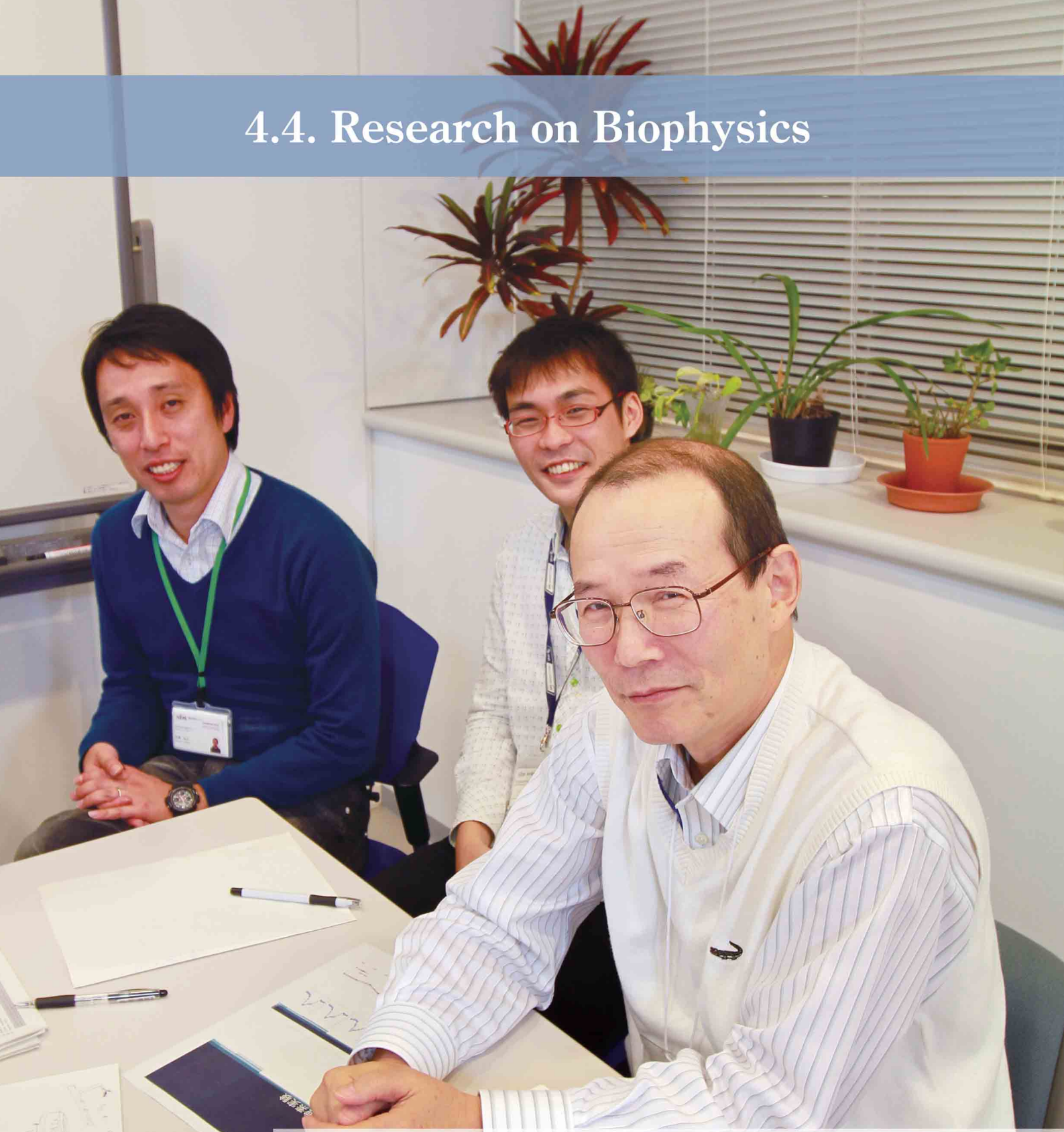
2) Masanao Ogawa, Yuuki Takada, Hisashi Suzuki, Kazuyoshi Nemoto, Toshimitsu Fukumura : Simple and effective method for producing [^{11}C] phosgene using an environmental CCl_4 gas detection tube, Nuclear Medicine and Biology, 37 (1) : 73-6, 2010

3) Kazunori Kawamura, Tomoteru Yamazaki, Jyoji Yui, Akiko Hatori, Fujiko Konno, Katsushi Kumata, Toshiaki Irie, Toshimitsu Fukumura, Kazutoshi Suzuki, Iwao Kanno, Ming-Rong Zhang : In vivo evaluation of P-glycoprotein and breast cancer resistance protein modulation in the brain using [^{11}C] gefitinib, Nuclear Medicine and Biology, 36 (3), 239-246, 2009

4) Ryuji Nakao, Takehito Ito, Kazutaka Hayashi, Toshimitsu Fukumura, Kazutoshi Suzuki: Rapid and efficient purification of positron emission tomography probes by hydrophilic interaction chromatography, Journal of Chromatography A, 1216 (18), 3933-3940, 2009

5) Koichi Kato, Ming-Rong Zhang, Kazutoshi Suzuki: Synthesis of (R, S) - [4-^{11}C] baclofen via Michael addition of nitromethane labeled with short-lived ^{11}C, Bioorganic & Medicinal Chemistry Letters, 19 (21), 6222-6224, 2009

4.4. 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 and completed 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 back in Akita in 1979. After a short stay 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 and heart circulation and metabolism. In 2006, he moved to the Molecular Imaging Center at NIRS in 2006 as the Centre Director and also as Group Leader of the Biophysics Group.

Contact point : kanno@nirs.go.jp

Photo:Kanno (front right)

Objectives :

The Biophysics Group aims to develop instruments and methodologies for quantitative measurements of in vivo molecular functions using PET, MRI and optical techniques. The group consists of four teams whose progress this year was as follows :

Progress in Research :

1) Magnetic Resonance Molecular Imaging Team

This team developed a therapeutic Drug Delivery Imaging technique using temperature-sensitive liposome and applied it to "deep-seated tumors" in vivo. The multimodal and multifunctional liposome was synthesized as an MRI contrast agent, optical imaging and anti-cancer drug with tumor targeting capability. The drug kinetics, including accumulation in a deep-seated tumor, drug release using thermo-triggering, and the anti-tumor effects were visualised in mice. MR temperature mapping during RF heating was also performed.

A multimodal Quantum-Dot nano-probe 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.

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

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.

2) Biosignal Physiology Team

This team succeeded in extracting a slowly diffusing water (SDW) signal using a new compartment model. The SDW signal was more highly correlated with neural-activity than conventional functional MRI (Kershaw et al. NMRBM 2009). The results indicate that diffusion functional MRI (DfMRI) has potential as a new brain functional imaging method.

The characteristics of cartilage degeneration in patients with recurrent patellar dislocation (RPD) following conservative treatment were examined using delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC). The negatively charged compound showed a significant correlation with degeneration of cartilage (Watanabe, Osteoarthritis Cartilage, 2009), indicating that it is a useful probe for MR molecular imaging.

The team also measured brain metabolites in the medial prefrontal cortex of schizophrenic patients and healthy controls with proton magnetic resonance spectroscopy (^{1}H MRS). A significant correlation between prefrontal cortex-related neurocognitive functions and brain metabolites in the medial prefrontal cortex was obtained. The data suggested that specific metabolites of the medial prefrontal cortex were associated with neurocognitive deficits in schizophrenia.

Experiments with two-photon laser microscope and closely related instruments were performed in order to better understand brain microcirculation and microenvironment. This year an experimental protocol was developed where the cortical microcirculation of a awake mice is 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

This team aims to realize algorithms and experimental apparatuses to measure and visualize various functionalities of humans and animals using PET. They proposed a new algorithm for partial volume correction. In the algorithm, anatomical information was acquired from MRI images and Wavelet transformation was applied to incorporate the brain structure to PET images. They also focused their research activities on applying the algorithms for PET data analysis to actual experimental data derived from both human and small animal studies. They evaluated a well-established algorithm for a reference tissue model for quantifying the dopamine transporter. The imidazorine subtype-2 receptor was also evaluated as a new target ligand in the brain.

The team also developed a new experimental apparatus to measure radioactivity concentration in the arterial plasma of mice. As blood samples from mice have a permitted volume of only around 1 μL, new system was required. In the system, sampled blood was dripped onto a specially designed disc with line-shaped channels etched on the surface to automatically absorb sampled blood with a capillary effect. The blood was centrifuged, and its volume and radioactivity was measured in the apparatus. The system is now under evaluation. Three patents were applied for and another patent was disclosed.

4) Imaging Physics Team

This team developed a method to improve OpenPET imaging using time-of-flight (TOF) information. The OpenPET geometry is an original innovation that consists of two detector rings separated by a gap. The OpenPET has three main applications : simultaneous PET/CT, extension of the axial FOV, and in-beam PET, which is a method for in situ and non-invasive monitoring of tumor-conforming charged-particle therapy. On the other hand, image reconstruction for the OpenPET system is an incomplete problem. The system suffers from loss of low-frequency components because the gap, where direct lines-of-response (LORs) do not exist, is imaged only from oblique LORs. Therefore, the recent focus of this team has been on TOF information. The influence of TOF information in OpenPET image reconstruction was investigated through numerical simulations. The results showed that TOF information can compensate for the loss of low-frequency components missing in the gap.

For the in-beam PET application, the team measured the influence of secondary particles from heavy-ion irradiation on the OpenPET detectors. An increased count rate caused by activation of the scintillators themselves degraded the performance of the detectors. Therefore some parameters of the circuit were optimized for high count rate capacity.

This team also proposed a new depth-of-interaction (DOI) PET detector design, which was named "X'tal cube". Recently, small, light, and thin photodetectors such as multi-pixel photon counters (MPPCs) have become commercially available as alternatives to photomultiplier tubes (PMTs). In this design, a number of small photodetectors are coupled to each of the six surfaces of a 3-dimensional scintillation crystal array. A prototype detector, in which PMTs were used instead of MPPCs, was developed and proof-of-concept of this detector was demonstrated in a preliminary experiment,

Major publications

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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 2009 ; 22 (7) : 770-778.

3) Miho Shidahara, Charalampos Tsoumpas, et al. : Functional and structural synergy for resolution recovery and partial volume correction in brain PET, NeuroImage, 44, 340-348, 2009.

4) Taiga Yamaya, Eiji Yoshida, Naoko Inadama, Fumihiko Nishikido, Kengo Shibuya, Makoto Higuchi and Hideo Murayama, A multiplex "OpenPET" geometry to extend axial FOV without increasing the number of detectors, IEEE Trans. Nucl. Sci., Vol. 56, No. 5, 2644-2650, 2009

5) Eiji Yoshida, Keishi Kitamura, Fumihiko Nishikido, Kengo Shibuya, Tomoyuki Hasegawa, Taiga Yamaya, Naoko Inadama and Hideo Murayama, Feasibility study of a highly sensitive LaBr3 PET scanner based on the DOI-dependent extended-energy window, Nuclear Instruments and Methods in Physics Research A, 604, 363-365, 2009.

5. 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 majoring 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 subject of his research was radiation-induced DNA damage and its repair, and the mechanism of radiation-induced cell death. From 1983 to 1985 he worked as a research fellow in the Genetics Division, Children's Hospital, Harvard Medical School. The research subjects there were gene amplification and cloning of genes responsible for radiosensitivity. He moved to the Central Research Institute of Electric Power Industry in 1999 to research biological effects of low dose radiation. He joined NIRS in 2006.

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Objectives ;

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

Overviews ;

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 activities of the Research Groups and the Nakaminato Laboratory are described in the respective section of this Report.

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 this institute were 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 conducted technical and diagnostic histopathological support for NIRS intramural research.

The Advanced Animal Research Section supports 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 the 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 involve the "Construction of Natural Radiation Exposure Study Network" from the Special Coordination Funds for the Foundation for the Promotion Science and Technology of 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 work utilizing its technologies and facilities.

The Research Center was designated by the International Atomic Energy Agency as a Collaborating Centre for the 2nd term (2009-2013) for Low Dose Radiation Biology.

In the Research Center 47 permanent and 57 temporary members actively conducted research during the fiscal year 2009. They produced 90 original papers and 72 reviews and proceedings. The Center held the second "KIDS Work shop : Radiation Protection for Children" in conjunetion with IAEA/NIRS Workshop on "Low Dose and Medical Exposure" and WHO Global Initiative Meeting on "Towards a Safer use of Radiation Paediatrics".

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; and Dr. Satoshi Yoshida, the Director of the Environmental Radiation Effects Research Group. As of July 2009, Dr. Kiyomi Eguchi-Kasai was named as the Head of the Planning and Coordination Section of the Research Center to promote its activity further.

5.1. Regulatory Sciences Research for Radiation Safety and Protection

Hidenori Yonehara,Ph.D.
Director,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.

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Photo:Yonehara (front right)

Objectives

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

1) Summarizing information on radiation protection issues

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

2) Radiation risk assessment and construction of information databases

The group constructs information databases on risk assessment for people who are exposed to low dose radiation and controllable natural radiation sources. Scientific information on radiological archives of experimental research, on the exposures and health effects of radiation among different human populations, and on effects of environmental radiation from epidemiological studies are collected for the databases. The group carries 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 develops 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 collects examples in which risk information on radiation safety would be communicated to the public, and the group analyzes methods of risk communication with sociological consideration.

Progress of Research

1) Construction of information databases for radiation risk assessment

An original database for information on exposure due to industrial use of naturally occurring radioactive materials (NORMs) has been developed previously and published on the web. The database provides a search system by which users of the materials can investigate the level of activity concentration in more than 1000 types of materials and estimate a dose when handling the materials.

The archive system for long-term animal experiment data/material was also constructed and is on a trial basis. The accumulated information associated with researchers, radiation sources, biological results, macro/micro-scopic observations, etc. are going to be registered in the "STORE", the international long-term animal experiment archive which is operated within the framework of EURATOM FP7.

2) Development of mathematical models

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

Recently, international concerns about framework for protection of non-human biota have been increasing and European and North American countries have respectively developed assessment frameworks and tools to evaluate the radiological impact on non-human biota. The last year, we applied the assessment tools developed by Europe and the U.S.A. to the environment of Japan. It was found that the assessment framework can work, although default parameters which are used in both tools were different from the Japanese environment, so that we collected Japanese concentration ratio data from the literature and compared the collected data with default values of the ERICA tool (European assessment model). For the purpose of comparison, we focused on the transfer factor of vegetables because of the amount of data available. From a comparison of the data for transfer factor value of grass and herbs in ERICA, we found that almost all TF values in ERICA were greater than those from Japanese data (i. e. ERICA has adapted a conservative value), except for Sb and Zr. The Japanese transfer factor of Sb was within the same order of ERICA TF ; however, Japanese TF of Zr was less than that in ERICA. Therefore, assessment with the ERICA default value of Zr will be an underestimation in the Japanese environment.

3) Epidemiological study

The possible effects of exposure to controllable natural radiation and medical radiation are our main research interests. We continued a case-control study of residential radon and thoron and lung cancer among cave-dwelling residents in Gansu Province, China, in cooperation with researchers inside and outside NIRS. A total of 103 cases and 200 controls have been entered in the study so far, and 1-year measurements for radon, thoron and their decay products will be soon completed for all subjects. Preliminary analysis of the interview

data from questionnaires showed an increased risk of lung cancer in relation to smoking which should be adjusted in the main analysis. Data on the detailed measurements were also analyzed, showing temporal variations according to dwelling type which should be taken into account for better assessment of exposure to radon and its decay products in epidemiological studies of residential radon.

We also continued a meta-analysis of second cancer risk among childhood cancer survivors treated with radiotherapy to quantitatively evaluate the possible effects of medical exposure. In the meta-analysis, we have developed a methodology to estimate an excess relative risk from individual studies in which only category-specific risk estimates were available. The number of eligible studies has increased more than two-fold, and detailed analysis is ongoing.

4) Investigation into justification of medical radiological procedures.

The surveys of national and international circumstances for judgement on whether radiation diagnostic procedures would be justifiable were investigated. The guidelines to determine the most appropriate diagnostic imaging examinations and to reduce unnecessary exposure of patients to radiation based on the available evidence have been well equipped in the UK and the USA. Few programs of undergraduate medical education have been achieved in order to choose the most appropriate imaging investigation or intervention for their patients in each Japanese medical college so far. Also few practical tools have been equipped for risk communication in hospitals regarding each radiodiagnostic examination and radiation exposure among medical doctors, radiological technicians and patients.

Results of survey on risk perception done in FY 2007 were analyzed using risk ranking techniques. The survey had been 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 academic majority, all groups examined perceived handguns, nuclear power and cigarettes as having the highest risk, while X-ray exposure was perceived as a moderate risk. Respondents tended to believe the information from TV more than that from public organizations. We also interviewed researchers within 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.

5) Dialogue seminars for risk communications among stakeholders

A series of meetings called "Dialog Seminars" on themes of optimization of radiation in medicine for children of radiodiagnostic exposure and radioactive waste was held to communicate information on risk among scientists, persons in regulatory authorities, those in relevant companies, mass communicators and the public. In the seminars regarding optimization of radiodiagnostic exposure, international trends, the present circumstances and experimental and epidemiological data of risk assessments, the present regulatory circumstances and problems in clinical fields issues related to protection of medical exposure were discussed among medical doctors, radiological technicians, experts for radioprotection and regulators.

In the seminar regarding radioactive waste, fundamental information on high-level waste and radiation health effects was provided by experts to the public, and issues related to radiation waste were discussed among stakeholders. To clarify the factors on risk perception and acceptance of nuclear fuel cycle, the record of the discussion has been analyzed in terms of message analysis.

