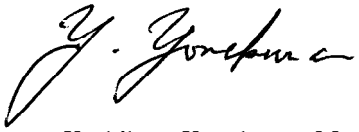
Preface

The National Institute of Radiological Sciences (NIRS) has pursued comprehensive research in science and technology related to radiation and human health since its initial establishment in 1957. We reorganized the structure of the institution and started its second 5-year plan in April 2006. This annual report summarizes the outline of our research activities during the past year.

All living creatures on the earth have been exposed to radiation for billions of years. In addition to this natural radiation, the discovery of X-rays in the end of the 19th century introduced a new era. The use of radiation and radioactive materials has completely changed the way of life, and it is now an essential tool in many areas from medical practice to energy production. The mission of NIRS, advancing radiological science and technology for human health, clearly meets the needs of modern society.

The objectives of the 5-year plan involve the promotion of research and development in radiation-related life science, radiation safety and emergency medical preparedness. In order to achieve our mission effectively and efficiently, we reorganized our research facilities into 4 research centers, Research Center for Charged Particle Therapy, Molecular Imaging Center, Research Center for Radiation Protection and Research Center for Radiation Emergency Medicine, as well as Fundamental Technology Center. We are also encouraging collaborative activities in a multidisciplinary approach among these research centers and also with other institutions. These efforts are particularly important not only for planning the future direction of NIRS but also for establishing the road map of research themes in radiological science.

We continue our efforts in contributing to the national and international projects for radiation safety and regulation. However, the facilities and specialists to conduct studies in basic radiation biology, radiation physics, radiation oncology, and regulatory science will not be sufficient for future advancement, and collaboration and networking could be one solution to solve this problem. We pursue our activities to contribute as one of the international core centers in radiological science, and we sincerely ask for your continuing support to NIRS and welcome any suggestions or critiques.



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

1. Outline of Research Activities

The National Institute of Radiological Sciences (NIRS) was reformed as an Independent Administrative Institution (IAI) in April 2001, and the first Mid-term Plan (2001-2006) has been completed successfully. This fiscal year (April 2006- March 2007) is the first year in the second Mid-term Plan. The research activities directly supported by the government were categorized and re-organized to five fields ; heavy charged particle therapy for cancer treatment, radiation effects on the human body for use in radiotherapy, molecular imaging, radiation safety, and radiation emergency medicine. To perform these researches, four research centers and one fundamental technology center were established. Details of these research activities will be presented in the following pages.

The transfer from the first to the second Mid-term Plan has been done smoothly, and many accomplishments were obtained in all the research fields. Judging from the number and quality of the presentations at scientific meetings and the research papers and reports, it can be concluded that the researchers were active and much progress was achieved this year. The number of original papers published by NIRS members reached 280 papers, and many of them were published in international journals with good reputations. Furthermore, we had more than 160 proceedings at international or domestic scientific meetings, 450 oral presentations, and 50 patent applications. Collaborative studies and exchanges of researchers were also very active : 84 collaborative studies were carried out, 1200 researchers worked as visiting staff, and 280 students were accepted as trainees.

The clinical study of cancer treatment using with the Heavy Ion Medical Accelerator (HIMAC), conducted in the Research Center for Charged Particle Therapy, experienced much progress and more than 500 patients were treated this year. The total number of patients treated has reached approximately 3200 since 1995. The development of new types of irradiation systems, such as the spot-scanning system and rotating gantry was started. The new irradiation facilities with these systems will become available at the end of this Mid-tem Plan (2011). Basic biological studies were also conducted to obtain biological evidences of particle therapy and to develop further an effective protocol of treatment. In the Molecular Imaging Research Center which was established last year, investigations on advanced imaging of cancer and neuronal function were carried out, mainly using positron emission tomography (PET). Development of advanced measuring techniques including new types of PET probes was continued and obtained many achievements. This year, the Center also started collaboration studies with other institutes and universities as a national center for molecular imaging with financial support of the Ministry of Education, Culture, Sports, Science and Technology (MEXT).

The research on radiation safety and emergency medicine, an important mission of our institute since its establishment, was mainly carried out in the Research Center for Radiation Safety and the Research Center for Radiation Emergency Medicine. Activities were focused on the health effects of low dose radiation, levels of natural radiation, radiation effect on the environment (non-human biota), and development of medical treatment and dose estimation in the event of radiation emergency. These centers also preformed as a national hub center for collaboration with international organizations including the International Atomic Energy Agency, International Commission of Radiation Protection, United Nations Scientific Committee on Atomic Radiation, World Health Organization, and so on.

The Fundamental Technology Center was newly established this year to support various studies of NIRS with advanced fundamental technology. Some developmental research was carried out including single particle irradiation system to cells, a neutron irradiation device for animal experiments, and radiation measurement apparatus for cosmic rays.

Some other research programs were also continued or newly started with supports of funding agencies including MEXT, the Ministry of Economy, Trade and Industry, the Ministry of Environment, and so on.

Readers will see in the following pages that all the research activities started smoothly in the first year of the second Mid-term Plan. I would like to finish with heartfelt thanks for cooperation and advice given to us during FY 2006.

Sentaro Takahashi, Ph. D.,
Executive Director for Research

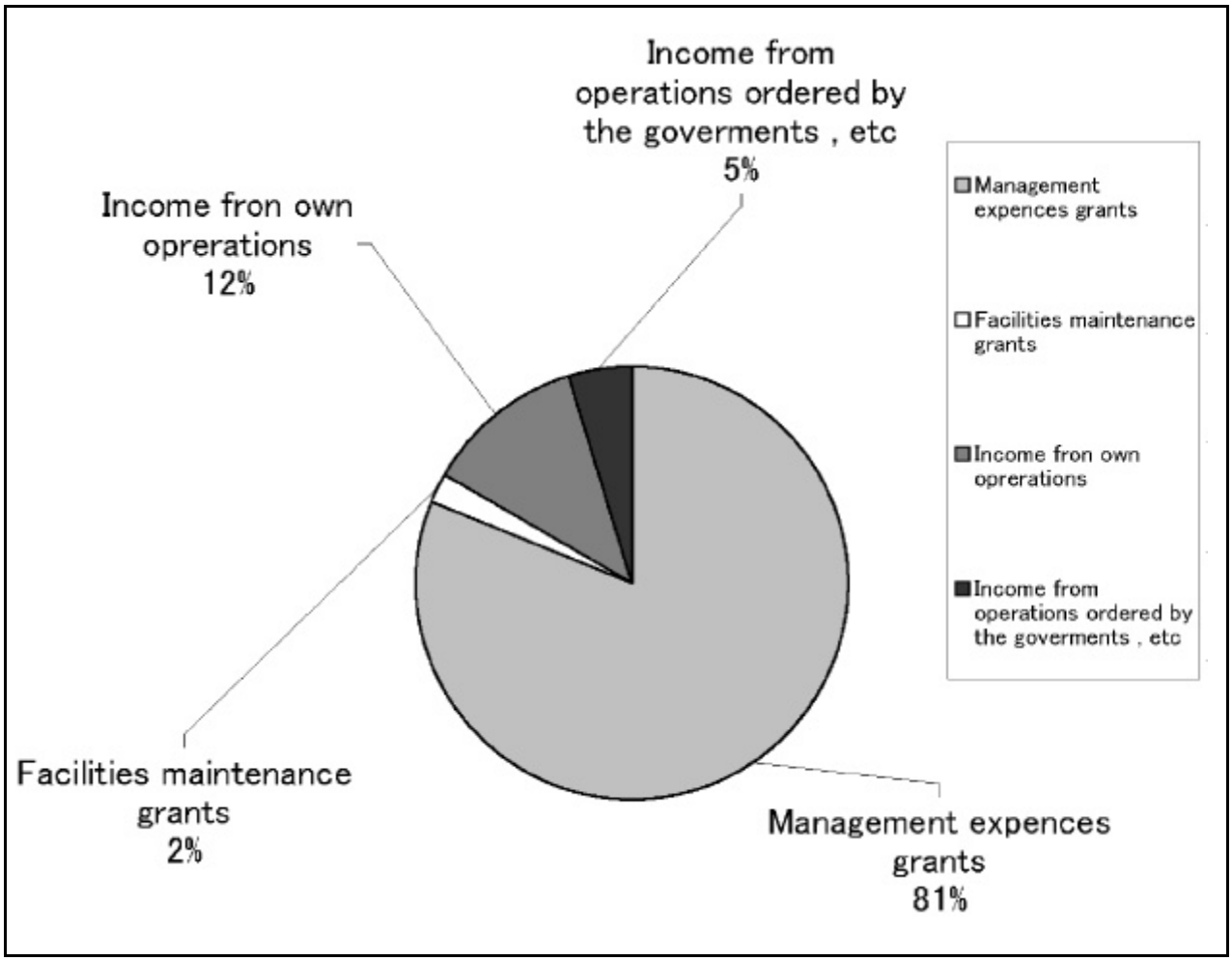
2. Organization Chart and Budget

(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 Office

(2) Budget (2006.4～2007.3)

Total	16,207 million yen	%
Management expences grants	13,140 million yen	81%
Facilities maintenance grants	380 million yen	2%
Income fron own oprerations	1,937 million yen	12%
Income from operations ordered by the goverments , etc	750 million yen	5%



3. Research Center for Charged Particle Therapy

Hirohiko Tsujii, M. D., Ph. D.
Director of Research Center for Charged Particle Therapy

Outline of Research Career :

Dr. Tsujii received a Ph. D. from Hokkaido University in 1985 for his study on radiation therapy. He has been majoring in radiation oncology since 1969, including particle beam therapy at New Mexico University, PSI, Tsukuba University and NIRS. He received Scientific Award from Princess Takamatsu Cancer Research Fund in 2005 and NISTEP Award from National Institute of Science and Technology Policy in 2006. He has been an honorary membership of ESTRO since 2001 and a Coordinate Member, Science Council of Japan since 2006. He has been a Director of Research Center for Charged Particle Therapy, NIRS since 2003.

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 experiences 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. 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 fiscal year of 2006 include : 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 the SNIPs ; research on HiCEP.

Overview :

The Center is organized of 6 research groups for two major topics (A, B and C). Progress of research for each topic is summarized.

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

① Development of advanced cancer radiotherapy with charged particle

This subject has been carried out by the Particle Therapy Research Group (GL; T. Kamada) consisting of 3 teams : Clinical Trial Research Team, Clinical Database Research Team, and Radiation Effect Research Team.

From June 1994 to February 2007, a total of 3,178 patients were enrolled in nearly 50 different phase I/II and phase II trials and also in Highly Advanced Medical Technology of carbon ion radiotherapy. In the year 2006, a total of 549 patients with a variety of malignant tumors were treated with carbon ions, in which nearly 75 % of the patients were treated in Highly Advanced Medical Technology. The hypofractionated radiotherapy with employment of larger doses per fraction and shorter overall treatment time as compared to proton or conventional photon radiotherapy has been effectively performed. The average number of fractions per patient was 13 given in 3 weeks. The new MLC having fine leaves has been developed since 2005 and in 2006 the amount of radiation leakage through this MLC was measured. It was found that the ratio of the leakage dose to the unshielded dose for 400 MeV/u carbon beams was measured to be about 1 % at the entrance while the currently used MLC gave about 0.6 %. The leakage dose decreased as the depth in water became larger. For effective performance of charged particle therapy, computer oriented information system is mandatory. In 2006, the Electronic Medical Record (EMR) was implemented and coordination among several database systems, including the Hospital Information System, Therapy Plan Database, Therapy Schedule Management System, PACS and Radiology Information System for Radiation Therapy, was improved. The TCP model proposed by Webb and Nahum has been used for analysis of clinical results, which provided useful data for clinical practice.

Four new protocol studies were initiated in 2006: chemoradiotherapy of pancreas cancer; single fraction treatment of metastatic liver tumor; short course radiotherapy of hilar, nodular type NCSLC; extended field radiotherapy of locally advanced cervix cancer.

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: Accelerator Development Research Team, Irradiation System Research Team, Therapy System Research Team, and Compact Heavy-Ion Therapy System Research Team.

In the fiscal year 2006, research was focused on development of 3-D scanning method with a pencil beam for the new treatment facility that was designed as an extension of HIMAC. In this new facility, 3D scanning method will be used for treatment of both the fixed target and moving target. For this purpose the fast scanning method and phase-controlled re-scanning with gated irradiation were experimentally evaluated. The fast scanning method was successfully realized by taking account for extra dose that was measured when the spot moves from one position to the next. It was also confirmed through computer simulation that the phase-controlled re-scanning gave a sufficient uniformity in both the lateral and depth-dose distribution even in the moving target. Furthermore, the design study on a rotating gantry system using 3D pencil beam scanning method was performed. The final 90-degree bending magnet is divided into the two for 60 and 30 degrees with the scanning magnets being installed between them. Total weight of the gantry system was successfully lowered to about 350 tons, which was about the half the weight of the gantry developed at GSI.