Major publications

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2. Francois BRECHIGNAC, Masahiro Doi: Challenging the current strategy of radiological protection of the environment : arguments for an ecosystem approach, Journal of Environmental Radioactivity, 100 (12), 1125-1134, 2009
3. Kazutaka Doi, Shinji Tokonami, Hidenori Yonehara, Shinji Yoshinaga : A simulation study of radon and thoron discrimination problem in case-control studies, Journal of Radiation Research, 50 (6), 495-506, 2009

5.2. Experimental Radiobiology for Children's Health Research Group

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

Outline of Research Career

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.

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Photo:Shimada (front right)

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 and the safety of the environment are being instituted, particularly in the USA and Europe. These regulations are mainly directed at foodstuffs and chemicals. Recently, 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 risk of carcinogenesis due to 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 cancer induction and lifespan shortening. Final goals of this research group are to propose age-weighting factors and relative biological effectiveness (RBE) of neutrons and heavy ions for fetuses and children for radiation protection.

Progress of Research

1) 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, 2MeV) at various ages during fetal to mature adulthood periods. The ages examined were pre-implantation (3 days post-conception (dpc)), major organogenesis (13 dpc), late fetal (17 dpc), neonatal (1 week after birth), prepubertal (3 weeks), post-pubertal (7 weeks) and mature adult stages (15 weeks). The doses ranged between 0.2 and 4 Gy for gamma rays, 0.2 and 2 Gy for carbon ions, and 0.05 and 1 Gy for neutrons. These mice are now being kept under observation other wise autopsied at moribundity or soon after death. The result of the experiment for gamma-ray exposure at the adult stage indicated that female mice appeared more susceptible to radiation-induced lifespan shortening than male mice. Male mice at the neonatal stage came to be more sensitive than those at the adult stage. Surprisingly, irradiation at the late fetal stage had little influence on lifespan shortening for both genders. Irradiation with carbon ions at the adult stage shortened the lifespan to a similar extent as that with gamma-rays. Carbon ions were more potent, however, in reducing lifespan than gamma rays when fetal and neonatal mice were exposed. These results suggest a larger relative biological effectiveness (RBE) of carbon ions for fetus and infants.

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

Radiation risks are dependent upon both tissue types and the age at exposure. Breast is one of the most susceptible organs to radiation-associated cancer. We have been using the Sprague-Dawley (SD) rat mammary cancer model to investigate the age effect of Cs-137 gamma rays or carbon ions (13 keV/μm) on breast cancer risk. In FY2009, pathological diagnosis for 250 rats and autopsy of 350 rats were performed. Tentative data suggest that gamma irradiation of prepubertal rats at 1 Gy resulted in smaller diminishment of the ovarian follicular pool and greater effectiveness on mammary cancer induction than irradiation at 2 Gy. A neutron irradiation experiment was also commenced, where the dose range was determined to be 0.05-0.5 Gy based on past literature. Genomic DNA analysis of gamma ray-induced mammary cancers of SD × COP hybrid rats indicated that copy number aberrations were high on chromosomes 2, 3 and 5 at a frequenct of more than 30%.

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

The effect of age on tumor development of kidney, brain (medulloblastoma), intestine, liver and lymphoid organ (thymus) was also examined using mutant and genetically engineered animals as well as B6C3F1 mice. Perinatal and infant stages were the most sensitive to the development of kidney and brain tumors in Eker rats and *Ptch1*$^{+/-}$ mice, respectively. Brain tumors developed in a dose-dependent fashion, showing considerable effects even at a low dose of 0.1 Gy. Late embryonic stages were also sensitive to radiation-induced brain tumorigenesis. We confirmed that radiation-induced brain tumors in *Ptch1*$^{+/-}$ mice had wild-type *Ptch1* loss cansed by interstitial chromosomal deletions, which was characteristic of radiation-induced tumors. This enabled us to distinguish radiation-induced and spontaneous tumors and consequently led to the finding of brain tumor induction even at a low dose, as low as 50 mGy. We also found that irradiation at the infantile stage induced more intestinal tumors in *Apc*$^{Min/+}$ mice than at the adult stage, and the second hit event was, again, intra-chromosomal deletions in tumors of mice irradiated. Crypt cells in infant colon were more resistant to apoptosis than those of adult

intestines, which may account for the age difference in the susceptibility to tumorigenesis. The incidence of T-cell lymphomas in B6C3F1 and *Mlh1*$^{-/-}$ mice exposed at 17 dpc, 2 or 10week of age was examined. Infant mice were the most susceptible to radiation, but 17-dpc mice were unexpectedly resistant. In the tumors from *Mlh1*$^{-/-}$ mice, frequent frameshift mutations at mononucleotide repeat sequences in *Ikaros* gene were observed, which resulted in the loss of protein.

3) Combined effect of radiation and chemical carcinogens on lung and intestinal 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 week 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 and adult stages, and the synergism was more effective at the pubertal stage. In *Mlh1*$^{-/-}$ mice, intestinal tumors were induced by combined exposure to X rays (2 Gy) and dextran sodium sulfate. In male but not female mice, the incidence of tumors increased in a supra-additive fashion. There was no significant age difference in the susceptibility to tumor induction.

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. We found that the dynamics of uranium deposition and the incidence of apoptosis in kidney differed between 1 week and 10 weeks of age in rats : uranium concentration was lower, and elimination was delayed in neonates than in adults. This was because the volume of S3 segments of the proximal tubules, which are the selective site of uranium accumulation and induction of apoptosis, was quite small in neonates. Moreover, rapidly growing S3 segments during the infant period re-accumulated uranium, which was released from somewhere in the body, thereby resulting in persistent apoptotic figures observed up to 3 weeks of age. Experimental groups for the late effect of uranium are being set up.

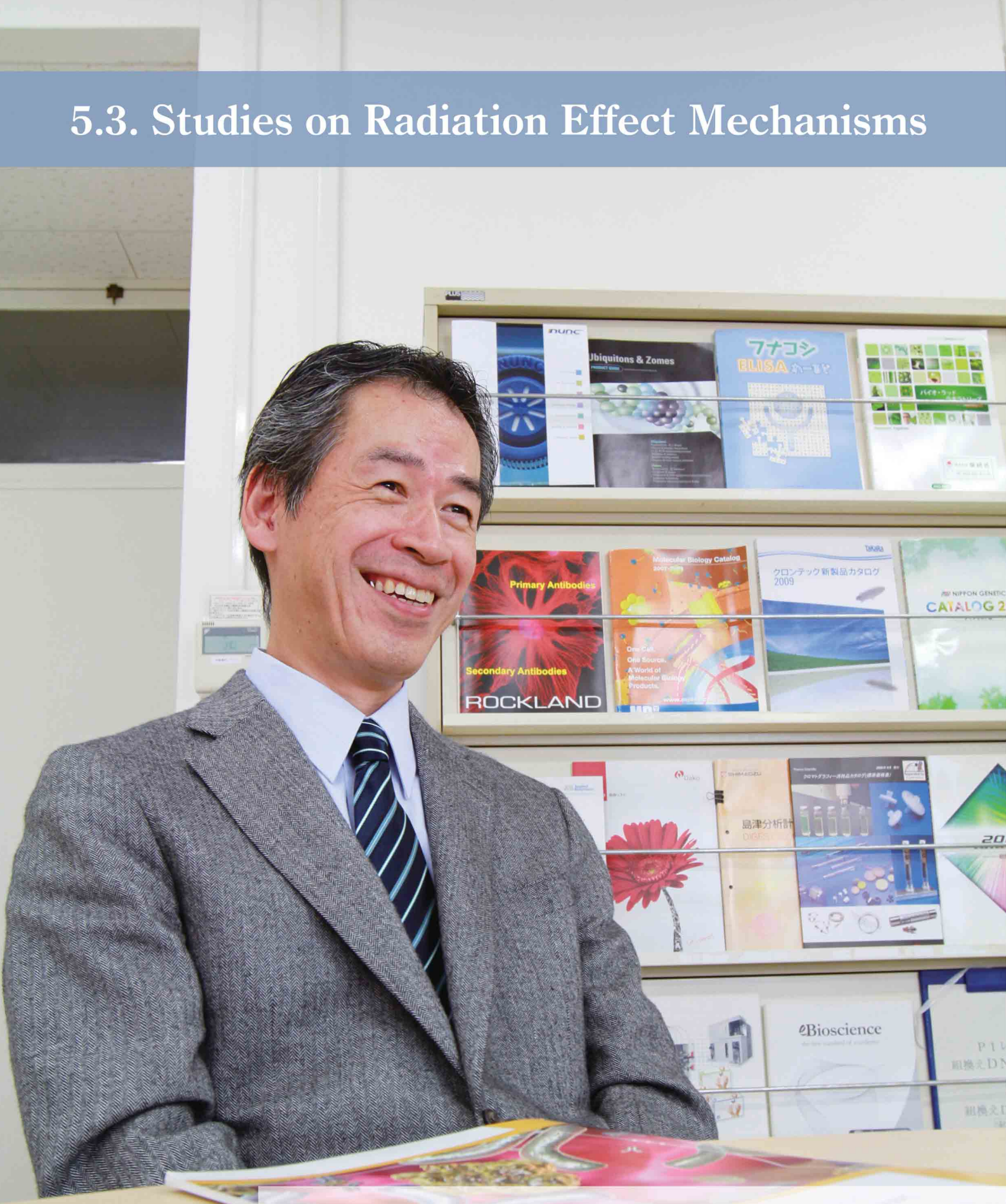
5) Mutation induction in the Aprt *locus*

In order to determine the age-dependence of mutation induction, *Aprt*$^{+/-}$ mice at 1 or 7 weeks of age were exposed to a single dose at 1 or 4 Gy, or four fractions at 1 Gy of X rays, as well as to a single dose of 0.25 or 1 Gy, or four fractions at 0.25 Gy of neutrons. Observations suggest that exposure at a younger age with the higher dose resulted in more *Aprt*$^{-/-}$ mutations in cultured kidney cells derived from the exposed mice. Fractionated exposure of X rays did not show any mutation inductions ; however, fractionated exposure of neutrons enhanced the effect of irradiation.

Major publications

1) T. Imaoka, Nishimura M., Iizuka D., Daino K., Takabatake T., Okamoto M., Kakinuma S., Shimada Y. : Radiation-induced mammary carcinogenesis in rodent models : What's different from chemical carcinogenesis?, J Radiat Res, 50, 281-293, 2009
2) S. Kakinuma, Yamauchi K., Amasaki Y., Nishimura M., Shimada Y. : Low-dose radiation attenuates chemical mutagenesis in vivo - Cross adaptation -, J Radiat Res, 50, 401-405, 2009
3) S. Homma-Takeda, Terada Y., Nakata A., Sarata Kumar S., Yoshida S., Ueno S., Inoue M., Iso H., Ishikawa T., Konishi T., Imaseki H., Shimada Y. : Elemental imaging of kidneys of adult rats exposed to uranium acetate, Nucl Instr Meth Phys Res Sect B, 267, 2167-2170, 2009
4) T. Miyoshi-Imamura, Kakinuma S, Kaminishi M, Okamoto M, Takabatake T, Nishimura Y, Imaoka T, Nishimura M, Murakami-Murofushi K and Shimada Y. : Unique characteristics of radiation-induced apoptosis in the postnatally developing small intestine and colon. Radiat Res 173, 310-318, 2010
5) Y. Yamaguchi, Takabatake T., Kakinuma S., Amasaki Y., Nishimura M., Imaoka T., Yamauchi K., Shang Y., Miyoshi-Imamura T., Nogawa H., Kobayashi Y., Shimada Y. : Complicated biallelic inactivation of Pten in radiation-induced mouse thymic lymphomas, Mutat Res 686, 30-38, 2010

5.3. Studies on Radiation Effect Mechanisms



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

Outline of Research Career

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

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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 the 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 animal experiments or in epidemiological data, this research group conducts studies on the mechanism of radiation effects caused by low-dose radiation. The purpose of this research group is to derive findings useful in the risk assessment of low-dose radiation that can be used as a basis for the development of an appropriate regulatory framework. The following study items are investigated respectively by the four teams.

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

Progress of Research

1) Radiation Carcinogenesis Research Team

Radiation risk of cancer induction has been evaluated based on direct effects of radiation on irradiated cells. It is known that radiation causes cancer through two types of damage: DNA damage directly induced in target cells and radiation-induced change of a microenvironment. The contribution of the latter untargeted carcinogenesis to radiation-induced cancer risk has not been evaluated. To elucidate its contribution to radiation risk, we have established a thymus transplantation system for assessment of untargeted effects of radiation on carcinogenesis. When thymuses of unirradiated 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, depending on the transplantation sites (subcutaneous or under the kidney capsule). The results indicate that low doses of (-rays induce untargeted lymphomagenesis in a Prkdc-deficient condition. Bone marrow transplantation prevented this untargeted 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 untargeted lymphomagenesis and thymic hypoplasia. We also determined whether Notch1, one of the major oncogenes related to lymphomagenesis, was rearranged in the 5' region of the locus in untargeted lymphomas. Notch1 was interstitially deleted in untargeted lymphomas at a frequency similar to that in lymphomas induced by whole-body irradiation. Furthermore, Notch1 was deleted in untargeted lymphomas through mechanisms similar to those in lymphomas induced by whole-body irradiation. These results suggest that the development of radiation-induced untargeted lymphomas share the same mechanisms with those in lymphomas induced by whole-body irradiation.

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 chromosomal rearrangements, including deletions and translocations. This chromosomal instability can promote carcinogenesis and accelerate aging. The repair of DSBs is indispensable for genomic integrity. Cells, therefore, have invested in at least two pathways to repair DSBs, namely homologous recombination repair (HRR) and non-homologous end-joining (NHEJ). In higher organisms, NHEJ 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, identification of the modulatory factor (s) for a low-dose radiation-risk in NHEJ and the elucidation of the molecular mechanism (s) involved with those factor (s) are the focus of our interest. Up to the present, we have established three cell lines having *XRCC4*, *Artemis* and *MDC1* (mediator of DNA damage checkpoint 1) disrupted, respectively, by a gene targeting technique in a human colon tumor cell line HCT116 to define the biological roles of NHEJ-related

genes on DNA damage induced by IR. We then demonstrated higher 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 that in the parental cells. In addition, we showed that MDC1 closely correlates with regulation of the phosphorylation, at least, of ATM and DNA-PKcs after IR.

In the current study, we determined that frequency of the HPRT gene mutation induced by X-rays (0.5-2 Gy) was significantly increased in a dose-dependent manner in *MDC1*$^{-/-}$ cells, whereas the induction of mutation beyond the basal level was not observed in parental cells up to 2 Gy of X-rays. This radiation-induced mutagenic phenotype of *MDC1*$^{-/-}$ cells is consistent with previous findings in survival rate and chromosomal aberration assays. Subsequently, these findings suggest that MDC1 plays an important role in DNA damage signaling/repair machinery in human cell lines.

Meanwhile, we analyzed gene expression by use of a DNA micro-array technique to find genes influenced by low-dose radiation in *MDC1*$^{-/-}$ cells as well as in parental HCT116. Enhancement of expression levels of genes coding for factors related to DNA replication, cell cycle and DNA repair was exhibited in *MDC1*$^{-/-}$ cells compared with parental HCT116 cells under normal culture conditions, 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 any event, MDC1 may regulate many aspects of DNA damage response pathways, and may be associated with stabilizing the interactions and retention of NHEJ components at the site of DSBs. We are currently working on validation of the expression profiles of the genes mentioned above, and investigating the influence of X-ray irradiation on gene expression profiles in *MDC1*$^{-/-}$ cells.

3) Developmental Anomalies Research Team

To elucidate the mechanism of the effects of low dose radiations on the development of mice as well as neural crest-derived cells, melanocytes 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). The effect was studied by scoring changes in the postnatal and prenatal development of mice as well as cutaneous coats 22 days after birth and in the melanocyte development in the prenatal epidermis and hair follicles. The percentage of live birth and body weight at day 22 were not affected by the irradiation, whereas the survival to day 22 was significantly decreased in mice irradiated with 0.75 Gy γ-rays. The frequency and size of white spots (white hairy skin devoid of melanoblasts and melanocytes) in the mid-ventrum increased in irradiated mice in a dose-dependent manner. In 18-day-old embryos, the frequency of abnormalities in tails and eyes as well as of hemorrhage increased as dose increased. In contrast, the number and body weight of embryos were not affected by the irradiation (0.1 to 0.75 Gy). The numbers of melanoblasts and melanocytes in the epidermis and hair follicles also decreased in a dose-dependent manner. The numbers decreased significantly even in mice irradiated with 0.1 Gy γ-rays. These results suggest that γ-rays seem to have a great effect on post- and prenatal development of mice as well as on melanocyte development.

4) Radioadaptive response research team

Exposure of low doses of ionizing radiation can induce protective mechanisms against a subsequent higher dose of irradiation. This phenomenon, called radiation-induced adaptive response (AR), has been described in a wide range of biological models. We previously demonstrated the existence of AR in mice during late organogenesis. In the present study, induction of AR by priming X-rays in combination with challenging irradiations from high LET accelerated heavy ions (HI) in C57BL/6J Jms mice was examined, using 30-day survival after challenging irradiations as an index. Three kinds of accelerated HI from mono beams of carbon, silicon and iron with LET values of about 15, 55, and 200 keV/μm, respectively were examined. The priming low dose of X-rays at 0.50 Gy significantly reduced mortality from the high challenging dose of carbon or silicon particles, but not from iron particles. These results indicate that AR could be induced by priming low LET X-rays in combination with subsequent challenging high LET irradiations from certain kinds of accelerated heavy ions, and successful induction of AR would be a possible event relating to the LET value or/and the HI particle of the challenging irradiations. We here demonstrated the existence of AR induced by low LET X-rays against high LET irradiations at the whole body level in a mouse model for the first time. These findings would provide new insight into studies on radiation-induced AR in vivo.

Major Publications

1. Hirobe, T., Shinpo, T., Higuchi, K. and Sano, T. Life cycle of human melanocytes is regulated by endothelin-1 and stem cell factor in synergy with

cyclic AMP and basic fibroblast growth factor. Journal of Dermatological Science 57, 123-131, 2010.
2. Hirobe, T. Ferrous Ferric Chloride Stimulates the Proliferation of Human Skin Keratinocytes, Melanocytes, and Fibroblasts in Culture, Journal of Health Science (Tokyo, Japan), 55, 447-455, 2009
3. Zakeri, F., Hirobe, T. A cytogenetic approach to the effects of low levels of ionizing radiations on occupationally exposed individuals, European Journal of Radiology, 73, 191-195, 2010
4. Taki, K., Wang, B., Nakajima, T., Wu, J., Ono, T., Uehara, Y., Matsumoto, T., Oghiso, Y., Tanaka, K., Ichinohe, K., Nakamura, S., Tanaka, S., Magae, J., Kakimoto, A., Nenoi, M. Microarray analysis of differentially expressed genes in the kidneys and testes of mice after long-term irradiation with low-dose-rate gamma-rays., Journal of Radiation Research, 50, 241-252, 2009
5. Nenoi, M. Regulation of the p21 gene promoter in response to clinically low dose radiation., Data Science Journal, 8, BR42-BR48, 2009

5.4. Studies on Environmental Radiation Effects

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

Outline of Research Career

Dr. Yoshida received a BE in safety engineering from Yokohama National University in 1983 and a ME and Ph.D. in environmental chemistry in 1985 and 1989, respectively, from Tokyo Institute of Technology. He joined NIRS in 1989. His main research interests are radioecology, environmental chemistry, and ecotoxicology.

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Photo: Yoshida (right)

Objectives

The recent rapid changes in energy production systems and life styles of people worldwide have made environmental radiation research even more important. In order to satisfy the needs for radiation safety and regulations, this research group aims to investigate three subjects related to environmental radiation and radioactivity: i. e. 1) effects of radiation on organisms and ecosystems ; 2) exposure of 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 2009.

Progress of Research

1) Effects on organisms and ecosystems

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

Terrestrial Radiation Ecotoxicology Research Team

To understand the impact of radiation on terrestrial ecosystems, plants, fungi, earthworms and springtails were selected, and the dose-effect relationships for radiation have been studied. In order to detect radiation responsive genes, a novel technology, high-coverage expression profiling (HiCEP), has been applied. Among many transcript-derived fragments (TDFs) up-regulated by irradiation, poly (ADP-ribose) polymeraseI gene was identified as a sensitive radiation responsive gene in several animals and plants, i. e. springtail *(Folsomia candida)*, a model plant *(Arabidopsis thaliana)* and an earthworm *(Enchytraeus japonensis)*.

Since the biological effects of long-term irradiation have more relevance to studies in radiation ecotoxicology, the team continued a study on chronic exposure. The model plant, *A. thaliana*, exposed to gamma rays for 2 weeks at a dose rate of 20 Gy/day was assessed for metabolic analyses. Among 125 compounds identified in metabolic profiling of the plant, 30 showed significant elevation in the levels following irradiation. The elevations were not only observed in primary metabolites in such processes as the TCA cycle, amino acid metabolism and sugar metabolism, but also notably in intermediates of secondary metabolism. This suggested that the metabolic balance had changed by irradiation, which probably caused successive growth reduction in the plant.

The effects of high LET radiation must be also considered because of the presence of alpha and beta emitters in the environment as well as gamma emitters. 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, we have studied the effects of heavy ions at NIRS-HIMAC on the growth of *E. japonensis*. Earthworms were exposed to C, Ne, Si, Ar or Fe ion with energy of 290, 400, 490, 500 and 500 MeV/u, respectively. Heavy ions clearly showed stronger effects than gamma rays with respect to the growth inhibition of the earthworm. As LET was increased, heavy ions appeared to inhibit growth more effectively ; however, the effects of Si, Ar and Fe ion were not significantly different.

Aquatic Radiation Ecotoxicology Research Team

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

We have been tried to generate medaka *(Oryzias latipes)* strains that have mutations in some DNA repair genes by the targeting induced local lesions in genome (TILLING) system, which includes random mutagenesis, followed by screening for induced mutations in target genes. We could obtain a homo mutant that has a point mutation in a conserved region of *gadd45α*, which is involved in cell cycle arrest and DNA double strand break repair. Radiosensitivity of this mutant will be examined.

Genome-wide gene expression was examined in acutely γ-irradiated green alga *Pseudokirchneriella subcapitata*, which is one of the species most commonly used for ecotoxicity evaluation of chemicals but for which genomic sequence information is lacking. Approximately 7,000 expressed genes were detected by HiCEP, which is based on an amplified fragment length polymorphism (AFLP) and thus requires no sequence information for analysis. Expression levels of approximately 800-900 genes were affected at 100 to 300 Gy. Nucleotide sequences of 41 up-regulated genes were determined. The quantitative reverse transcription polymerase chain reaction (qRT-PCR) validated the up-regulation. Two genes had homology to some DNA repair genes. One resembled DEAD/DEAH box helicase genes, and the other resembled

SNF2/RAD54 family genes and *rad26*. Further characterization of the affected genes will contribute to finding biomarkers for detection of radiation effects and elucidating molecular mechanisms of radiation responses.

In our previous studies, bacterial community structure in the flooded paddy soil microcosm had been affected by chronic γ-irradiation at a dose rate of 1.2 Gy/day for 5 days. This year, the bacterial species composition of the pre-irradiated soils was comprehensively clarified by 16S rDNA clone library analysis and bacterial species affected by irradiation were isolated from the microcosm. Effects of chronic γ-irradiation on fungus communities were also examined in this microcosm by denaturant gradient gel electrophoresis (DGGE) of 18S rDNA. Differences were not observed in DGGE band profiles between control and irradiated microcosms, suggesting that fungus communities are less radiosensitive than bacterial communities.

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 investigates the concentration and exposure doses of radon (^{222}Rn), thoron (^{220}Rn), and related radionuclides, mainly in areas with high natural radiation, and analyzes the results together with epidemiological data. The group also aims to collect scientific information on dose and effects of cosmic radiation in aircraft and to provide them in an intelligible and easy to access way for the general public such as on the Internet.

Natural Radiation Exposure Research Team

Recent epidemiological studies indicated that lung cancer risk significantly increases due to exposure to relatively low-level residential radon (100 Bq/m^3). We are conducting an epidemiological study in China, cooperating with the Radiation Epidemiology Team of the Regulatory Sciences Research Group. Passive radon detectors developed by NIRS are used for this study. Measurements with passive detectors are conducted as follows : (1) a large number of passive detectors are assembled at NIRS, (2) these detectors are sent to China by post, (3) Chinese collaborators place them in dwellings selected in studied areas, (4) they are retrieved after six months of exposure, (5) the exposed detectors are sent back to NIRS, and (6) they are processed at NIRS and radon concentration for each dwelling is estimated. This series of work was conducted twice in 2009 and the estimated radon concentrations will be used for an epidemiological study.

We are also investigating potential exposure due to natural radionuclides contained in building materials. Building material samples were collected for this purpose and concentrations of natural radionuclides such as radium and uranium were estimated using a high purity germanium detector (HPGe) and inductively coupled plasma - mass spectrometry (ICP-MS). Exposure due to these radionuclides was estimated assuming typical 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 crew on aircraft 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 makes efforts to collect scientific information on dose and effects of cosmic radiation and also to provide them in an easy-to-understand way by the general public. Major tasks are (1) calculation of aviation route doses (effective doses received in aircraft) using the most up-to-date method, (2) development of new detectors to verify calculations in aircraft, and (3) improvement of a comprehensive system for radiation protection dosimetry of aircraft crew. Some research outputs of the team are open to the public as a web program entitled "Japanese Internet System for Calculation of Aviation Route Doses (JISCARD) " on the NIRS home page. In FY 2009, we summarized the results of in-flight measurements that were performed for verification of the simulation code developed for aviation dose calculation. In the measurements, we employed advanced instruments such as an extended energy rem meter and a Bonner-ball neutron detector (BBND) ; the BBND was borrowed from the Japan Aerospace Exploration Agency (JAXA). Satisfactory precision was found in the results. A real-time monitoring system of cosmic-ray neutrons in the upper atmosphere has been constructed at the summit of Mt. Fuji. We also continue to cooperate with airline companies in Japan, regarding management of radiation exposure for aircraft crew.

3) Marine dynamics of important radionuclides

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

their activities and isotopic ratios to understand their environmental behavior in marine ecosystems.

Marine Radioecology Research Team

The chemical form is one of the most important factors controlling iodine environmental behavior in the ocean. The actual mechanisms responsible for iodate reduction and iodide oxidation, however, have yet to be fully elucidated due largely to the lack of sensitive iodine speciation analytical methods. In addition, the knowledge of biogeochemical cycling of stable iodine can be useful for the safety assessment of radioactive iodine which is released from nuclear facilities. We have developed a sensitive hyphenation technique, HPLC-ICP-MS for the speciation of stable iodine in seawater. The vertical distributions of total iodine, iodide and iodate in coastal seawater off Aomori, Japan were investigated using the developed method. The concentration of total iodine increased with depth down to 700 m. On the contrary, iodide decreased with depth from 12 ng/ml in the surface seawater to 1.2 ng/ml in the bottom layer at 700 m. The highest concentration of iodide was found in the surface water, suggesting the reduction of iodate due to high biological productivity in the surface water.

To deal with the problem of global warming, a rapid growth in nuclear power generation is expected in East Asia. Prior to this expected growth, it is important to study the behavior of plutonium (Pu) isotopes in coastal seas of East Asia. Seawater samples were collected in the East China Sea and Yellow Sea, and their $^{240}Pu/^{239}Pu$ atom ratios were determined by sector-field ICP-MS. The atom ratios of $^{240}Pu/^{239}Pu$ for surface and bottom water on the East China Sea continental shelf had no significant difference, ranging from 0.222 ± 0.011 to 0.246 ± 0.019. The atom ratios in the Yellow Sea were 0.199 ± 0.013 for surface water and 0.211 ± 0.017 for bottom water and were slightly lower than those in the East China Sea. The atom ratios in Chinese coastal seawaters were significantly higher than the mean global fallout ratio of 0.18. We proposed that Pu isotopes were transported from the open ocean to the East China Sea by oceanic currents and removed to the sediment column by enhanced scavenging from the water column by high particle fluxes in the Changjiang Estuary. Data on $^{240}Pu/^{239}Pu$ atom ratios will provide useful keys for presenting the background data of $^{240}Pu/^{239}Pu$ atom ratio before the expected expansion of nuclear power capacity in East and South Asian countries and for distinguishing potential sources of Pu in the future.

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3) N. M. Hassan, T. Ishikawa, M. Hosoda, A. Sorimachi, S. Tokonami, M. Fukushi, S. K. Sahoo : Assessment of the natural radioactivity using two techniques for the measurement of radionucliede concentration in building materials used in Japan, J. Radioanal. Nucl. Chem., 283, 15-21, 2010
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5) Y. Zhang, J. Zheng, M. Yamada, F. -C. Wu, Y. Igarashi, K. Hirose : Characterization of Pu concentration and its isotopic composition in a reference fallout material. Science of the Total Environment, 408, 1139-1144, 2010

5.5. Office of Biospheric Assessment for Waste Disposal

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

Outline of Research Career

Dr. S. Uchida received his doctor degree from Kyoto University. He has about 30 years' experience in the fields of radioecology and environmental radiochemistry, and, especially, his interest is the behaviors of long-lived radionuclides in the environment, e. g., ^{63}Ni, ^{79}Se, ^{90}Sr, ^{99}Tc, ^{129}I, ^{137}Cs, Th, U, etc. He has improved models and parameters for radionuclides in soil-to-crop systems. He has been proceeding a project to collect and estimate environmental transfer parameters of radionuclides in relation to radioactive waste management.

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Photo:Uchida (front right)

Objectives

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

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

Progress of Research

1) Radionuclide behavior in Japanese estuarine areas

For estuarine systems, we made a report on sediment-water distribution coefficients (Kds) observed in four estuarine areas, that is, Mabechi River (off Aomori), Mogami River (off Yamagata), Yura River (off Kyoto), and Kuma River (off Kumamoto). The total concentrations of stable elements and naturally occurring radionuclides (i. e., Na, Mg, K, Ca, V, Mn, Fe, Co, Ni, Cu, Rb, Sr, Y, Mo, Cd, La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu, Pb, and U) in the estuarine water at each sampling point and in the corresponding sediment sample were measured since stable elements can be used as analogues of radionuclides. The results showed that the Kds of most of the elements varied within one order of magnitude regarding their differences between minimum and maximum values of each element at all the stations. However, a wide variation of Kds of Mn, Fe, Co, Cu, Rb, and La was observed. In addition, geometric means (GMs) of observed Kds were compared with the recommended values in the IAEA Technical Report Series 422 (TRS-422). The results showed that GMs of Kds for most of the elements agreed well with the recommended values, but GMs of Kds for Mn, Fe, and Cd were more than 10 times lower than the recommended values. The obtained Kd values could be important to investigate the behavior, transport, and fate of artificial radionuclides and to assess the radiological doses in estuarine areas. In order to provide more generic Kd data, we have been collecting samples from other estuarine areas.

2) Carbon-14 mobility in agricultural soil systems

Among the tranuranic (TRU) waste-related radionuclides, ^{14}C in organic forms is important for dose assessment. Because there is little information regarding reliable migration and realistic transport models for such organic ^{14}C, the possible migration of organic ^{14}C from a TRU repository sited to the biosphere through groundwater presents some concern, especially in soil systems. This year, therefore, the partitioning ratios of ^{14}C in solid, liquid, and gas phases were determined by batch sorption tests using 97 paddy soil samples. Each of the soil samples was suspended in deionized water containing [1, 2-^{14}C] sodium acetate, one of the possible organic ^{14}C forms from TRU waste, and shake-incubated for 7 days. More than 65% of the spiked ^{14}C was released into the air, approximately 30% was partitioned into the solid phase, and the ^{14}C remaining in the liquid phase was only a few percent. These results suggested that if the ^{14}C incorporated into acetate migrated from a TRU repository site to paddy fields, most of the ^{14}C would be released into the air and the rest would be partitioned into the soil phase. It is likely that microorganisms in the soils are responsible for these partitioning ratios because about 97% of the spiked ^{14}C remained in the liquid phase in the microorganism-depleted sample.

3) Estimation methods for environmental parameters

Estimation models for soil-to-plant transfer factors (TFs) of some elements and radionuclides were developed using several crop and soil characteristics ; one of them is the TF of ^{226}Ra (TF-Ra). The radionuclide should be assessed to determine the safety of geological disposal of high-level radioactive and TRU wastes. However, reported TF data for ^{226}Ra are still limited due to the low concentration of ^{226}Ra in plants in the natural environment. Thus, we collected TF-Ra for crops and then applied a statistical approach to estimate TF-Ra instead of directly measuring the radionuclide. Since TF is defined as the plant/soil concentration ratio, concentrations of ^{226}Ra in soil and crops were estimated separately. Among the various soil characteristics, that

is, water content, pH (H_2O), and 58 elemental concentrations, we found the highest correlation between concentrations of log (^{226}Ra) and log (U) in soils with a high correlation factor, R=0.82 ($p<0.001$), possibly because ^{226}Ra is a progeny in the ^{238}U series. We also found a high correlation between concentrations of log(^{226}Ra) and log(Ba) in plants with R=0.89 ($p<0.001$) because they could be chemically similar in plant uptake. Using concentrations of U in soil and Ba in plant, we could estimate TF-Ra with good accuracy as shown in Fig. 5-1. The difference between estimated and measured TF-Ra values was a factor of 1.2 on average for crops. The method could estimate TF-Ra for the soil-to-plant systems; however, ^{226}Ra concentration in plants may increase linearly with increasing ^{226}Ra concentration in soil. Thus, the soil-plant systems should be considered as under normal Ba and Ra concentration range conditions in soil to use an equation to estimate ^{226}Ra concentration in plants. As for the normal ^{226}Ra and Ba ranges, the following values can be used for a rough estimation: 8.5-95 Bq/kg-dry for ^{226}Ra (or that for U in soil is 0.8-7.1 mg/kg-dry), and 84-960 mg/kg-dry for Ba for these values were within the range of reported values for non-contaminated soils.

Major publications

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2) Masahiro Hosoda, Atsuyuki Sorimachi, Yumi Yasuoka, Tetsuo Ishikawa, Sahoo Sarata Kumar, Masahide Furukawa, Mohamed Hassan Nabil Mohamed, Shinji Tokonami, Shigeo Uchida: Simultaneous Measurements of Radon and Thoron Exhalation Rates and Comparison with Values Calculated by UNSCEAR Equation, Journal of Radiation Research, 50 (4), 333-343, 2009.
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5) Nobuyoshi Ishii, Hiroyuki Koiso, Hiroshi Takeda, Shigeo Uchida: Partitioning of ^{14}C into Solid, Liquid, and Gas Phases in Various Paddy Soils in Japan, Journal of Nuclear Science and Technology, 47 (3), 238-243, 2010.