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: Image Diagnosis Research Team, Image Processing Research Team, Quality Control Research Team, and Radiological Protection Research Team.

Image diagnosis research team studied fundamental aspects on application of new PET tracers for oncology imaging. This year, tumor hypoxic imaging using $^{62}Cu^{-}$ATSM was initiated and bone metastasis imaging using ^{18}F- FNa was also investigated. Image processing research team studied a various type of organ motion using single/serial 4D CT. Quality control research team developed a graphite calorimeter for absolute dosimetry in carbon ion irradiation and demonstrated a good linearity of response as a function of absorbed dose. Radiological protection team studied on the doses given to the patients in X-ray CT examination, in which TLDs were used for measurement.

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: Genetic Information Team, Molecular Radio-oncology Team, and Molecular Biostatistics Team.

Normal tissue reactions of cancer patients vary considerably after radiotherapy. A number of observations have indicated that certain genetic factors play important roles in this variability. The aim of the RadGenomics Research Group is to explore the genetic characteristics for both the patient and its bearing tumor, by which the potentially most effective radiotherapy can be delivered. This, from the molecular-biological standpoint, would open the way to the development of an individual-oriented radiotherapy. In the fiscal year 2006, four researches were primarily conducted. First, we developed a novel optical detection system for on-chip allele-specific primer extension to conveniently genotype multiple SNPs simultaneously. Second, microarray analysis with murine tumor models revealed activated molecular pathway with carbon-ion irradiation responsible genes and pathological evidences of superior effectiveness of carbon-ion irradiation. Third, using F2 mice descended from two inbred strains, radiation-induced apoptosis sensitive C57BL/6JNrs and radiation-induced apoptosis resistant C3H/HeNrs, we identified a significant locus on chromosome 15 for jejunal crypt cell apoptosis. This result will provide useful tools to identify the new radiosensitive loci. Finally, analyzing RAD18-knockout (RAD18-/-) cells generated from human HCT116 cells suggested a new function of RAD18 for S phase-specific DNA single-strand break repair.

These results will contribute to identify predictive markers for individual radiosensitivity for both malignant tumors and surrounding normal tissues. Furthermore, we have established a collaborating network with five university hospitals and our Hospital of the Center to allow for "from bench to bedside" research.

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: Biophysics Team, Experimental Therapy Team, Cellular and Molecular Biology Team, and Radiation Modifier Team.

Biophysics Team: RBE studies on DNA double strand break (DSB) repair indicated indirect effects of radiation damage even in the cells irradiated with high-LET radiation. Our method of using remaining number

of chromatid breaks after irradiation could be used for prediction of an individual radiosensitivity. Experiments on bystander effects with micro beams were started at TIARA/JAERI, PF/KEK, and Spring-8/JASRI. Experiments concerning the inter-comparison of RBE values among domestic and/or international ion-beam radiotherapy facilities were completed this year.

Experimental Therapy Team : The studies on a mouse model of tumor induction revealed that 15 KeV/μm carbon irradiation gave a lower induction rate than gamma-irradiation. New studies on tumor heterogeneity were started using the mixture of two tumor types with varying levels of radio-sensitivity. Among three mixed tumor groups, one showed a different sensitivity as compared to the control with single tumor type.

Cellular and Molecular Biology Team : Biological differences between X-ray and heavy ion particle (C, Fe, Ne) irradiation were identified using several quantitative assays with therapeutic level radiation doses. Both DNA microarrays and HiCEP analysis demonstrated some characteristic molecular features with high LET irradiation. The mechanism of radiosensitization by 17-AAG was identified with X-rays, and radiosensitization was also observed with carbon ions. RNA interference (RNAi) strategy was used to increase radiosensitivity of tumor cells.

Radiation Modifier Team : One of Vitamin-E analogs showed a scavenging rate constant three times larger than that of natural vitamin E. Tocopherol monoglucoside (TMG) and γ-tocopheryl-N, N-dimethylglycine (γ-TDMG) showed a significant in vivo radioprotection even in post-irradiation administration. An (-Lipoic acid was found to be a good protector for the brain and its functions. For the study of redox- and oxygen-mapping, T1-weighted MRI was shown to have a great advantage in evaluating the pharmacokinetics of newly modified and/or designed nitroxyl contrast agents.

③ Transcriptome Research for Radiobiology

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

HiCEP is an ideal method for transcriptome analysis, in which the principle is different from hybridization-based methods. This year an automatic HiCEP reaction machine (HiCEPer) was developed, which permitted to achieve 96 reactions simultaneously within 3 days. This enables us to perform 10,000 reactions per year and to analyze many applications such as diagnosis, human molecular epidemiology and so on. In order to generate an assay system for genome reprogramming, we established fibroblast cell lines in which reporter gene was inserted by homologous recombination. Stem-cell specific promoter that was identified by us controls the reporter gene. This system allows us to assess candidate genes, because if the candidates reprogrammed the fibroblast cells, the reporter gene would be expressed. In addition, we performed functional analyses of the four genes using their knockout mice, which were generated last year. Two lines out of the four strains, abnormal chromosome integrity, radiosensitivity, oncogenesis and aging have been suggested. One out of the four, defects of circadian rhythm and carcinogenesis have been also suggested. The remaining one showed a male infertility. Detail analysis of their testis demonstrated that spermatogonial stem cells are defective.

Finally, our proposals for medical use of HiCEP were submitted to the ethical committee of our institute. Then, protocol study for esophageal cancer was just authorized and other study using the blood is also under consideration.

C. Research Project with Heavy Ions at NIRS-HIMAC

Proposals of 121 were accepted and were carried out in FY2006 at HIMAC. The beam time of 5,457 hours was supplied to those researches.

The 72 papers, 53 proceedings were published, and 245 papers were presented at various meetings. Total of 528 researchers, including 61 foreign researchers, participated in the project.

3.1. Developing advanced clinical therapy with charged particle

Tadashi Kamada, M. D., Ph. D.
Head, Clinical Oncology

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 27 years of experience in clinical research on radiation oncology, including 12 years experience in carbon ion radiotherapy at NIRS. Since 2006, he has been group leader of the Particle Therapy Research Group for developing advanced clinical therapy with charged particle.