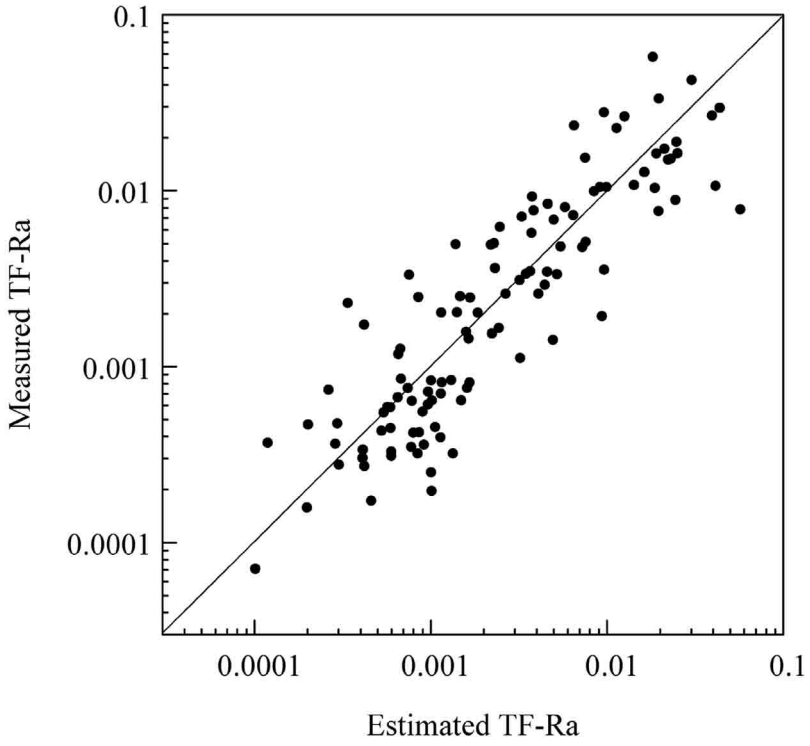

Fig. 5-1. Comparison of measured TF-Ra values with estimated TF-Ra values obtained by using Ba in plant and U in soil concentrations to estimate Ra concentrations in plant and soil, respectively.

6. Research Center for Radiation Emergency Medicine

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

Outline of Research Career

Dr. Akashi started his medical career at 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.

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Objectives

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

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

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

Overview

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

In June 1980, the Nuclear Safety Commission (NSC) came up with a guideline entitled "Off-site Emergency Planning and Preparedness for Nuclear Power Plants. " This guideline nominated NIRS as a tertiary radiation emergency hospital that serves as the final stage hospital for receiving victims heavily exposed to radiation and/or contaminated with radioactive materials due to nuclear or radiological accidents. In 2000, NSC published the 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). The Research Center carries out the following activities to maintain and enhance or strengthen the emergency preparedness system required to fulfill its role as a tertiary radiation emergency hospital.

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.

1-1) 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 expert's 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. In FY 2009, a communication exercise was performed for members of the council as a general drill for radiation emergencies on 22 December) and the council annual meeting was held on 15 January 2010.

1-2) Chromosome Network Council

The Chromosome Network Council forms a network among nearly 10 experts on cytogenetic radiological dosimetry to strengthen its capability and establish technical standards of dose estimation methods using chromosomes. The members are from six areas of Japan and will cooperate with NIRS to do cytogenetic dosimetry when a number of people are involved in a radiation accident. An inter-

comparison study on the dose estimation by chromosome analysis is performed among the council members when the national drill for radiation emergencies is held every year.

In FY2009, prematurely condensed chromosome (PCC) preparations from two blood samples experimentally exposed to six different doses (0 - 30 Gy) were analyzed by member institutions. Each member scored PCC-ring chromosomes of the samples without knowing of the true doses and estimated the doses based on a common calibration curve. By comparing the results, it was found that there was still a problem in sample preparation for the PCC-ring biodosimetry. This year, NIRS held a "Symposium on Radiation Emergency Medicine : Biodosimetry Based on Chromosomal Aberrations" on 22 January 2010 (Tokyo, in Japanese) and 66 researchers participated. In this symposium, recent progress in radiation cytogenetics and biodosimetry was presented by five researchers and actively discussed.

1-3) Physical Dosimetry Network Council

This council is a network of experts for radiation detection and/or physical dose assessment. The network assists and provides advice to NIRS for physical dose evaluation at radiation/nuclear accidents. In FY 2009, a real-time communication system with high security was developed. Using transmission function of measurement data such as gamma energy spectrum of Whole Body Counter (WBC), it enables us to perform prompt and precise dose evaluation through real-time discussion among members in a remote place. Since the main server installed at NIRS has huge storage, members of other Network Councils can share information. Analysis of dicentric chromosome aberration is possible on the website. In the annual meeting, various levels for decision making in triage 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 each-collaboration system with NIRS is mandatory and it must specify the steps to be performed in the smooth transfer of patients from an accident site to the hospital whose staff are well trained.

On 13 February 2009, the Ministry of Internal Affairs and Communications (MIC) pointed out to the Ministry of Education, Culture, Sports, Science and Technology (MEXT) that the appropriate system for transportation of contaminated victims from on site to NIRS has not been established in some local governments, and recommended that such a system has to been built soon and that support from the Ministry of Defense (MOD) should be included in the system. Based on the recommendation, NIRS discussed with local governments on transportation of patients and clarified a role of the MOD in transportation of patients in a radiation emergency. To discuss the issues, meetings were held in Hokkaido, Aomori, Miyagi, Niigata, Ibaraki, Fukushima, Kanagawa, Ishikawa, Fukui, Kyoto, Osaka, Okayama, Ehime, Shimane, Saga, Nagasaki and Kagoshima Prefectures and the information regarding treatment of internally-contaminated victims was also provided there. Moreover, a desk-top drill using a several scenarios including combined injury was introduced in each meeting. In the annual meeting held in October in Tokyo with 19 local governments with nuclear facilities, discussion focused on transport of contaminated victims to NIRS in cooperation with the MOD. Relevant ministries and agencies such as MEXT, and the Fire and Disaster Management Agency (FDMA) also attended this meeting.

2) Training

The primary goal for training is the development of radiation emergency medicine skills for medical professionals and disaster response personnel ; these include doctors and nurses involved in nuclear disaster, medical first responder crews, 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 2009, response to malicious events and transport accidents of radioisotope were newly added to the following course's curriculums.

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

In FY 2009, 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 18-20 November with 25 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 exercises.

In addition to this course, upon a request from Hirosaki University School of Health Sciences, another hospital course was organized for medical professionals with 20 participants from 31 August to 2 September 2009. Aomori Prefecture has a reprocessing factory for nuclear fuel in addition to nuclear power plants. The Hirosaki University Hospital is one of the main hospitals and is responsible for radiation emergency medicine in Aomori Prefecture. Therefore, NIRS and the Hirosaki University have exchanged a memorandum of understanding (MOU) for radiation emergency medicine. Based on the MOU, this course was held.

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 8-10 February 2010 with 24 participants including personnel from the Japan Coast Guard and the Japan Ground Self-Defense Force.

3) Exercises for Radiation Emergency

National and local governments annually hold drills for nuclear emergencies. NIRS sent staff members to these drills to give advice from the viewpoints of medical care and radiation protection. On 21-22 December 2009, the Japanese government conducted a nuclear drill at the Tokai No. 2 Power Station of the Japan Atomic Power Company (Ibaraki Prefecture) to enforce readiness for an accident; 3,020 people from 113 organizations participated and some experts from foreign countries including France and Korea observed the drill. The 2-day long drill assumed that a trouble occurred in the cooling system, which caused radioactivity leaks. From NIRS, medical doctors and experts on radiation protection participated. In this drill, a mock victim was transferred from the plant to NIRS by a helicopter of the Chiba City Fire Department. Following the drill, NIRS conducted an additional exercise to simulate emergency handling of a patient, especially decontamination and dose assessment. The drill activities at NIRS were open to media representatives.

4) Follow-up Studies

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

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

On 1 March 1954, the 23 crew members (18 to 39 years old at the time) of the Japanese fishing vessel Daigo Fukuryu Maru (which means "Lucky Dragon") from Yaizu City, Shizuoka Prefecture saw bright light in the South Pacific resembling a sun rise. Seven or eight minutes later there was a terrific sound. They did not know what it was at the time. The blast, equivalent to about 12 million tons of TNT, was 750 to 1,000 times more powerful than the atomic bomb exploded 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 to study 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 2009, 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 intra-vascularly for the visualization of vascular structures. Long-term retention of thorotrast in the reticulo-endothelial system, in the liver, spleen and bone marrow produces lifetime alpha particle irradiation of these organs and considerable epidemiological follow-up work has been performed. The major cohorts that can be used for risk evaluation are German, Danish and Japanese patients subjected to thorotrast. The incidence of leukemia has increased among these persons. In

Japan, the product was used from 1932 to 1945 for 10,000 to 20,000 patients, the majority of whom were killed in World War II. This follow-up examination estimates the amount of thorium deposited in surviving patients, investigates their clinical symptoms, analyzes the relationship between the deposited amount and carcinogenesis, and elucidates the effects of long-term internal radiation exposure on human bodies. This year, a medical check-up was carried out for only one patient.

5) Database

Since radiation accidents requiring medical care are extremely rare, the medical information must be collected from each accident and accumulated to help medical professionals to make decisions for strategies to treat victims, and establish and improve therapeutic methods. A medical database including the cases of radiation exposure at Bikini Atoll in the South Pacific and cases of thorotrastosis is being constructed. Today, there are many database systems on radiation accidents and their victims, but most are only accessible from the related countries. Under the supervision of the WHO, an international program called REMPAN exchanges information on radiation accidents, including those in the database owned by the US REAC/TS (Radiation Emergency Assistance Center/Training Site). REMPAN has a collaborating center at Ulm University in Germany and manages a SEARCH database of patient information. It aims to construct an international database by registering cases that are attributable to the Chernobyl accident and other radiation accidents. The NIRS registered the Daigo Fukuryu Maru accident in the SEARCH database. In addition, the center is constructing a database by collecting medical data of the victims of radiation accidents and exchanging information with countries that have developed radiation accident medicine.

6) Operation of 7 days/ 24 hours Radiation Emergency Call System

Since FY 2008, the NIRS has been operating 7 days/ 24 hours 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 assistance on a 24-hour basis can be reached by phone. After business hours, the phone call is automatically transferred to a staff member of the Research Center for Radiation Emergency Medicine (which include a medical doctor and a health physicist).

7) Other consultation for health effects of radiation

The NIRS receives consultations on health effect of radiation. The number of phone calls for consultation of radiation effects is increasing. This year we received 27 consultations. Of those, 11 were consultations on radiation exposure (10 cases were about exposure to radiation in medical use and 1 was accidental exposure). Nine were questions about radiation or the radiation emergency medicine system. 7 cases were from persons who believed that they had been exposed to radiation without reasonable evidence. Since some events occurred in Japan last year which were about uncontrolled or stolen radioactive sources, some consultations or questions we received were associated with these cases. To deal with these situations, the NIRS also released important information about each event to the public on it's homepage.

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), NIRS held a NIRS Training Course for Korean Medical Professionals on Radiation Emergency Medical Preparedness from 9-11 December 2009 and 19 Korean medical professionals attended the courses.

8-2) International workshop

The NSC/NIRS workshop on medical response to nuclear accidents in Asia was held from 19-21 January 2010 organized by the Nuclear Safety Commission (NSC) and NIRS in cooperation with the IAEA and the WHO. As part of this workshop, information on internal contamination and other topics was exchanged; total of 22 people (10 from 8 Asian countries, 8 from other area countries, and 4 from IAEA and WHO) were invited. In this workshop, one person from Australia and two from IAEA participated in the workshop via a TV system.

8-3) Invited lectures

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

a) IAEA National Workshop on Medical Response to Radiation Emergencies held in Riyadh, Saudi Arabia, 2-6 May 2009.
b) First Conference on Radiation Protection Issues in GCC Countries held in Riyadh, Saudi Arabia, 11-12 May 2009.
c) IAEA Workshop on Infrastructures Needed for Off-site and On-site Emergency Preparedness and Response Activity, and on Medical Treatment held in Kuala Lumpur, Malaysia, 11-16 November 2009.
d) 1st International Seminar on Biodosimetry held

in Seoul, Korea, 25-26 November 2009.

e) VAEI/JAEA Joint Training Course on "Nuclear and Radiological Emergency Preparedness" held in Hanoi, Vietnam, 26 November-1 December 2009.

f) IAEA Regional Training Course on Medical Response to Radiation Emergencies held in Doha, Qatar, 13-17 December 2009.

g) International Workshop on Acute and Protracted Radiation Biodose Studies and International Networking System in Taipei, Taiwan, 4-5 February 2010.

8-4) International meetings / conferences

NIRS staff members attended the following meetings and exercises.

a) American Association for Cancer Research 100th Annual Meeting held in Denver, CO, USA, 18-22 April 2009.

8-5) Members of international committees

NIRS staff members participated in the following committees.

a) Consultancy Meeting to Review the IAEA Technical Report on Cytogenetic Analysis for Radiation Dose Assessment held in Vienna, Austria, 6-9 April 2009.

b) IAEA Consultancy Meeting to Finalize the Training Material on Medical Response to Radiation Emergencies held in Vienna, Austria, 25-29 May 2009.

c) IAEA Consultancy Meeting to Completing Development Materials for Medical Response to Malicious Events with Involvement of Radioactive Materials held in Vienna, Austria, 7-9 October 2009.

d) Global Health Security Initiative : GHSI Radiological and Nuclear Working Group Teleconference on 26 June 2009.

e) Global Health Security Initiative : GHSI Meeting held in Washington, D. C., USA, 3-6 November 2009.

f) The International Commission on Radiation Units and Measurements (ICRU) Annual Meeting held in Dresden, Germany, 11-16 September 2009.

g) ICRU low dose report committee held in Bethesda, MD. USA, 9-12 January 2009.

h) RANET 2nd Technical Meeting on Guidelines for National Assistance Capabilities held in Vienna, Austria, 15-19 February 2010.

i) IAEA Reviewing the draft manual on Biodosimetry application in Radiation Emergency held in Vienna, Austria, 1-8 November 2009.

8-6) Other Visitors

a) A registered nurse from Chulalongkorn University Hospital visited our facility to get a lecture on 16 April 2009.

b) A chemist from Universite Paris 13 was invited to NIRS from 22-24 July 2009 to discuss and give a lecture regarding rational design and syntheses of powerful Uranyl ligands.

c) Two medical professionals from the Hopital d'Instruction des Armees Percy in France were invited to NIRS on 30 July 2009 to give lectures regarding mesenchymal stem cell transplantation and an accident report in Chile, 2005.

d) A scientist from the Mahidol University in Thailand visited NIRS to study radioprotective agents against gastrointestinal injury, from 1-26 March 2010.

8-7) Establishment of REMAT (Radiation Emergency Medical Assistance Team)

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, and there are also few chances to become knowledgeable about radiation. Radiation cannot be seen by the human eye, smelled, heard, or otherwise detected by our normal senses, nor do symptoms/ signs appear soon after exposure. Therefore, dose assessment is essential for taking care of patients involved in radiation accidents, providing appropriate treatment including administration 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 January of 2010, the NIRS has established a medical assistance team, called the Radiation Emergency Medical Assistant Team (REMAT), which consists of physicians, nurses, radiation protection experts, and health physicists ready to respond to radiation emergencies. Upon request by foreign governments of countries affected or international organizations such as the International Atomic Energy Agency (IAEA) or the World Health Organization (WHO), NIRS activates REMAT.

REMAT provides rapid dose assessment, radiological and medical triage, diagnosis and management in radiation incidents. REMAT is

equipped with radiological and medical equipment and devices that are transportable to affected sites.

8-8) Exchange of human resources and information

a) A medical doctor from NIRS is working as a consultant at the IAEA Incident and Emergency Centre (IEC) to exchange information about radiation/nuclear accidents.

b) Based on the MOU between NIRS and the Institut de Radioprotection et de Surete Nucleaire (IRSN), one health physicist from NIRS is studying bioassay for radiation emergency at IRSN.

c) Staff members visited the Shanghai Institute of Materia Medica, Chinese Academy of Sciences to exchange information concerning medicines for internal contamination with radionuclides on 4 March 2010.

8-9) Memorandum of Understanding

a) NIRS and KIRAMS agreed to extend the MOU signed in 2004 for another 5 years. Eight Korean delegation visited NIRS to attend a signing ceremony on 4 November 2009.

b) The NIRS exchanged a MOU on radiation emergency medicine with King Abdulaziz City for Science and Technology (KACST) on 1 March 2010.

8-10) Other topics

a) Staff members attended the IAEA general meeting and introduced the center's activities by poster presentation.

b) The NIRS has the Radiotoxicology Research Building, which is the only biological research facility for accidents involving actinoides in Japan. The NIRS has started to re-organize the facility for research on radiation emergency medicine. The NIRS has developed research for biological effects of actinides for over than 20 years. In order to enhance the research project and to facilitate cooperation with other institutions, the NIRS established a management office in October.

6.1. The Study for Medical Treatment for High Dose Exposure

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

Outline of Research Career

Dr. Akashi started his medical career at 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 criticality accident in Tokai-mura.