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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.
- ＊To maximize and disseminate the therapeutic effect of charged particle technology, five hundred patients are to be treated annually. 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.
- ＊The therapeutic effects of treatments developed by the Institute are evaluated 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 particle consists of clinical trial research team, clinical database research team, and radiation effect research team. It does research and development on charged particle therapy. Progress of research in each team is summarized.

1) Clinical trial research team

From June 1994 to February 2007, a total of 3178 patients were enrolled into 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. The number of the patients in each tumor site treated with carbon ion beam are listed in Table 1.

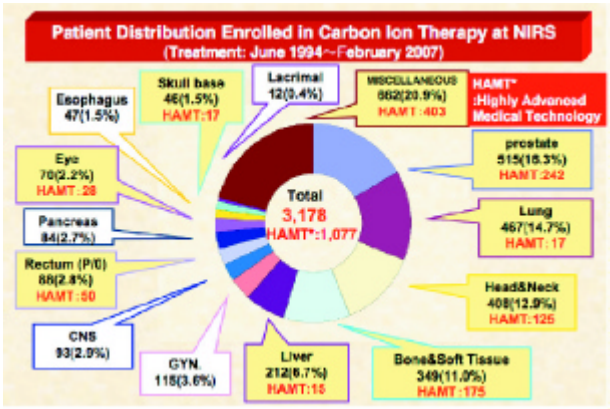

Table 1. The number of the patients in each tumor site treated with carbon ion beam.

We treated 549 new patients in 2006. Prostate, lung, head and neck, bone and soft tissue, and liver tumors are the leading 5 tumor types in the trials. A total of 2,867 patients who had a follow-up period of 6 months or more were included in this report. The clinical trial revealed that carbon ion radiotherapy provided definite local control and offered a survival advantage without unacceptable morbidity in a variety of tumors that were hard to cure with other modalities. Using carbon ion beams, hypofractionated radiotherapy, with application of larger doses per fraction and a reduction of overall treatment times as compared to conventional photon radiotherapy was possible. 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 75 % of the patients receiving carbon ion

radiotherapy were treated by HAMT in 2006.

When irradiating a patient with carbon beam, the patient should be protected from being exposed on an unwanted dose. A multi-leaf collimator (MLC) and patient collimators are used to spatially limit the carbon beam for the sake of delivering high localization of the dose to a target. The MLC can easily form an arbitral aperture shape which conforms to a cross sectional shape of the target by computer control. However, since each leaf of the present MLC is 6.5 mm thick, it is difficult to make the fine shape which is required for the cases of cancers which are abutting critical organs, such as head and neck cancers. It the case, the patient collimator is used, which is manufactured by boring an aperture in a brass block, and it takes a couple of days and cost. Furthermore, use of the patient collimator has enforced radiation therapy technologists to set the heavy collimator just above a patient in positioning. Omitting the patient collimator reduces the expense and the human burden.

A new MLC has been under development since 2005 to be applicable to the case in which the patient collimator is usually required. The MLC is equipped with 88 pairs of 2.5 mm thick leaf with 0.15 mm spacing. We would like to notify that the thickness is almost 1/3 of the present thickness of 6.5 mm. Each leaf has a step-like structure, instead of a tongue-and-groove structure. The thin multi-leaf, however, gives rise to a problem that the area occupied by the gaps relatively increase with respect to the total area. Since the gap is shielded by a half-length leaf, the beam leakage would increase more than the present MLC. The ratio of the leakage dose to the unshielded dose for 400 MeV/u carbon beams was experimentally proved to be about 1 % at the entrance while the present MLC gives about 0.6 %. The leakage dose decreases as the depth in water becomes deeper.

2) Clinical database research team

At October 2006, we had implemented the Electronic Medical Record (EMR) and developed a simple input method for the patient's findings, symptom, tumor response, and toxic reactions that should be estimated by the physician during the clinical interview. We improved the coordination among several database systems (Hospital Information System, Therapy Plan Database, Therapy Schedule Management System, PACSs and Radiology Information System for Radiation Therapy). These systems are connected to each other and data are transmitted to the destination systems. We could gather data directly from the information source. We also developed the IHE (Integrating the Healthcare Enterprise) EUA (Enterprise User Authentication) and PSA (Patient Synchronized Application) functions on the existing systems. These functions made it easy to operate multiple systems. Two PCs (for example : EMR and PACS viewer) are commonly used for the Hospital Information System in one clinical unit. Many physicians have to enter a user ID and password to login to these systems. To solve the troublesome manipulation, we developed the function of the IHE-ITI EUA and PSA. We developed middle-ware for the EUA/PSA to reduce the implementation load among the EMR, PACS-viewer, report-viewer, radiation scheduling sys-tem and radiation information system. The EUA/PSA was based on the HL7 CCOW standard and did not support multi PCs. So we enhanced the EUA/PSA mechanism for use with several PCs. We realized that EUA/PSA 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/PSA function will be inevitable for visual integration.

Among hospitals and/or medical institutions we implemented the system to share medical data. This system is based upon the IHE Cross-Enterprise Document Sharing (XDS) which uses SOAP, ebXML RIM and Web Service Description Language (WSDL) and HL7. We prepared the Open Source Software license for the delivery of software. We are now developing a document source, document repository, document registry and document consumer that were defined by the IHE XDS. We are planning to open this software made by our project until autumn 2007. We think that it is very important to maintain this software and to improve them periodically. We are making effort to establish a maintenance framework for open source software.

We continued to promote standardization of the database, and the XML module for radiation therapy and to prepare to communicate clinical radiotherapy data with other hospitals and/or medical facilities. We analyzed the physician's workflow in radiation oncology departments of the Japanese hospitals. In this workflow analysis, we classified the flow into 4 categories (initiation of radiation therapy, daily treatment, interruption and resume, termination). This categories were suitable for Japanese environment.

The NIRS Hospital Information System renewed at October 2006 is shown in Figure. 1.

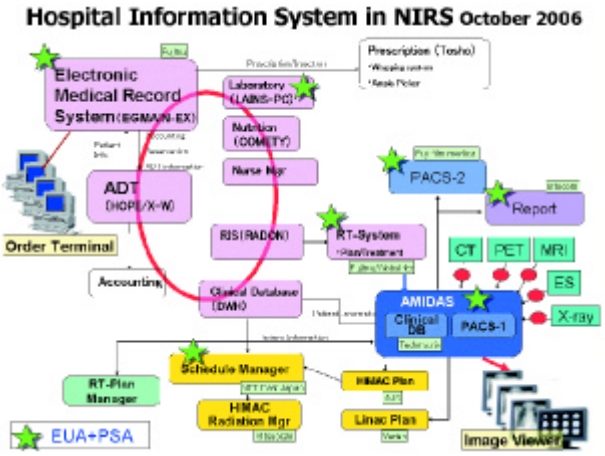

Figure. 1 Current status of Hospital Information System in NIRS.

3) Radiation effect research team.

The RBE model currently used at HIMAC yields a clinical dose distribution that depends only on LET as a function of depth while excluding the other factors such as dose level, tumour type or fraction schedule. This principle contributes for reducing those unproven factors in the methodology and on the contrary enables to estimate them from clinical results.

The TCP model proposed by Webb and Nahum has been used for the analysis of the clinical results. The remarkable point of the model is that it takes the variation in radiosensitivity among patients into account, and was proven to be effective through the analysis of NSCLC. This year, the analysis was extended to the following sites : skull-base chordoma, bone and soft tissue sarcoma and rectum cancers. Local control probability of these tumours under 16 fractions was analyzed with the model. a term in the LQ model, which denotes the radiosensitivity at smaller dose level, was derived from the analysis for each site. It was revealed that the rectum cancer shows similar radiosensitivity with the NSCLC. These sensitivities are also close to that of HSG, cultured cell line originated from human salivary gland tumor, which provides a standard response to carbon ions in the HIMAC RBE model. On the other hand, the rest sites showed slightly higher radiosensitivity than that of the HSG. It suggests room for further decreasing unwanted dose exposure to healthy normal tissues surrounding a tumour by optimizing dose distribution depending on its own radiosensitivity. The other interesting finding is that the bone and soft tissue sarcoma tends to be controlled by less dose than the NSCLC is while the sarcoma is in general considered to be radioresistant against conventional X-rays. Difference in the mechanism of biological effect caused by radiations between carbon and X-rays may play a role for this apparent contradiction.

Next to the NSCLC, clinical trials on liver metastasis from colorectal cancer have been preceded into a single irradiation. Based on the success of the retrospective TCP estimation in the case of NSCLC, predictive estimation for the case of the liver metastasis from colorectal cancer was tried in order to determine appropriate starting dose. Here, the TCP analysis was performed using clinical data of the local control with carbon ions on colorectal cancer. The single fraction dose that corresponds to expected 96 % of TCP level was estimated to be 35.0 GyE in the case. Together with the clinical aspects, single irradiation was initiated with the fraction size of 36.0 GyE.

The microdosimetric spectra for high-energy beams of photons, proton, helium, carbon, neon, silicon and iron ions (LET=0.5-880 keV/mm) were measured with a spherical-walled tissue-equivalent proportional counter at various depths in a plastic phantom. Survival curves for human tumor cells were also obtained under the same conditions. The survival curves were compared with those estimated by a microdosimetric model based on the spectra and the biological parameters for each cell line. The estimated terms of the LQ model with a fixed value reproduced the experimental results for cell irradiation for ion beams with LETs of less than 450 keV/mm, except in the region near the distal peak.

Major Publications :

1) Ishikawa H, Tsuji H, Kamada T, Hirasawa N, Yanagi T, Mizoe JE, Akakura K、Suzuki H, Shimazaki J, Tsujii H : Risk factor of late rectal bleeding after carbon ion therapy for prostate cancer, *Int J Radiat Oncol Biol Phys.* 66 : 1084-1091,2006
2) Ishikawa H, Tsuji H, Kamada T, Yanagi T, Mizoe JE, Kanai T, Morita S, Wakatsuki M, Shimazaki J, Tsujii H, Working Group for Genitourinary Tumors: Carbon ion radiation therapy for prostate cancer ; results of a prospective phase II study, *Radiother Oncol.* 81 (1) : 57-64,2006
3) Imai R, Kamada T, Tsuji H, Tsujii H, Tsuburai* Y, Tatezaki* S, Cervical spine osteosarcoma treated with carbon ion radiotherapy, *The Lancet Oncology,* 7 : 1034-1035, 2006
4) Kanai T, Matsufuji N, Miyamoto T, et al. 2006 Examination of GyE System for HIMAC Carbon Therapy Int. J. Radiation Oncology Biol. Phys. 64 : 650-656.2006
5) Kase Y, Kanai T, Matsumoto Y, et al. 2006 Microdosimetric Measurements and Estimation of Human Cell Survival for Heavy-Ion Beams. Radiation Res. 166 : 629-38.2006

3.2. Research on the Next-generation Irradiation System

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

Outline of Research Career :

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

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Objectives :

A design study and R&D work on a new treatment facility with HIMAC has just been initiated, in order to further development of carbon-ion therapy. This facility, which will be connected with the HIMAC synchrotron, will consist of three treatment rooms : two rooms equipped with horizontal and vertical beam-delivery systems and another with a rotating gantry. Both the fixed beam-delivery and rotating gantry systems employ a 3D beam-scanning method with the gated irradiation for a moving target as well as with the irradiation for a fixed target. The treatment in the new facility can increase its accuracy considerably and will bring an adaptive treatment.

Progress of Research :

The new treatment facility will be connected with the HIMAC accelerator complex and has three treatment rooms. Two of them are equipped with both horizontal and vertical beam-delivery systems and the other is equipped with a rotating gantry. A schematic view of the new facility with HIMAC is shown in Fig. 1. One of the greatest challenges in this project is to realize treatment of a moving target by 3D scanning irradiation. In particle therapy, 3D irradiation with pencil beam scanning, which can realize a high irradiation accuracy even in the case of an irregularly shaped target, has been developed and already utilized for treatment at PSI (Paul Scherrer Institute) and GSI (Gesellschaft fur Schwerionenforschung mbH). However, pencil beam scanning is more sensitive to organ motions compared with the conventional broad-beam irradiation. Although the online motion compensation method and the rescanning method have been developed to address this problem in pencil beam scanning, these methods have not yet been employed for practical use. In 3D pencil beam scanning irradiation, the interplay effect between the scanning motion and the target motion brings about hot and/or cold spots in the target volume even in the gated irradiation, because the size of the distal and lateral dose profiles of the pencil beam is comparable to the residual motion range. Therefore, we decided to employ a combination of the rescanning technique and the gated irradiation method to avoid producing hot/cold spots. In order to realize a relatively large number of rescannings within an acceptable irradiation time, we carried out our design study in two steps : 1) conceptual design of a fast scanning system, and 2) simulation of moving target irradiation with rescanning and gating. The fast scanning strategy was studied with respect to the scanning method, the scanning magnets and their control. Based on the uniform time structure of beam from the HIMAC synchrotron, we developed a novel optimization technique for fast scanning to cut the irradiation time, in which the exposure during transition of each spot is taken into account. We performed simulation studies of irradiation of a moving target combined with rescanning and the gated irradiation method. We found that the phase-controlled rescanning (PCR) method gave a feasible solution in which the dynamic beam intensity control technique plays an important role to adequately control the phase correlation under a relatively small number of rescannings. In the PCR method, it is necessary to adjust the irradiation time for each depth slice to be within 1-2 seconds of the respiration gate width. Consequently, we obtained a feasible solution for moving target irradiation by our raster scanning method with rescanning and gating functions.