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Objectives

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

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

Progress of Research :

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

Several Fibroblast growth factors (FGFs) are able to protect against radiation-induced intestinal damage. An FGF1 : FGF2 chimera (FGFC) showed greater structural stability than FGF1. FGFC was capable of stimulating epithelial cell proliferation much more strongly than FGF1 or FGF2 even without heparin. In this study we evaluated and compared the protective activity of FGFC and FGF1 against radiation-induced injuries. FGFC and FGF1 were administered intraperitoneally to BALB/c mice 24 h before or after total body irradiation (TBI). The numbers of surviving crypts were determined 3.5 days after TBI with γ-rays at doses ranging from 8 to 12 Gy. As a result, the effect of FGFC was equal to or slightly superior to FGF1 with heparin. However, FGFC was significantly more effective in promoting crypt survival than FGF1 ($P < 0.01$) when 10 μg of each FGF was administered without heparin before irradiation. In addition, FGFC was significantly more effective at promoting crypt survival ($P < 0.05$) than FGF1 even when administered without heparin at 24 h after TBI at 10, 11, or 12 Gy. FGFC post-treatment significantly promoted BrdU incorporation into crypts and increased crypt depth, resulting in more epithelial differentiation. However, the number of apoptotic cells in FGFC-treated mice decreased to almost the same level as that in FGF1-treated mice. These findings suggest that FGFC strongly enhanced radioprotection with the induction of epithelial proliferation without exogenous heparin after irradiation and is useful in clinical applications for both the prevention and post-treatment of radiation injuries.

2) A cell-permeable C-terminal fragment of PIDD 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) . 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). When the PIDD (773-917) fragment was overexpressed in these cells, the PIDD-mediated activation of caspase-2 was dominant-negatively inhibited. In order to use the PIDD (773-917) fragment as an anti-apoptotic drug, we purified a recombinant PIDD (773-917) fragment fused with a basic 11-amino acid peptide 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 could protect gastrointestinal cells from ionizing radiation-induced cell death.

3) TNFα is required for erythropoiesis in irradiated mice

Tumor necrosis factor α (TNFα) is a pro-inflammatory cytokine that has a wide variety of bioactivities, and over-production of TNFα leads to damages of tissues. To determine the role of TNFα in high-dose radiation exposure, we used wild-type of TNFα (WT) and its knockout (KO) BALB/c mice. The survival duration in KO was shorter than that in WT after irradiation and administration of TNFα to KO before irradiation improved the survival rate, the numbers of red blood cells (RBC), the levels of hemoglobin (Hb), the hematocrit values (Ht) and the unsaturated iron binding capacity (UIBC) that were significantly lower compared with WT. We also showed that the activity of erythroid burst-forming

units (BFU-Es) and erythroid colony-forming units (CFU-Es) was significantly reduced in KO than in WT following irradiation, and that administration of TNFα improved activity in irradiated KO. Furthermore, bone marrow transplantation (BMT) markedly increased the survival rate in both groups of irradiated mice. These results show that irradiation-induced death was mainly caused by myelosuppression. Our results suggest that endogenously-produced TNFα plays important roles in protection and mitigation from radiation injury; an optimal concentration of TNFα effectively enhances the recovery of bone marrow suppression by irradiation, especially erythroid hematopoiesis.

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, inhibit caspase activity directly or indirectly. XIAP is the best-characterized IAP in terms of both its structure and biochemical mechanism. XIAP contains three BIR domains (BIR1, BIR2, and BIR3) and a RING domain. The BIR2 domain of XIAP directly inhibits caspase-3 and caspase-7, whereas the BIR3 domain inhibits caspase-9.

In order to prevent gastrointestinal syndrome, we purified cell-permeable recombinant cIAP2 and XIAP (full-length, BIR2 domain, and BIR3-RING domain with or without mutations of autoubiquitilation sites) proteins fused with 11 amino-acids derived from the HIV-Tat protein and examined the effects of these proteins on radiation-induced cell death in IEC6 cells. When the TAT-conjugated IAP proteins were added to IEC6 cells, these protein were delivered into the cells and inhibited apoptosis after irradiation. Our results suggest that the TAT-conjugated IAP proteins may be useful for protection of gastrointestinal cells from radiation-induced cell death.

5) Diurnal modification of radiation dose-dependent augmentation of mRNA levels for DNA damage-induced genes in mouse hematocytes

Messages for p21 and mdm2 that reflect growth-arrest, and for bax and puma that initiate apoptosis, are expressed in various cells after the exposure of radiation. Although the intracellular levels of the mRNAs seem to reflect the extent of DNA damage, quantitative knowledge is not enough to analyze cellular events particularly in cells from a living body. For detailed quantification of these mRNAs, we established an accurate real-time RT-PCR method and obtained highly reproducible values among various hematocytes as relative RNA levels of these genes per GAPDH. In x-irradiated murine macrophage RAW264.7 cells, the peak levels of mRNAs of p21, mdm2 and puma strongly correlated to the radiation dose and were consistent with cellular damage. 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 C3H/He mice. However, some of this responsiveness in the mRNA levels was strongly affected by circadian rhythm of the irradiated mice. In peripheral blood, induction levels of all messages after nighttime irradiation were reduced by half as compared with daytime irradiation. In marrow cells, levels of p21 and mdm2 mRNAs after nighttime irradiation were higher than daytime irradiation. This shows that early-stage cellular responsiveness in DNA damage-induced genes in the isolated cells is modified by the irradiation clock-time of the animals between diurnal and nocturnal irradiation in the cells from living animals.

6) Anabolic steroid stimulates the regeneration of mucosa in small intestine damaged by ionizing radiation

Acute intestinal damage is a serious problem after high-dose radiation. We focused on the regeneration process following irradiation in intestinal mucosa and performed pharmaceutical studies. To examine the proliferation in IEC-6 cells, hormones clinically used were compared. The most prominent effect on growth was observed by an anabolic steroid, nandrolone (19-nortestosterone). Single injection of 19-nortestosterone ester to C3H/He mice 24 h after abdominal irradiation at a lethal dose of 15.7 Gy of x-ray showed a significant life-saving effect. We also studied the effect of 19-nortestosterone on regeneration of intestinal mucosa in irradiated mice. A microcolony assay in a Brd U-incorporated cell, 19-nortestosterone enhanced regeneration on Day 5 and the expression of c-myb mRNA was stimulated on Day 4 in these mice. The results suggest that this anabolic steroid enhances the regeneration of small intestinal mucosa after radiation exposure.

7) Induction of heme oxygenase-1 by polyphenols from whisky congeners in human endothelial cells

Phenolic compounds are known to induce HO-1 mRNA and protein in various cells. Production of the cytoprotective heme oxygenase-1 (HO-1) protein in endothelial cells would ameliorate vascular injuries. We investigated the effect of whisky, which contains various phenolic substances on HO-1 expression. A study of quantitative real-time RT-PCR showed the

whisky congeners activated dramatically the transcription of the HO-1 gene in mouse macrophages.

The HO-1 protein was also induced by the whisky congeners in human umbilical vein endothelial cells. The congeners of brandy and beer also induced expression of the HO-1 protein. The congeners of freshly distilled whisky spirit had no activity, while those of whiskies stored from 4 to 30 years in oak barrels induced the HO-1 protein. To determine the compounds with potent HO-1-inducing activity in whisky congeners, several chemicals that had been reported to exist in whisky were screened. We found that coniferyl aldehyde and sinapyl aldehyde exhibited HO-1-inducing activities. Thus the elements which emerged in whisky during storage in barrels induced the cytoprotective protein, HO-1, in human endothelial cells.

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6.2. 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. He has had over 30 years of experience in research on radioactive aerosols and their internal exposure at NIRS. Between 1986 and 1987 he was at the Inhalation Toxicology Research Institute (ITRI) of Lovelace Foundation, USA as a visiting scientist where he studied aerosol deposition within respiratory tracts.

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Photo: Yamada (left)

Objectives :

Radiation accidents can be classified into those resulting from external exposure and those resulting from internal exposure. For heavy exposure, stem transplantation may be considered depending on the external exposure dose received, or administration of medicine may also be considered to inhibit deposition and promote excretion of radioactive materials incorporated into the body. Dose assessment of victims in radiation accidents has to be made within a short time in combination with investigation for the details of the accident to estimate the radiation effects and to initiate appropriate 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 to 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 applied studies for clinical use of agents in removing radionuclides, especially alpha emitters like plutonium or uranium that are incorporated into the body.

Progress of Research :

1) Development of ESR dosimety using human nail

Electron spin resonance (ESR) dosimetry is a method to measure radical numbers produced by radiation in substances and to estimate exposure dose. This method is useful for dose estimations when workers are exposed while not wearing personal monitors and when the general public is exposed accidentally. Tooth enamel is typically used for this purpose. However, teeth can not be removed easily from patients in all cases. It is necessary to find out other human tissues or substances around exposed persons for estimating personal exposure. Nail samples are easily obtained from exposed persons compared with tooth enamel samples. Therefore, nail samples were applied to ESR dosimetry in the case of γ-irradiation. A protocol was established based on a hypothesis that there was no difference of radical fading rates among personal nails. A fading constant depending on a fading temperature and a background level of sample were used for the dose estimation. Doses (around several gray) were estimated in a 90-180% precision in 2-3 days.

2) Chromosome aberration analysis for dose assessment

Dicentric chromosome analysis (DCA) has been used for biological dosimetry since the mid 1960s. It is now called the gold-standard assay for accurately estimating unknown radiological doses in individuals following radiological or nuclear accidents. However, there is no generally accepted way of deriving its uncertainty. Thus, we are studying differences of calibration curves among individuals to see if there are any permissible limits in a standard curve. By the DCA of four male and three female blood donors aged 20s - 40s, no significant differences were detected thus far. Effects of different qualities of radiation and tube voltages on the dose-response curve were also studied. A DCA for one blood sample was performed using 0 to 5.0 Gy-radiation doses with ^{60}Co-γ-rays, ^{137}Cs-γ-rays, and X-rays (120 kV). Although no significant differences were detected among them, more dicentric yields per cell were detected with lower LET at higher doses over 3.0 Gy. By X-ray-irradiation at a constant exposure dose (3.0 Gy) emitted in different tube-voltages from 80 to 240 kV for one blood sample, no significant differences of dicentric yields per cell were detected. Now, further analysis is in progress by collecting more blood donors to see individual differences in the dose-response curve.

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

A system that evaluates dose distribution in homogenous external exposure by a photon spectrum has been constructed. The evaluation of basic performance of the system was completed by using a tissue equivalent semi-conductor detector which measures the Compton spectrum directly. The photon spectrum concerning X-rays, ^{60}Co, ^{137}Cs, or ^{133}Ba reconstructed by the unfolding method from the Compton spectrum has already been obtained.

4) Nasal swab for alpha emitters

A nasal swab is good evidence for the possibility of internal contamination just after inhalation accidents. Also it is expected to be a useful method for rapid dose assessment. To improve the preliminary estimation of intake activity by the nasal swab method, sample collection efficiency was experimentally investigated. Focusing on swab materials and aerosol particle sizes, sample collection efficiency was examined for plane disk or sham nasal cavity. Two types of swab materials were used for the experiment : a strip of filter paper or cotton cloth wrapped around the end of a swab stick. Whatman 40 (Whatman International Ltd., England) and Cotton Ciegal® (Chiyoda Co., Ltd., Japan) were selected for filter paper and cotton cloth respectively.

Whatman 40 is prepared for nasal swabs in emergency medicine at the NIRS (National Institute of Radiological Sciences, Japan) considering alpha emitter measurement. Cotton Ciegal is no-dust pure cotton used for precision instruments. Fluorescent latex and $^{239}PuO_2$ particles were prepared for experimental contaminants. The particle number for latex was counted by fluorescence microscopy before and after swabbing, and the alpha activity of $^{239}PuO_2$ was measured by an alpha spectrometer. The sample collection efficiency was calculated from the ratio of remaining particle number or alpha activity to initial particle number or alpha activity. The sample collection efficiency varied depending on the particle size and swab materials. The collection efficiency of $^{239}PuO_2$ particles was plotted on an extended curve for fluorescent latex particles. These results suggest that sample collection efficiency depends on particle diameter. Cotton had a higher collection efficiency than filter paper, and the efficiency showed a clear dependence of aerosol particle diameter - either disk or sham nasal cavity. On the other hand, sample collection efficiency for filter paper showed more or less the same tendency for sham nasal cavity, and a lower value (average = 17.7%) than that for disk. Filter paper had advantage : steady efficiency with less dependency of particle size. On the other hand, cotton showed higher efficiency, two-fold or more. Correction of sample collection efficiency would be essential to reduce uncertainties for the nasal swab method. To obtain higher and steady sample collection efficiency, cotton may require a more uniform structure as filter paper.

5) Development of in-vivo measurements

This year, minimum detectable activity (MDA) was obtained by using BOMAB phantoms in all whole body counter (WBC). It was confirmed that MDA allows us to use WBC for screening and for detailed measurements of internal contamination. For some kinds of BOMAB phantom and point radiosources were used for age dependency and to assess the distribution of radionuclides. Moreover, since surface contamination was assumed, point radiosources were on the BOMAB phantom and measured. It is well known that counting efficiency is greatly different depending on energy and ages. After the Ge detector had been set up, volunteers were measured for the first time. Two patients with mesothelioma and five healthy volunteers were measured. We would distinguish relatively easily even radionuclides of natural origin or radionuclides with a small emission ratio.

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

Dose evaluation for internal contamination is more complicated than that for external dose exposure. Especially, there is difficulty comparing internal dose estimation from α- and β-emitters than from γ-emitters. For this purpose, chemical analyses of urine and feces (bioassay) were conducted to estimate the amount of radioactive materials in human bodies. However, chemical analyses are usually complicated and time consuming. In a radiation emergency, analytical results will be required for treatment of exposed persons as soon as possible. In this study, three kinds of extraction resin columns, a liquid scintillator, and an α-spectrometer were combined to develop a rapid measurement system for strontium, americium, and uranium in human urine and feces samples. After spiking an aliquot of 90Sr to the urine sample, the ^{90}Sr fraction was purified by an Sr-specific resin column and detected by a liquid scintillator. Am and U were separated by UTEVA and TRU resin columns and measured by an α-spectrometer and/or inductively coupled plasma mass spectrometry. A good recovery (above 80-99%) was obtained in all cases. The total analysis time per urine sample was within a working day (ca. 8 hrs). It would be an effective bioassay method for radiation emergencies.

7) Effects of chelating agents on removal of uranium in simulated wound model of rats

The effects of a chelating agent, CBMIDA, on removal of uranium via wounds (as the model of uranium contamination with a shallow injury) in which uranium was injected intracutaneously in the rat's back skin and the combination effects with the surgical excision of uranium-injected skin were examined. About 86% of the injected dose of uranium was removed when the skin was excised 30 min after DU-injection (uranyl nitrate, pH 1), and the uranium in the surrounding skin after the excision was less than 1%. At the same time, the amount of uranium on the surface of the femur decreased. The urinary excretion rate of uranium in the excision + CBMIDA group increased compared to that of the excision alone. The effects of combinations of local (infusion of chelating agents into the uranium-injected site) and systemic administration of chelating agents after the intramuscular injection of uranium in rats were examined. When CBMIDA was administered into the uranium-injected sites and systemically, the amount of uranium in the kidneys, femur, and muscles (uranium-injected site) decreased significantly. We also performed screening tests of newly synthesized agents. The effects of newly synthesized chelating agents, TREN-Bisphosphonate, TREN-methyle-Bisphosphonate, or Hydroxypyridinone-Bisphosphonate on removal of uranium were determined. However, no effects were

observed. One of other nine new agents decreased the concentration of uranium in the liver and femur at the same time.