In order to prove our strategy of the fast scanning described above, the beam test of the raster scanning irradiation cooperating with the extended flattop of the HIMAC synchrotron was carried out by using the HIMAC spot scanning test port. The irradiation control system was slightly modified so as to be capable of the raster scanning irradiation instead of the spot scanning

irradiation. In the present stage, we employed the meas ured dose response of the pencil beam with an energy of 350 MeV/u, which corresponded to a 220-mm range in water. The beam size at the entrance and the width of the Gaussian-shaped mini-peak were 3.5 and 4 mm at 1σ, respectively. The validity of the beam model and the optimization calculation had been verified experimentally. In the experiment, the spherical target of 40 mm diameter was irradiated to generate uniform physical dose field. The total irradiation time was decreased to 20 s due to extended flattop compared with the fixed cycle operation of 40 s. A cross monitor, consisting of 128 small ionization chambers, was employed to measure the dose distribution in the water. The measured dose distribution was compared with the calculated one, as shown in Fig. 2. The measured dose distributions were in good agreement with the calculation result at different penetration depth. Furthermore, it should be noted that there was no difference of the field quality i. e. the homogeneity and absolute dose at the center of the field.

On the other hand, we have carried out a design study of a rotating gantry system with 3D pencil beam scanning as steps toward the construction of a new treatment facility at HIMAC. Maximum energy and field size were set to be 400 MeV/u and 150mm square, respectively. Final 90 degrees bending magnet is divided into two bending magnets of 60 and 30 degrees to install the scanning magnets between them. Although 30 degrees magnet has relatively larger aperture, total weight of the gantry system was suppressed to be around 350 tons. Furthermore, the phase-space asymmetry compensation method will be employed by using a thin scatterer foil in the beam line. This technique makes it possible that the beam sizes and distributions in both planes do not depend on the rotating angle of the gantry owing to the symmetric condition.

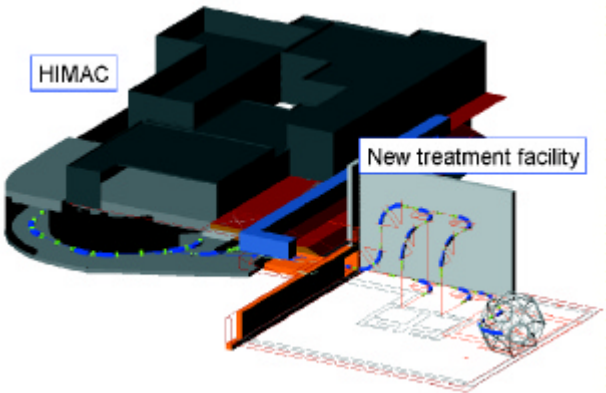

Fig. 1. : Schematic view of HIMAC and new treatment facility

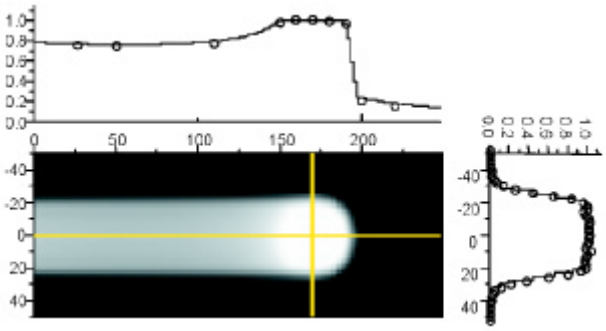

Fig. 2. : Comparison between measured (open circle) and calculated (line) dose distribution.

Major Publications :

1. K. Noda et al., "New accelerator facility for carbon-ion cancer-therapy", J. Radiat. Res., 48, 43-54 (2007).
2. T. Furukawa, T. Inaniwa, S. Sato, T. Tomitani, T. Minohara, K. Noda, T. Kanai, "Design study of a raster scanning system for moving target irradiation in heavy-ion radiotherapy" , Med. Phys. 34, 1085-1097.
3. S. Sato, T. Furukawa, and K. Noda, "Dynamic intensity control system with RF-knockout slow-extraction in the HIMAC synchrotron", Nucl. Instrum. Methods Phys. Res. A 574, 226-231 (2007).
4. T. Inaniwa, T. Furukawa, T. Tomitani, S. Sato, K. Noda, and T. Kanai, "Optimization for fast-scanning irradiation in particle therapy" , Med. Phys., 34 (8) 3302-3311
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3.3. Standardization and Improvement of Therapeutic and Diagnostic Techniques

Tadashi Kamada, M. D. Ph. D.
Head, Clinical Oncology

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 27 years of experience in clinical reseach on radiation oncology, including 12 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.

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Objectives :

* Development of software to create integrated clinical images, determine early therapeutic effects and analyze prognostic factors using a combination of multiple diagnostic imaging techniques.
* Improvement of treatment plans by using integrated images obtained from advanced dynamic imaging devices such as 4-dimensional CT.
* 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, image processing research team, quality control research team and radiological protection research team, and performs research into the advancement and standardization of radiation therapy and diagnostic methods. 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. We started tumor hypoxic imaging using Cu-62-ATSM. We assessed the tracer distribution and pharmacokinetic analysis in normal human volunteer in preparation for later applying the tracer to heavy ion radiotherapy patients. Activity of blood decreased relatively rapidly and reached to low level at about 10 minutes after injection. Liver and Urinary system showed very intense activity in Cu-62-ATSM whole body image. Liver activity reached middle or high level about 3 minutes after injection and continued to increase gradually.