Major Publications

1. K. Shiraishi, S. Ko, P. V. Zamostyan*, N. Y. Tsigankov*, I. P. Los*, V. N. Korzun* : Dietary intakes of alkaline metals, alkaline earths and phosphorus in Ukrainians, Biomedical Research on Trace Elements, 20 (1), 62-68, 2009
2. K. Shiraishi, S. Ko, Y. Muramatsu*, P. V. Zamostyan*, N. Y. Tsigankov* : Dietary Iodine and Bromine Intakes in Ukrainian Subject, Health Physics, 96 (1), 5-12, 2009
3. Y. Yamada, K. Fukutsu, M. Yuuki, M. Akashi: Air Contamination Analysis during Emergency Medical Treatment, Radiation Protection Dosimetry, 134 (2), 113-121, 2009
4. K. Fukutsu, Y. Yamada, M. Akashi: Characterisation of Nasal Swab Samples by Alpha Spectrometry, Radiation Protection Dosimetry, 134(2), 87-93, 2009
5. A. Furukawa, M. Minamihisamatsu, I. Hayata : Low-Cost Metaphase Finder System, Health Physics, 98 (2), 269-275, 2010

7. Fundamental Technology Center

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

Outline of Research Career

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

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Photo:Kusakabe (left)

Objectives

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

Overview

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

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

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

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

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

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

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

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

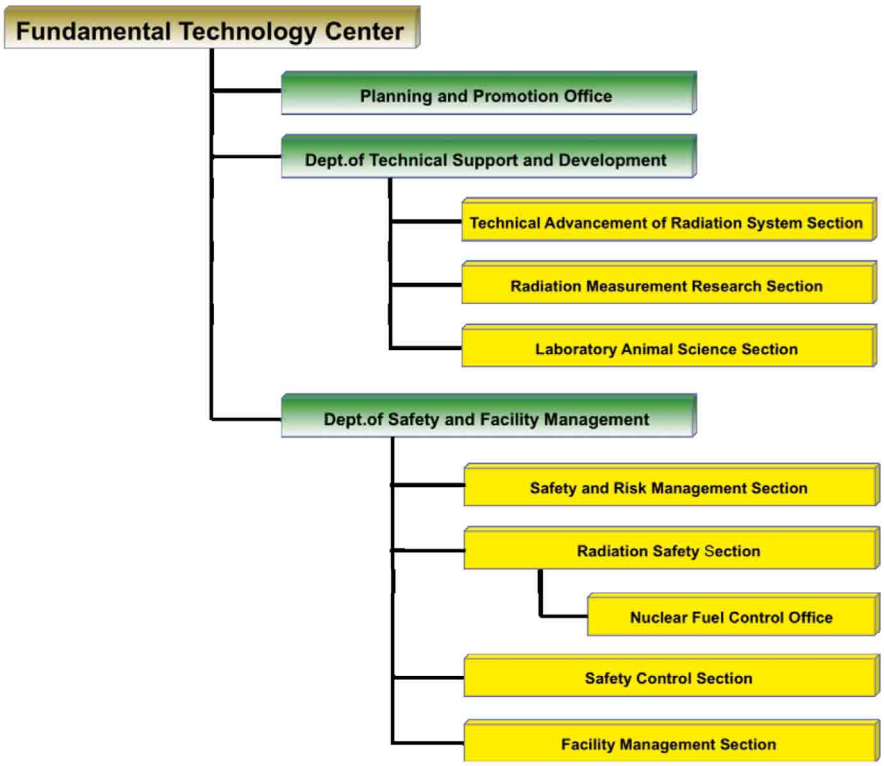
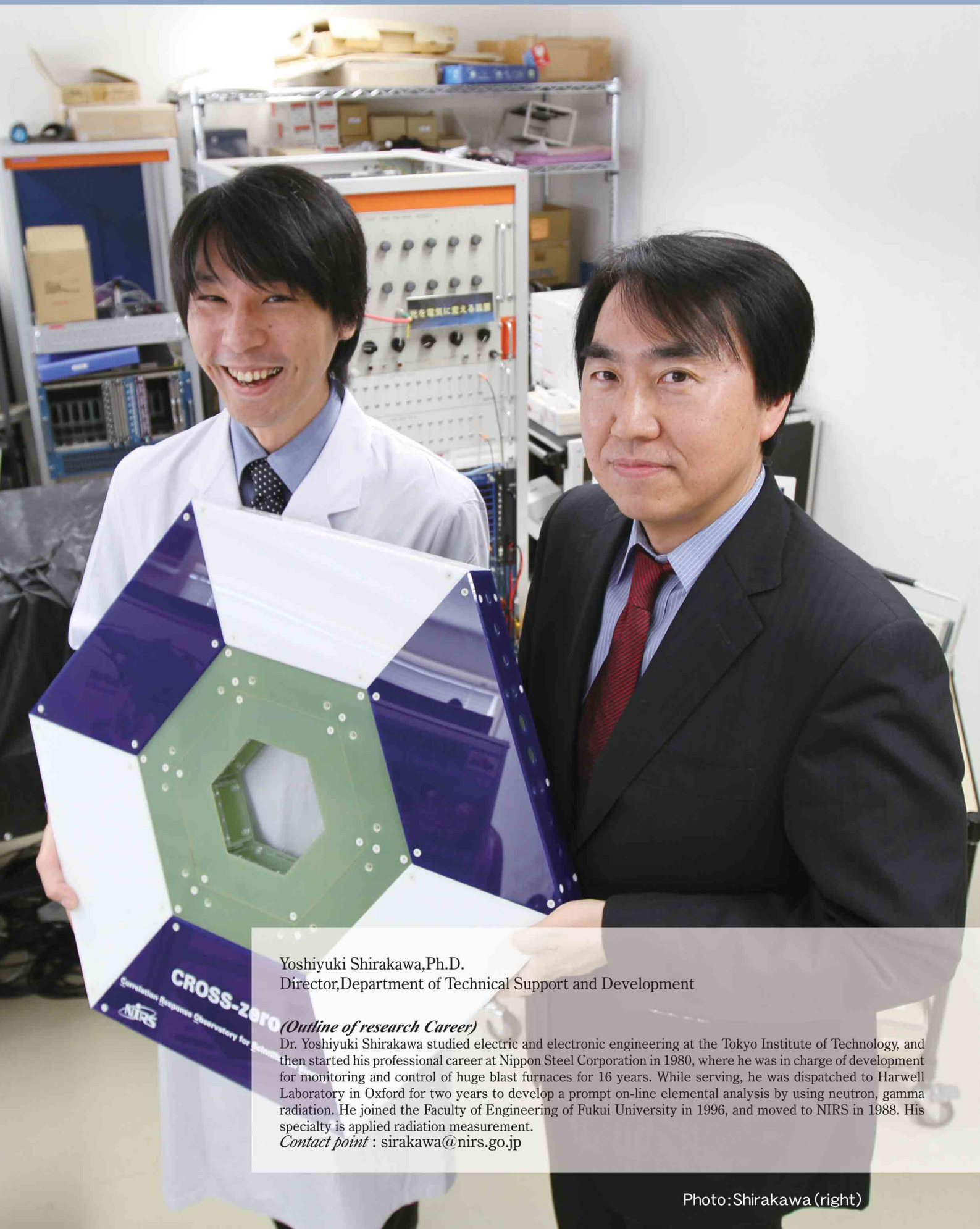


Fig. 7-1 Organization of Fundamental Technology Center.

7.1. Department of Technical Support and Development



Yoshiyuki Shirakawa,Ph.D.
Director,Department of Technical Support and Development

(Outline of research Career)

Dr. Yoshiyuki 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 serving, he was dispatched to Harwell Laboratory in Oxford for two years to develop a prompt on-line elemental analysis by using neutron, gamma radiation. He joined the Faculty of Engineering of Fukui University in 1996, and moved to NIRS in 1988. His specialty is applied radiation measurement.

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Photo:Shirakawa (right)

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. One is to carry out several types of fundamental developments to promote research activities in NIRS. The other is to support researchers working in other centers by using facilities, equipment, and techniques, which are mostly developed by ourselves.

Our department has three sections. They are the Technical Advancement of Radiation Systems Section, the Radiation Measurement Research Section, and the Laboratory Animal Science Section. Every section is proud of possessing original state-of-art technologies and providing them to promote studies in the field of radiological sciences. Our department is unique in that it 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 in one team when supporting, and work together, and contribute success of research activities done in NIRS and in collaborative universities and research institutes in the world.

Overview

Here three sections of our department are briefly introduced and details on research and support activities are described in the 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 reformed. 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 the demand, we provide technical support to use such equipment correctly and advise to researchers working in NIRS or 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. Themes are selected from the view point of support and promotion of many studies in NIRS and outside. For example, the Micro Beam Scanning PIXE has been improved by installing a new radiation detector and a data acquisition system. Another example, an excellent result, was by improving the focus of beams to 2 μm, a first in the world.

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 fields such as radiation biology and radiation physics.

The members in this section are to perform research and development for pursuing state-of-the-art radiation detection, measurement and dosimetery. 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 try to create unique neutron detectors and plastic scintillation detectors for multiple uses such as space radiation and medical applications. This section carries out a famous international project called ICCHIBAN Project, which is an intercomparison of experiments of several space radiation dosimeters on ground base and in the Russian Service Module in the International Space Station.

3) Laboratory Animal Sciences Section

This section has developed and supplied the laboratory animals needed for biological effect and medical studies in the field of radiological sciences. We have maintained important animal species, for example, mice, rats and monkeys. In our site, there are 11 animal facilities that are maintained under clean conditions.

This section performs several research programs, which are a new genetic monitoring system of mouse, cannibalism of mouse-strain differences, and shortening the operation time of an isolator.

7.1.1. Technical Advancement of Radiation System Section

Nobuyuki Miyahara,Ph.D.
Head,Technical Advancement of Radiation System Section

Outline of research career

Dr. Miyahara received a Ph. D. from Nagaoka University of Technology in 1992 for his study on fracture mechanics of engineering ceramics. He joined HIMAC construction and development in 1992. He worked for a compensator and patient collimator fabrication system of HIMAC. He worked in MGH to construct the Northeast Proton Therapy Center (NPTC) from 1997 to 1999.
Currently he is head of the Technical Advancement of Radiation System Section.

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Photo:Miyahara (right)

Technical Advancement of Radiation System Section

Objectives

In order to provide high quality service to scientists and technologists in NIRS and other research institutes, we are carrying out development of radiation engineering resources for basic biological and physics research, improvement of radiation research environment in NIRS, and promotion of new irradiation technique.

Progress of Research

1) Advanced irradiation and analysis technique development by using PASTA (PIXE Analysis System and Tandem Accelerator)

PASTA is an electrostatic accelerator mainly designed for PIXE analysis. A tandem accelerator accelerating process is started with negatively charged proton and helium from an ion source (with Li oven for helium ion source). The acceleration terminal electrode, which is charged up to 1.7 MV, pulls negative ions. At the terminal electrode, there is little nitrogen gas which is stripped of electrons on negative ions ; the ionic charge is exchanged to positive. Finally the positive ion is kicked by an electrode. The tandem accelerator structure uses high voltage twice. Therefore, maximum accelerated proton energy is 3.4 MeV.

2) Development of micro beam scanning PIXE (micro PIXE)

A Data taking system of micro PIXE, which replaced OM-DAQ2007 (Oxford Microbeams), runs on Windows XP. Due to the improvement of computer performance and software technology, the new data taking system provides a list data taking mode that taking X-Y coordinates with X-ray energy data simultaneously, and taking list data in one measurement. We are tuning the data taking system, beam scanning system and modules.

The Cd-Te diode detector (XR-100T-CdTe : Amptek) is installed in the micro PIXE system to detect much higher characteristic X-rays from Pt in a chemotherapy drug (cisplatin). The detector is set 3 mm behind a sample to measure a wide stereo angle of 1 μsr. A 0.2 mm thick carbon foil is attached to the Cd-Te detector window to stop primary particle beams and low energy X-rays from the sample. The carbon foil is also used as a Faraday cup for measuring the current of primary beams.

Fig. 7-2 shows a PIXE spectrum of shark spine bone. Blue and red lines are measured with an Si (Li) diode detector and a Cd-Te diode detector, respectively. Sr peak counts of the Cd-Te detector is 6 times higher than the Si (Li) detector. The Cd-Te detector is more efficient for heavy element PIXE spectrum measurement.

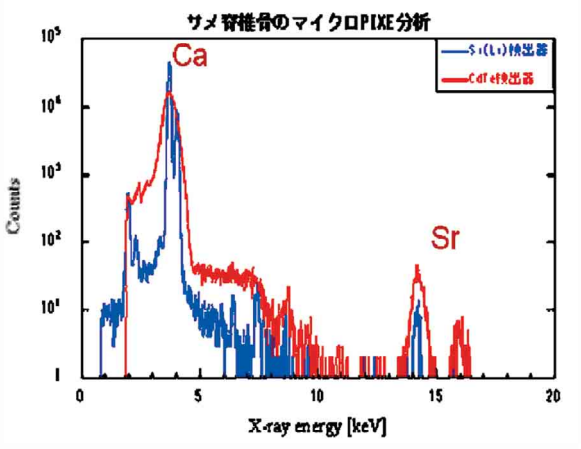
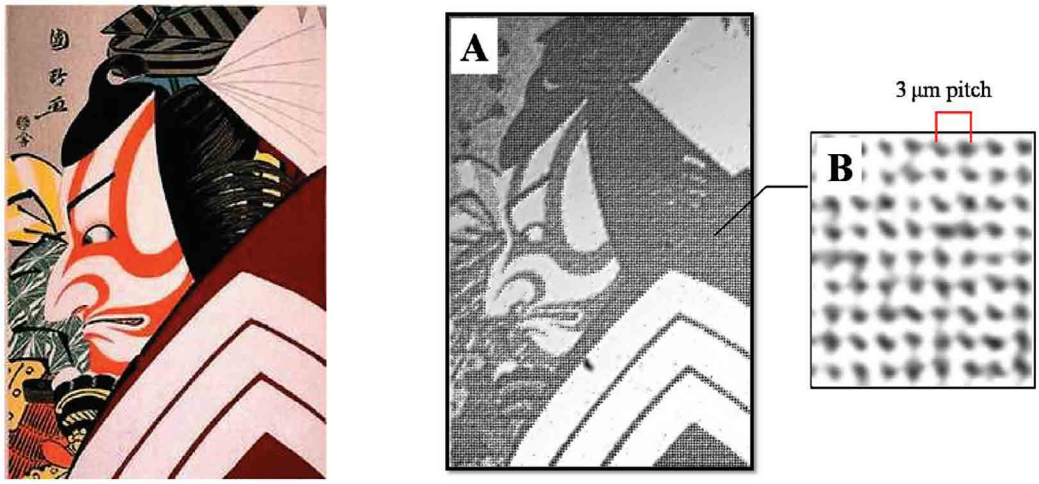


Fig. 7-2 A PIXE spectrum of shark spine bone

3) Development of Single Particle Irradiation system to CE11 (SPICE)

SPICE is a beam line of the PASTA accelerator facility. The beam spot of SPICE is focused to 2 μm in diameter using a beam line focusing element. The size of the beam spot was measured by CR-39 (HARTZLAS TD-1). Fig. 7-3 shows a Japanese Edo-era picture, painted by Kunimasa Utagawa that was reprinted with micro beam scanning on CR-39. The drawing was performed automatically according to the text file of a preset number of protons and X-Y coordinates of the sample stage positions, which consist of 13784 irradiation positions. The drawing takes about 30 min. The beam window of the SPICE beam line is a 200 nm thick Si_3N_4 membrane, and the distance between beam window and sample was set to 100 μm. This setup configuration reduces primary beam scattering and defocusing.



(a) Original painting (b) Reprinted drawing with protons

Fig. 7-3 Reprinted Ukiyoe with micro beam scanning on CR-39

4) Development of Neutron exposure Accelerator System for Biological Effect Experiment (NASBEE)

NASBEE is used in radiation biological effect research. It is able to accelerate protons and Helium to 4 MeV. By a nuclear reaction with a metal Beryllium target and these accelerated particles, it generates neutron beams of mean energy 2 MeV. Regularly, this system exposes 2 Gy/hour neutrons for mice or cell irradiation experiments.

To expand the operating time, we developed a target which has a newly designed water-cooling system. In addition, we are preparing Lithium-based target for generating monochromatic neutron beams. It has the possibility to become a valuable neutron calibration source which is in high demand by many institutes and manufacturing corporations using neutron measurement instruments in Japan.

5) Development of Quality Assurance system using by X-ray facility

There are two X-ray irradiation systems (TITAN320 & PANTAK HF-320) in the X-ray facility. X-ray dose rate and field size of TITAN320 is 3.51-0.21 Gy/min and 100-440 mm in diameter, respectively.

X-ray experiments are the most basic and important tool for radiation biology. In biological experiments with X-rays, dose rate, field flatness and X-ray spectrum have to be stable and reproducible. To maintain the quality of the X-ray field in routine work, an IP measurement X-ray field checking technique was developed to check X-ray field flatness and relative dose rate. An absolute dose measurement is conducted with NIRS secondary standard ion chambers, which are calibrated with the national primary standard each year that ensures the traceability of X-ray irradiation fields.

Major publications

1) Nobuyuki Miyahara, Toshihiro Honma, Takashi Fujisawa, 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

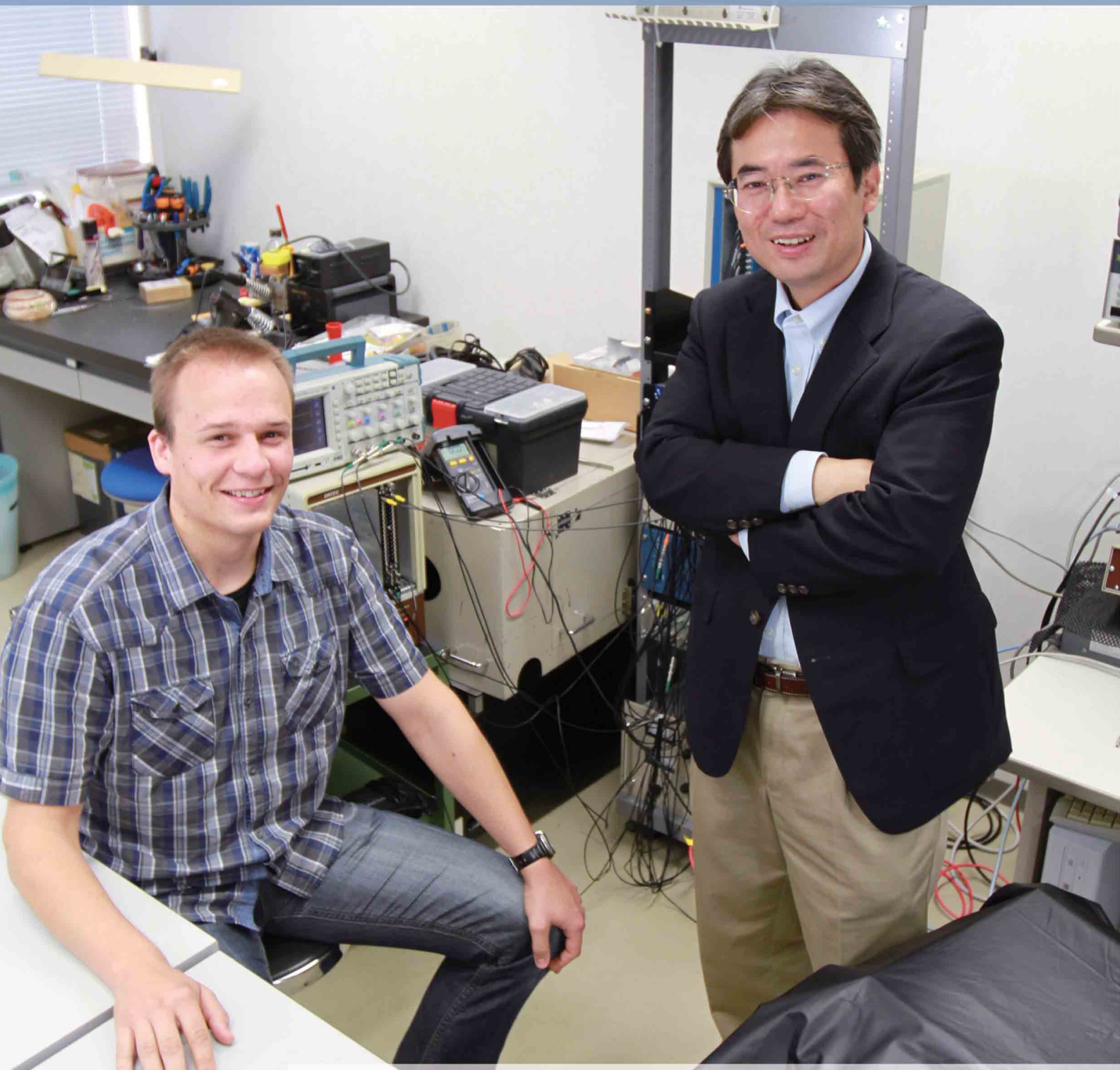
2) Shino Homma-Takeda, Yasuko Terada, Hiroyuki Iso, Takahiro Ishikawa, Masakazu Oikawa, Teruaki Konishi, Hitoshi Imaseki, Yoshiya Shimada, Rubidium distribution in kidney of immature rats, International Journal of PIXE, 19, 1-2, 39-45.