We were also planning to perform F-18 FNa PET imaging for precise detection and diagnose of bone metastasis. F-18-Fluoride has higher bone uptake and faster blood clearance, resulting in a better target-to-background ratio. F-18-Fluoride PET has been shown to be more accurate than Tc-99m-methylene diphosphonate (MDP) bone scintigraphy for the detection of both sclerotic and lytic lesions in various malignancies and was suggested as an alternative to bone scintigraphy, mainly in patients at high risk for metastatic bone disease but also in patients for whom the detection of metastatic bone disease and its extent is important in selection of treatment, especially for eligibility decision of carbon ion radiotherapy. A working group, we are one of members, for F-18-Fluoride ion PET study was formed in The Japanese Society of Nuclear Medicine and begun its activity in this year.

A method for HIMAC radiotherapy planning using C-11-methionine PET and MRI/CT fusion image was developed in cooperation with head and neck oncologist group of our hospital for brain and head and neck cancer patients. Malignant gliomas are the most common primary brain tumors in adults. CT and MRI are the standard diagnosis methods and treatment planning of malignant gliomas. PET enables observation of the biological pathways of tumors, giving additional information about metabolism, physiology and molecular biology of tumor tissue. One of the most important tracers for diagnosis of gliomas is C-11-methionine. The image fusions between PET and planning CT (PET/CT) were performed manually with a treatment planning system, Pinnacle. Target delineation in PET/CT fusion was used for practical carbon ion

radiotherapy.

F-18-FLT PET imaging for carbon ion radiotherapy patients was started in cooperation with Diagnostic Imaging Group of Molecular Imaging Center. F-18-FLT is a thymidine derivative that can image tumor cell proliferation. It is considered a good candidate for a marker of therapeutic response. We started to apply this tracer for assessment of carbon ion radiotherapy effect for patients with lung cancer. Comparative discussion of F-18-FLT with C-11-methionine will be made.

A new PET/CT was introduced in our department this year. We have set the environment for clinical study, and we checked its performance according to NEMA NU-2001.

2) Image processing research team

Clinical experience with charged particle beam treatment at several institutions has demonstrated superior dose conformation in comparison to photon beam therapy.

Organs in the thorax and abdomen may move significantly during respiration, complicating treatment in these locations. Voluntary or forced breath-hold techniques have been proposed to reduce or eliminate the effects of breathing during both imaging and radiotherapy treatment, but these approaches prolong treatment and in many cases, are poorly tolerated by patients. Respiratory motion during treatment results in uncertainties, especially, when irradiating with heavy charged particle beams. During respiration, the radiological pathlength can vary as a function of time, as organs move in and out of a given ray, or as the density of voxels along the path change. There is a need to appreciate these temporal variations in the planning process. We quantified range variations due to intrafractional motions (respiratory and heart beat) and interfractional changes (tumor shrinkage, chest wall thickness, density changes etc.) using single/serial 4DCT lung data.

3) Quality control research team

As for hadron therapy, the team studied both ab solute and relative dosimetry. Graphite calorimeter was developed for absolute dosimetry, since the uncertainty of dosimetry with ionization chamber was relatively large due to the uncertainty of w-value for hadron beams. The calorimeter showed experimentally good linearity of response as a function of absorbed dose with uncertainty less than 1%. Regarding relative dosimetry new multi-layer ionization chamber (MLIC) was developed for daily depth-dose measurement. Tissue equivalent materials were adopted for the new MLIC to improve the effect of nuclear fragmentation. Depth-dose curve measured by the new MLIC showed good agreement with the depth dose distribution in water. New calculation method was also developed for evaluation of output factor for small field size. The calculation was based on empirical formula taken from HIMAC experiment and showed good agreement with measurements within ±1 % down to 20mm square field. These achievements were applicable to QC and QA for hadron therapy.

As for photon therapy, new treatment planning systems, XiO and Pinnacle, were introduced to NIRS hospital. Before the systems were used clinically, the team had carried out comprehensive commissioning, which based on international standards such as IAEA, AAPM and ESTRO guidelines. The team were also conducting periodic QA system after the commissioning. NIRS is the Secondary Standard Dosimetry Laboratory (SSDL) in radiation therapy. To establish nation-wide external audit system for dosimetry in photon therapy, the team carried out pilot study in which postal glass dosimeters were sent to approximately 100 radiation therapy centers in Japan. Each center was requested to irradiate 1 Gy to the postal dosimeter in the standard condition defined the dosimetry protocol. The dose irradiated to postal glass dosimeter was estimated using the calibration coefficient of the dosimeter, which was determined at SSDL. The pilot study showed 1.6 % standard deviation of dose among 100 centers. The maximum deviation exceeded 5 % for a center. The team tried to improve the deviation by consultation with a personnel of the center. Finally, every center satisfied 5 % level criteria. Comparative study was also done between the glass dosimeter and TLD which had been used as postal dosimeter. The results showed that glass dosimeters were appropriate for the postal dose audit with their promising features. The team also preformed similar study to Asian countries, China and Korea. The results of two facilities for each country showed good agreements within 2 %.

4) Radiological protection research team

As dose estimations in FY2006, patients' doses of X-ray CT examinations were estimated by the measurements using physical anthropomorphic phantoms of adult and child with Thermoluminescence dosimeters (TLDs) encapsulated in glass for several X-ray CT apparatuses and their conditions of diagnoses in hospitals. Each organ dose was directly measured by dosimeters put in the organ position inside the phantoms, and effective doses were calculated by multiplying radiation and tissue weighting factors of ICRP Publication 60. There were differences of estimated doses among X-ray CT apparatuses and conditions. Patients' doses of developing 256-slice CT scanner examinations were also measured and reported.

Since the heavy ion radiation therapies performing in NIRS etc. are state-of-the-art technologies in radiology, any regulatory system of their specific radiation protection for occupational exposures has not been established in Japan. For considering the propriety to apply current regulatory system for the therapies, occupational exposures of radiation workers in domestic heavy ion radiation therapy institutions were estimated by the measurements of exposures radiated from activated materials of accelerators and phantoms as alternatives of patients in cooperation with researchers of other institutions. The results show that no specific regulation except current one is needed considering the measured data.

As internal dose calculations, dose estimations of patients on nuclear medicine include a lot of uncertainties caused by the parameters and calculation models themselves. Using a voxel phantom and Monte-Carlo simulation method, the uncertainties were evaluated in some injection cases of radiopharmaceuticals. The distributions of doses varied depending on the conditions of the injections and patients.

The surveys of medical radiation usage have long been continuously performed in our section of NIRS. In FY2006, X-ray CT examinations were selected as the survey subject, and a nationwide survey on X-ray CT diagnoses was done sending questionnaires to hospitals and clinics possessing X-ray CT. The kinds of diagnoses, frequencies, exposure positions of patients, setting parameters of apparatuses, patients' data such as age, sex etc. were inquired in the questionnaires, and the analyses of the data of returned questionnaires are in progress.