3) Takahiro Ishikawa, Hiroyuki Iso, Masakazu Oikawa, Teruaki Konishi, Hisashi Kitamura, Yuichi Higuchi, Noriyoshi Suya, Tsuyoshi Hamano, Hitoshi Imaseki, Development of a real-time beam current monitoring system for microbeam scanning-PIXE analysis using a ceramic channel electron multiplier, Nuclear Instruments & Methods in Physics Research Section B, 267, 12/13, 2032-2035.

4) Teruaki Konishi, Hiroyuki Iso, Takahiro Ishikawa, Nakahiro Yasuda, Masakazu Oikawa, Noriyoshi Suya, Yuichi Higuchi, Kumiko Kodama, Takeshi Katou, Kurt Hafer, Tsuyoshi Hamano, Hisashi Kitamura, Kotaro Hieda, Hitoshi Imaseki, Current status of micrbeam irradiation system for mammalian cells, SPICE at NIRS, Journal of Radiation Research, 50, Supplement A, A89.

5) Mayu Isono, Masahiro Otsu, Teruaki Konishi, Takashi Nakayama, Nobuo Inoue, Effects of X-irradiation on embryonic stem cells-derived neural stem cells, Journal of Neurochemistry, 110, Suppl. 2, 25-25.

7.1.2. Research Work in the Radiation Measurements Research Section



Yukio Uchihori,Ph.D.
Head,Radiation Measurement Research Section

Outline of Research Career

Dr. Uchihori received a Ph. D. from Osaka City University in 1995 for his study on cosmic-ray physics on high mountains and deep underground. He joined extremely high energy cosmic-ray experiments as a fellow in the Institute for Cosmic Ray Research, Tokyo University. In 1996, he moved to NIRS and worked on space radiation protection and measurement. He worked in the MEXT (Ministry of Education, Culture, Sports, Science and Technology) in FY 2006 and in the Planning Section in NIRS. He was head of the Radiation Measurement Research Section and head of the Space Radiation Research Unit, International Open Laboratory.

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Photo:Uchihori(right)

Objectives

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

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

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

Progress of Research

Passive detectors (Nakahiro Yasuda, Satoshi Kodaira, Mieko Kurano, Hajime Kawashima)

Development of a fluorescent nuclear track detector technique

We are developing a next generation radiation detector which will be used as a personal radiation monitor. A fluorescent nuclear track detector (FNTD) was verified as a possible spectroscopic technology for mixed radiation fields with proton, heavy charged particles and gamma rays. The technique uses a luminescent aluminum oxide single crystal having aggregate oxygen vacancy defects and doped with Mg (Al_2O_3: C, Mg) as the detector in combination with a laser scanning confocal fluorescence microscope. The fluorescence amplitude has not yet reached saturation even at large LET values. We also prove that FNTDs can easily detect high energy protons. The ability to detect low LET ions makes FNTDs attractive for high energy neutron detection. The results of this study can be of particular importance to radiobiology, radiotherapy, space and neutron dosimetry and nuclear reaction diagnostic experiments. [Done in collaboration with : Landauer Inc. (USA) and Nagase Landauer Inc. (Japan)]

Verification of the performances of CR-39 detectors for space radiation measurements

Performance verifications of temperature and air pressure for CR-39 detectors, which are now mainly used as personal radiation monitors for astronauts, were experimentally determined using Fe ion beams from HIMAC. Changes in the track registration sensitivity with temperature were studied at temperatures between 213 and 293 K. The charge and mass shifts around Fe ions are possibly 0.11 cu and 0.47 amu. A decrease in track registration sensitivity as air pressure decreases has been observed between 13 Pa and 27 kPa. The charge and mass shifts around Fe ions are inferred to be 0.02 cu and 0.09 amu, respectively, when pressure varies between 20 and 27 kPa. These basic data allow us to correct dose and dose equivalent values in various circumstances.

Development of new technologies to control detection threshold in CR-39 detectors for high LET particle measurements

High LET secondary particles produced by proton-induced target fragmentation reactions may give dose contributions in proton therapy and space radiation fields. Their LET values typically range from 30 to 200 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. We developed a two-step etching method using PEW-x solution [17wt% KOH + xwt% C_2H_5OH + (83-x) wt % H_2O] as the pre-etching and 7N NaOH solution as the post-etching, which increases the detection threshold and improves the charge resolution for high LET particles in CR-39 detectors as shown in Fig. 7-4.

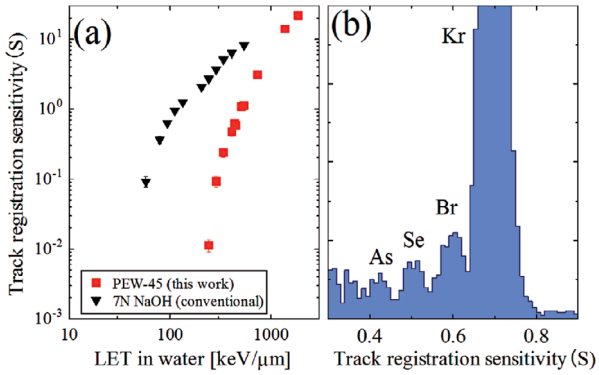


Fig. 7-4. (a) Detector responses as a function of LET for PEW and NaOH, respectively. (b) Charge histogram around Kr ions.

Neutron detectors (Masashi Takada)

A neutron energy spectrum from 7 to 180 MeV, a photon energy spectrum from 4 to 50 MeV and a proton energy spectrum from 94 to 145 MeV were simultaneously measured onboard an aircraft using a newly developed phoswich-type neutron detector at 10.8 km altitude (atmospheric depth of 249 g/cm^2) and geographical latitude of 39 °N (a vertical cut-off rigidity of 10.2 GV) near Japan on February 13, 2008 (at a heliocentric potential of 312 MV). Our results were compared with other measurements obtained using 3He-loaded or extended-energy multi moderator neutron spectrometers (Bonner balls) at aviation altitudes, an organic liquid scintillator on the ground, and a double-scatter neutron telescope at the top of the atmosphere and with calculations using the LUIN2000, EXPACS and RMC codes. Our measured results give a large, sharp peak around neutron energy of 70 MeV, although Bonner balls present a broad peak around 100 MeV due to low energy resolution. Our neutron fluxes agree well with those of others. The measured photon energy spectrum is between the LUIN2000- and EXPACS-calculated spectra and agrees with measured vertical photon spectra at the top of the atmosphere. This onboard study provides the first experimental neutron energy spectrum in a high-energy region (over 10 MeV) with high energy resolution.

Scintillation detector (Hidehito Nakamura)

The NaI (Tl) scintillator is one of the most common inorganic scintillators used for radiation measurements and radiation protection. Standard NaI (Tl) scintillators have only one optical window and are housed in airtight protective enclosures to protect against hygroscopicity from moisture in the air. For these reasons, NaI (Tl) scintillators are unsuitable for the collection of scintillation photons and for the detection of low-energy charged particles. A rectangular NaI (Tl) scintillator has been newly developed to overcome this disadvantage.

Here, we demonstrate the performance of this new NaI (Tl) scintillator. The ability to detect low-energy particles was confirmed by successful measurement of low-energy charged particles from a ^{137}Cs thin film radioisotope source in Fig. 7-5.

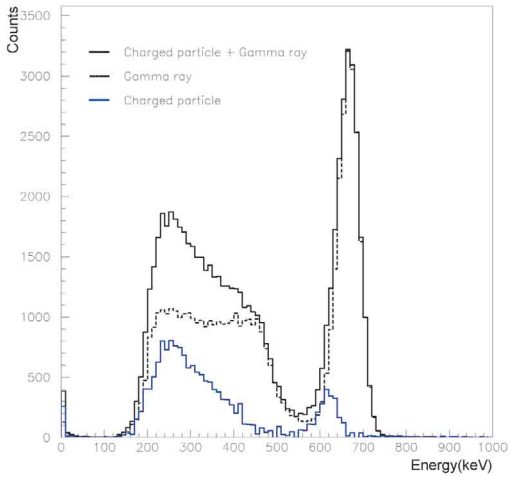


Fig. 7-5. Energy spectrum of radiation from a ^{137}Cs thin film source

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

From recent space intercomparison experiments (Space-ICCHIBAN-1 to 3), an international society for space radiation monitoring requests and recommends to perform intercomparison 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 intercomparison experiments (Proton-ICCHIBAN-2) were performed in the cyclotron facility in NIRS. In the cyclotron facility, we have prepared a radiation field to provide wide and uniform proton beams. The beam profiles were confirmed with a multi-channel scintillation counter and radiation doses were measured by a corrected standard ion chamber. Luminescence detectors which have been used for radiation measurements in a space environment by institutes and universities in world, were gathered in NIRS and packed in some kinds of holders. (Fig. 7-6) These holders were exposed to 70 and 40 MeV proton beams on Jan. 29th and Feb. 5th. A total of 13 institutes and universities in 10 countries participated in these experiments. The exposed luminescence detectors were returned to researchers and analyzed. These analyzed results will be reported in the near future and discussed in some international workshops.

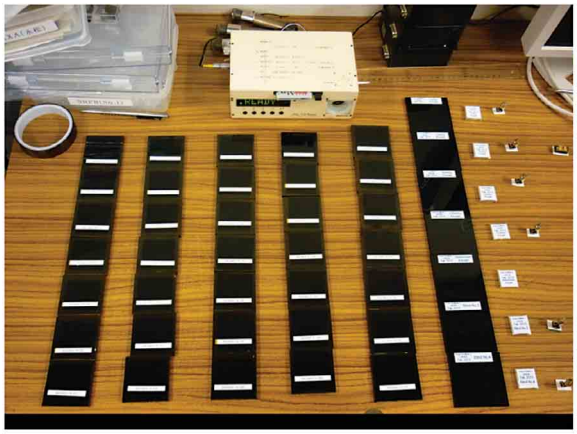
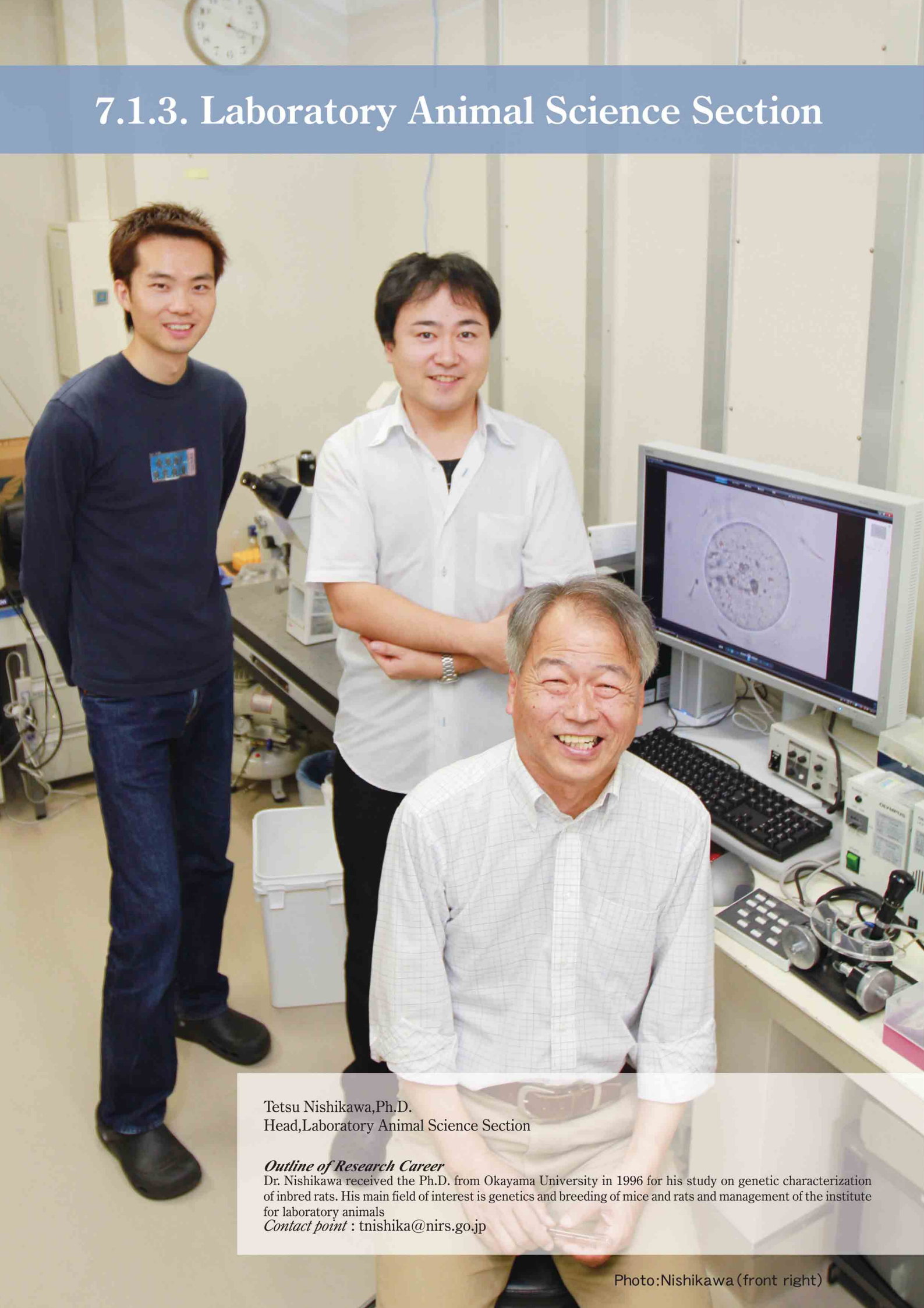


Fig. 7-6. Photograph of detector packages in the 2nd Proton-Intercomparison experiments.

Major Publications

1. N. Yasuda, S. Kodaira, M. Kurano, H. Kawashima, H. Tawara, T. Doke, K. Ogura, N. Hasebe, "High speed microscope for large scale ultra heavy nuclei search using solid state track detector", Journal of the Physical Society of Japan, 78 (Suppl. A), 142-145, 2009.
2. S. Kodaira, N. Yasuda, H. Kawashima, M. Kurano, N. Hasebe, T. Doke, S. Ota, K. Ogura, "Control of the detection threshold of CR-39 PNTD for measuring ultra heavy nuclei in galactic cosmic rays", Radiation Measurements, 44, 861-864, 2009.
3. S. Kodaira, N. Yasuda, H. Tawara, K. Ogura, T. Doke, N. Hasebe, T. Yamauchi, "Temperature and pressure conditions for the appropriate performance of charge and mass resolutions in balloon-borne CR-39 track detector for the heavy cosmic rays", Nuclear Instruments & Methods in Physics Research Section B, 267 (10), 1817-1822, 2009.
4. H. Nakamura, H. Kitamura, R. Hazama, " Development of a new rectangular NaI (Tl) scintillator and spectroscopy of low-energy charged particles", Rev. Sci. Instrum., 81 (1), 1-4, 2010.
5. G. Reitz, T. Berger, Y. Uchihori, N. Yasuda, H. Kitamura, et al., "Astronaut's Organ Doses Inferred from Measurements in a Human Phantom Outside the International Space Station", Radiation Research, 171, 225-235, 2009.

7.1.3. Laboratory Animal Science Section



Tetsu Nishikawa,Ph.D.
Head,Laboratory Animal Science Section

Outline of Research Career

Dr. Nishikawa received the Ph.D. from Okayama University in 1996 for his study on genetic characterization of inbred rats. His main field of interest is genetics and breeding of mice and rats and management of the institute for laboratory animals

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Photo:Nishikawa (front right)

Following research are performing in our laboratory.

1. Establishment and improvement of genetic monitoring system of the mouse with microsatellite markers.

A genetic monitoring system was established with microsatellite markers among 15 inbred strains of mice maintained at the National Institute of Radiological Sciences (NIRS). However, it was difficult to determine the genotype by naked eye because the DNA fragment pattern after agarose gel electrophoresis (AGE) was unclearly and the PCR product size in one locus was about the same size. To solve these problems, we used an automatic electrophoresis apparatus MultiNA, performed electrophoresis and determined the genotype. MultiNA shows the PCR product size numerically so we determined the genotype from the numerical value (Fig. 7-7). There were differences in 10 loci out of 18 loci when MultiNA was used, and which could not be detected by AGE. Although it was difficult to determine the genotype by naked eye using AGE, the genotype could be examined thoroughly with MultiNA.

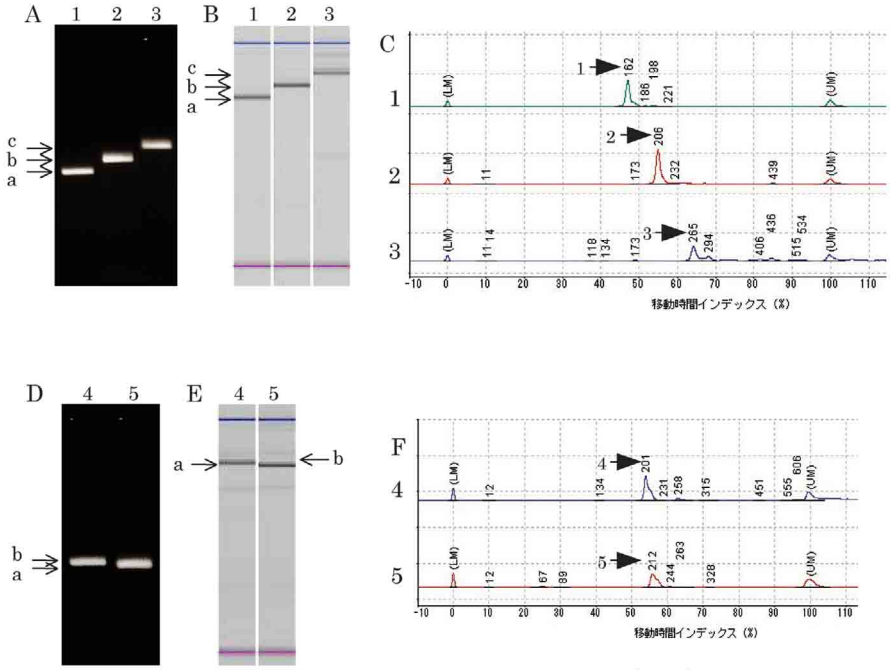

Fig.7-7 Electrophoretic patterns on an agarose gel (A, D), and with MultiNA (B, E), and the electropherogram with MultiNA (C, F). MSM is D6Mit15 (A, B, C) and D4Mit53 (D, E, F), and mouse strains are STS/A (lane 1), BALB/c-nu/+ (lanes 2, and5), and C57BL/6JNrs (lanes 3, and 4). In C and F, the PCR product size is indicated by the numerical value for the highest peak (arrows) between the lower marker (LM) and the upper marker (UM).

2. Research of breeding and reproduction of mice and rats.

1) annibalism of mice.

To survey the most suitable foster mother, we research mouse cannibalism by mothers which nurse foster infants. The incidence of cannibalism was compared among three ICR sub-strains, ddY and four inbred strains. The result of C3H/HeSlc was the most suitable strain for becoming a foster mother. The 15 inbred strains of mice maintained in our laboratory, C3H/HeNrs, was also suitable for becoming a foster mother.

2) The improvement for shortening the operation time of isolator.

Weprototype of a new kind of metal stopper to reduce the working time (Fig. 7-8).

The average time for installing this metal stopper is the same for experienced and inexperienced workers.

We applied a microbiological test to isolators with a rubber metal stopper for 30 months. The result showed that the inside of all the isolators were kept germ-free.

(Fig. 7-8)

3) Research of artificial feeding of mice and rats.

At the NIRS, we conduct experiments in which we irradiate neonates with radioactive substances of various types of radiation and nuclides, and study their effects. In these experiments, we irradiate the neonates for a fixed period and then let their mothers rear them. However, the mothers sometimes eat their young. Therefore, in order to prevent such cannibalism, we aimed establish a hand-rearing technique that uses milk formula. We first tried hand-rearing Slc : SD rats with a nursing bottle developed by Hoshiba. Date, results show that the weaning ratio has been 24/30 (80%) in the hand-reared group and 17/17 (100%) in the mother-reared group. At all measurement times, body weights were lower in the hand-reared group than in the mother-reared group, and were as low as 27.3 g for males and 26.1 g for females at the time of weaning. Here we report the procedure for using a Hoshiba nursing bottle.

8. List of Original Papers

This list includes main publications by the staff members issued during the period from April 1,2009 to March 31,2010

* Outside Co-research

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

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3. Hidetsugu Nakayama, Shinji Sugahara, Hideyuki Sakurai*, Koji Tsuboi*, Kouichi Tokuue*, et. al : Proton Beam Therapy for Hepatocellular Carcinoma : The University of Tsukuba Experience, Cancer, 115 (23), 5499-5506, 2009
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5. Yoshiko Oshiro*, Shinji Sugahara, et. al : Proton Beam Therapy Interference with Implanted Cardiac Pacemakers, International Journal of Radiation Oncology Biology Physics, 72 (3), 723-727, 2008
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9. Shingo Kato, Tatsuya Ohno, Kullathorn Thephamongkhol*, Yaowalak Chansilpa*, Anita Zarina Binti Bustam*, Miriam Joy C Calaguas*, Rey H De Los Reyes*, Cho Koo Chul*, Dung To Anh*, Supriana Nana*, Hideyuki Mizuno, Takashi Nakano*, Hirohiko Tsujii, et. al : Multi-Institutional Phase II Clinical Study of Concurrent Chemoradiotherapy for Locally Advanced Cervical Cancer in East and Southeast Asia, International Journal of Radiation Oncology Biology Physics, 77 (3), 751-757, 2010
10. Reiko Imai, Tadashi Kamada, Hiroshi Tsuji, Shinji Sugahara, Itsuko Serizawa, Hirohiko Tsujii, Shinichiroh Tatezaki : Effect of Carbon Ion Radiotherapy for Sacral Chordoma : Results of Phase I-II and Phase II Clinical Trials, International Journal of Radiation Oncology Biology Physics, 77 (5), 1470-1476, 2010
11. Takeshi Yanagi, Junetsu Mizoe, Azusa Hasegawa, Ryo Takagi, Hiroki Bessho, Takeshi Onda, Tadashi Kamada, Yoshitaka Okamoto, Hirohiko Tsujii : Mucosal malignant melanoma of the head and neck treated by carbon ion radiotherapy, International Journal of Radiation Oncology Biology Physics
12. Masashi Mizumoto*, Koji Tsuboi*, Hiroshi Igaki*, Tetsuya Yamamoto*, Yoshiko Oshiro*, Hidetsugu Nakayama, Shinji Sugahara, Hideyuki Sakurai*, Akira Matsumura*, Kouichi Tokuue*, et. al: Phase I/II Trial of Hyperfractionated Concomitant Boost Proton Radiotherapy for Supratentorial Glioblastoma Multiforme, International Journal of Radiation Oncology Biology Physics
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2. Hiroshi Toki, Kenji Satou : Three Conductor Transmission Line Theory and Origin of Electromagnetic Radiation and Noise, Journal of the Physical Society of Japan, 78 (9), 094201-1-094201-8, 2009
3. Yoshiki Kubota*, Kota Aoki*, Hiroshi Nagahashi*, Shinichi Minohara : Quantification of Pulmonary Motion from 4D-CT Images Using 3D-KLT Tracker, Medical Imaging Technology, 27 (3), 193-199, 2009
4. Azusa Ishizaki, Nobuyuki Kanematsu, Tatsuaki Kanai, Shunsuke Yonai, Yuka Takei, Yuuki Kase, Masataka Komori, et. al : Development of an irradiation method with lateral modulation of SOBP width using a cone-type filter for carbon ion beams, Medical Physics, 36 (6), 2222-2227, 2009
5. Taku Inaniwa, Takuji Furukawa, Ai Nagano, Shinji Satou, Naoya Saotome, Kouji Noda, Tatsuaki Kanai: Field-size effect of physical doses in carbon-ion scanning using range shifter plates, Medical Physics, 36 (7), 2889-2897, 2008
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10. Nobuyuki Kanematsu : Semi-empirical formulation of multiple scattering for the Gaussian beam model of heavy charged particles stopping in tissue-like matter, Physics in Medicine and Biology, 54 (5), N67-N73, 2009
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16. Arne Drentje*, Atsushi Kitagawa, Masayuki Muramatsu : Isotopic anomaly for Carbon ions in an ECRIS, Review of Scientific Instruments, 81 (2), 02B502-1-02B502-3, 2010
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18. Hirohiko Tsujii, Shinichi Minohara*, Kouji Noda : Heavy-Particle Radiotherapy : System Design and Application, Reviews of Accelerator Science and Technology, 2 (1), 93-110, 2009

Standardization and improvement of therapeutic and diagnostic techniques

1. Katsumi Tamura, Kyosan Yoshikawa, Hiroyuki Ishikawa, Mitsuhiko Hasebe, Hiroshi Tsuji, Takeshi Yanagi, Kazutoshi Suzuki, Atsushi Kubo*, Hirohiko Tsujii : Carbon-1 1-Methionine PET Imaging of Choroidal Melanoma and the Time Course after Carbon Ion Beam Radiotherapy, Anticancer Research, 29 (5), 1507-1514, 2009
2. Keisuke Fujii, Takahiko Aoyama*, Chiyo Kawaura*, Shuji Koyama*, Masato Yamauchi*, Susumu Ko*, Keiichi Akahane, Kanae Nishizawa : Radiation dose evaluation in 64-slice CT examinations with adult and paediatric anthropomorphic phantoms, British Journal of Radiology
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5. Shinichiro Mori, Takeshi Yanagi, Ryusuke Hara, Sharp Gregory*, Hiroshi Asakura, Motoki Kumagai, Riwa Kishimoto, Shigeru Yamada, Hirotoshi Katou, Susumu Kandatsu, Tadashi Kamada : Comparison of Respiratory-gated and -ungated Planning in Scattered Carbon Ion Beam Treatment of the Pancreas Using Four-dimensional CT, International Journal of Radiation Oncology Biology Physics, 76 (1), 303-312, 2010
6. Behnaz Goudarzi, Riwa Kishimoto, Syuhei Komatu, Hiroyuki Ishikawa, Kyosan Yoshikawa, Susumu Kandatsu, Takayuki Obata : Detection of bone metastases using diffusion weighted magnetic resonance imaging : comparison with 11C-methionine PET and bone scintigraphy, Magnetic Resonance Imaging, 28 (3), 372-379, 2010
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12. Chiyo Kawaura*, Keisuke Fujii, Takahiko Aoyama*, Masato Yamauchi*, Shuji Koyama* : Evaluation of radiation doses from MDCT-imaging in otolaryngology, Radiation Protection Dosimetry
13. Kimiichi Uno*, Tomio Inoue*, Keiichiro Yamaguchi*, Tatsuo Ido*, Keigo Endo*, Atsushi Kubo*, Kiyoko Kusakabe*, Kan Takeda*, Kouji Murakami*, Kyosan Yoshikawa, Kanji Torizuka* : Comparative Study between 99mTc-diphosphonate Bone Scintigraphy and 18F-fluoride PET or PET/CT in Terms of Clinical Usefulness and Cost-

effectiveness in Detection of Bone Disorders, Radioisotopes, 58 (7), 461-468, 2009
14. Shinichiro Mori, Motoki Kumagai, Suguru Dobashi, Toshio Sugane, Masayuki Baba, et. al : Practical Approaches to Four-dimensional Heavy-Charged-Particle Lung Therapy, Radiological Physics and Technology, 3 (1), 23-22, 2010
15. Hiroshi Asakura, Motoki Kumagai, Nobuyuki Kanematsu, Shinichiro Mori : A treatment planning strategy for heavy-charged-particle radiotherapy of lung cancer by the use of computed tomography with projection data-based temporal maximum-intensity projection, Radiological Physics and Technology, 3 (1), 58-64, 2010
16. Shinichiro Mori, Ryusuke Hara, Takeshi Yanagi, Sharp Gregory*, Motoki Kumagai, Hiroshi Asakura, Riwa Kishimoto, Shigeru Yamada, Susumu Kandatsu, Tadashi Kamada : Four-dimensional Measurement of Intrafractional Respiratory Motion of Pancreatic Tumors Using a 256-Multislice CT Scanner, Radiotherapy and Oncology, 92, 231-237, 2009

RadGenomics Project for radiotherapy

1. Miyako Nakawatari, Mayumi Iwakawa, Tatsuya Ohno, Shingo Kato, Etsuko Nakamura, Yu Ohkubo, Tomoaki Tamaki, Takashi Imai: Change in fibroblast growth factor 2 expression as an early-phase radiotherapy responsive marker in sequential biopsy samples from cervical cancer patients during fractionated radiotherapy., Cancer, 000-000, 2010
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3. Tomoaki Tamaki, Mayumi Iwakawa, Tatsuya Ohno, Kaori Imadome, Miyako Nakawatari, Minako Sakai, Hirohiko Tsujii, Takashi Nakano*, Takashi Imai : Application of Carbon Ion Beams or Gamma-Rays on Primary Tumors Does Not Change the Expression Profiles of Metastatic Tumors in an in vivo Murine Model, International Journal of Radiation Oncology Biology Physics, 74 (1), 210-218, 2009
4. Megumi Ueno, Kaori Imadome, Mayumi Iwakawa, Kazunori Anzai, Nobuo Ikota, Takashi Imai: Vascular Homeostasis Regulators, Edn1 and Agpt2, are Upregulated as a Protective Effect of Heat-treated Zinc Yeast in Irradiated Murine Bone Marrow, Journal of Radiation Research, 000-000, 2010

Biological Research Concerning the Improvement of Radiation Therapy

1. Aya Okajo*, Iori Ui*, Sushma Manda, Ikuo Nakanishi, Kenichiro Matsumoto, Kazunori Anzai, Kazutoyo Endo* : Intracellular and extracellular redox environments surrounding redox-sensitive contrast agents under oxidative atmosphere, Biological & Pharmaceutical Bulletin, 32 (4), 535-541, 2009
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Research Work in the Radiation Measurements Research Section

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2. Atsushi Jinno-Oue*, Nobuaki Shimizu*, Nobuyuki Hamada, Seiichi Wada*, Atsushi Tanaka*, Masahiko Shinagawa*, Takahiro Ohtsuki*, Takahisa Mori*, Manujendra N. Saha*, Ariful S. Hoque*, Salequl Islam*, Kimitaka Kogure*, Tomoo Funayama*, Yasuhiko Kobayashi*, Hiroo Hoshino* : Irradiation with carbon ion beams induces apoptosis, autophagy, and cellular senescence in a human glioma-derived cell line, International Journal of Radiation Oncology Biology Physics, 76 (1), 229-241, 2010
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13. Nobuyuki Hasebe*, Satoshi Kodaira, et. al: First Results of High Performance Ge Gamma-Ray Spectrometer Onboard Lunar Orbiter SELENE (KAGUYA), Journal of the Physical Society of Japan, 78 (Suppl. A), 18-25, 2009
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Other

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9. Roster of Researchers

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Takashi Murata, Executive Director

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Ohtsura Niwa, Ph. D., Deputy Director
Planning and Promotion Office
Sadayuki Ban, M. D., Head[1] and 4 staffs

Hospital
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Administration Section
Yoichi Kawamura, Head and 7 staffs
Medical Informatics Section
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Gen Kobashi, M. D.
Masami Mukai, M. S.
Akira Kobayashi
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Masayuki Baba, M. D., Ph. D., Head
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Takamichi Morikawa, M. D.
Shigeru Yamada, M. D., Ph. D.
Shigeo Yasuda, M. D., Ph. D.
Reiko Imai, M. D., Ph. D.
Naoyoshi Yamamoto, M. D.
Hiroshi Imada, M. D., Ph. D.
Azusa Hasegawa, M. D., Ph. D.
Hiroki Kiyohara, M. D.
Tohru Okada, M. D.
Makoto Shinoto, M. D.
Clinical Diagnosis Section
Susumu Kandatsu, M. D., Head
Kyosan Yoshikawa, M. D., Ph. D., Head
Tokuhiko Omatsu, M. D., Ph. D.
Riwa Kishimoto, M. D., Ph. D.
Nursing Section
Yoko Nakamura, Head
Sadayo Saito, Chief Nurse
Kiyoko Tahara, Chief Nurse
Yoko Yamasita, Chief Nurse
Yayoi Daigo, Chief Nurse
49 staffs and 2 assistants
Pharmacy Section
Shin Watanabe, Head and 4 staff
Clinical Laboratory Section
Shingo Kato, M. D., Ph. D., Head
Hidehumi Ezawa, M. D.
Katsunori Shimizu
Taijyu Yamada
Mari Motomura
Radiological Technology Section
Kazuhiro Watanabe , Head and 25 staffs

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Koji Noda, Ph. D., Head[1]
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Atsushi Kitagawa, Ph. D.
Takuji Furukawa, Ph. D.
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Masayuki Muramatsu
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Cyclotron Operation Section
Mitsutaka Kanazawa, Ph. D., Head
Satoru Hojo
Beam Delivery Systems Section
Shinichi Minohara, Ph. D., Head[1]
Shigekazu Fukuda, Ph. D.
Therapy Systems Section
Shinichi Minohara, Ph. D., Head
Nobuyuki Kanematsu, Ph. D.
Naruhiro Matsufuji, Ph. D.
Shin-ichiro Mori, Ph. D.

Quality Control Section
Akifumi Fukumura Ph. D., Head
Hideyuki Mizuno, Ph. D.

Radiological Protection Section
Keiichi Akahane, Ph. D., Head
Shunsuke Yonai, Ph. D.
Kanae Nishizawa, Ph. D.

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Atsushi Kitagawa, Ph. D., Head[1]
Yoshiyuki Iwata, Ph. D. [1]
Takeshi Murakami, Ph. D. [1]

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2) Visiting Researcher
3) Postdoctoral Fellow

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