The results of the previous survey on annual examination data of nuclear medicine in 1997 were reported. The total number of examinations on nuclear medicine was 1.56 million, and collective effective dose was estimated as approximately 3.33x104 man Sv based on ICRP Publ. 53 and 80. The analyses of recent survey data on nuclear medicine are in progress.

Major Publications :

1) S. Mori, K. Nishizawa, M. Ohno, M. Endo. Conversion factor for CT dosimetry to assess patient dose using a 256-slice CT scanner, *Br. J. Radiol, 79,* 888-892, 2006.
2) M. Matsumoto, K. Nishizawa, K. Iwai, K. Akahane, T. Maruyama. Nationwide survey of nuclear medicine practice and estimation of collective effective dose in Japan, *Jpn. J. Med. Phys., 26,* 75-82, 2006.
3) S. Mori, M. Endo, S. Kandatsu et al, 'A combination-weighted Feldkamp-based reconstruction algorithm for cone-beam CT', *Phys. Med. Biol, 51,* 3953-3965 (2006)
4) Y. Kusano, T. Kanai, Y. Kase, N. Matsufuji, M. Komori, N. Kanematsu, A. Ito and H. Uchida, Dose contributions from large-angle scattered particles in therapeutic carbon beams, *Medical Physics, Med. Phys., 34*, 193-198, 2007
5) Y. Kutsutani-Nakamura, S. Sakata, K. Tabushi, H. Mizuno, T. Ishii, Mohd Moktar bin Nudin, N. Xuan Cu, L. Dong Han, Rafael Cabrigas Solis, Y. Naiguo, L. Apipunyasopon, Chumpot Kakanaporn, K. Hozumi, T. Teranaka, H. Tsujii, Field survey of Physical QA/QC for intracavitary brachytherapy of the uterine cervical cancer in 7 countries of East Asia, *Jpn. J. Med. Phys., 26*, Sup. 3, 173-174, 2006

3.4. RadGenomics Project for Radiotherapy

Takashi Imai, Ph. D.
Director

Outline of Research Career :

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

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Objectives :

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

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

Progress of Research :

Patients

The 2,090 patients who were registered between 2001 and 2007 included 703 breast cancer patients, 272 cervical cancer patients, 461 prostate cancer patients, and 278 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.

On-chip optical detection system for allele-specific extension of 3'-LNA modified oligonucleotides

SNPs are useful as genetic association markers for various human diseases as well as for prediction of individual responses to therapeutic treatment such as drugs and ionizing radiation. For routine molecular biology research and bedside clinical diagnosis, readily available technologies are required to genotype limited numbers of SNPs that were selected in previous large scale association studies. To this end, easy and rapid protocols with inexpensive instruments running at reasonable cost are required for the technology to be widely adopted.

In the present work, a novel optical detection system for on-chip allele-specific primer extension has been developed to conveniently genotype multiple SNPs. Optimization of the procedure was achieved by i) locked nucleic acid (LNA) modification of the 3'-end of immobilized oligonucleotide primer, ii) titration of magnesium concentration of the reaction mixture iii) utilization of optimum reaction temperature. Efficient primer extension without an annealing step using

double-stranded template DNAs was demonstrated for LNA-modified oligonucleotides immobilized on an S-Bio PrimeSurface plastic base. This property provided simplification of experimental procedures and reduction of reaction time to as short as 10 minutes at a constant temperature of 65°C. Incorporation of biotin-dUTP during primer extension, followed by binding of alkaline phosphatase-conjugated streptavidin, allowed optical detection of the typing results through precipitation of colored alkaline phosphatase substrate onto the surface of the plastic base. Oligonucleotide primer sets were designed to genotype three SNPs in the genes APEX1, TGFB1 and SOD2, previously investigated for association with radiation sensitivity. The simultaneous evaluation of these SNPs in 25 individuals has produced considerably reliable results.

The experimental system developed in this study is not oriented towards high throughput analysis. Rather, limited numbers of SNPs are easily analyzed within a couple of hours. Dividing the surface of the plastic base into multiple areas can increase the number of individuals analyzed per chip without affecting experimental processes. In conclusion, all the benefits described above make this system applicable to routine molecular biology research and bedside clinical diagnosis.

Microarray analysis of the transcriptional response to carbon ion irradiation in murine tumors

The purpose of this study was to identify molecular mechanism induced by carbon ion radiotherapy in order to provide information on potential targets for prediction of its effectiveness. Murine squamous cell carcinomas, NR-S1 (resistant to gamma-irradiation), and SCCVII (sensitive), were transplanted in hind legs of C3H/He male mice and established solid tumors (7.5-8.5 mm in diameter) were locally irradiated with carbon ion beam at 30 Gy. Carbon-12 ions were accelerated by the Heavy Ion Medical Accelerator in Chiba or HIMAC synchrotron up to 290 MeV/u with a dose rate of approximately 3 Gy /min. Tumor growth delay (TGD) time, reduction rate of tumor, and recurrence rate of tumor were investigated as parameters of radiosensitivity of tumors. The mice were sacrificed and immediately dissected before irradiation and after different time points, such as 6, 12, 18h, 1, 3, 5, 7, 10, 15, 20 days after irradiation or recurrence for transcriptome assays and pathological investigation. Expression analyses were performed using single-color analysis microarrays consisting of 55k genes. Principal Compornent Analysis (PCA) was used to investigate similarity of comprehensive overview of the changes in gene expression between expression profiles of two tumors. Analysis of variance (ANOVA) was applied to the intensity of each tumor at different time point to evaluate significant differences.

Results: TGD time of NR-S1 and SCCVII was 30 days and 56 days, reduction rate of NR-S1 and SCCVII was 40% and 100%, and recurrence rate of NR-S1 and SCCVII was 75% and 50%, respectively. PCA showed that all expression profiles of NR-S1 were identified as a group, while those of SCCVII were identified as another group. Recurred tumors showed different profiles from non-irradiation control tumors. We detected genes, whose expressions were significantly up-regulated or down regulated at each time point after carbon-irradiation (p value < 0.0001). At 6 hours after irradiation, fourteen genes, which were related with cell cycle regulation, were differentially expressed in both tumors. Eleven genes, which were related with inflammation or extracellular matrix, were up-regulated at 6 hours in both tumors, however, their expression changes on time-course were different. Pathological specimen showed duplet cells in both tumors 1 day after irradiation and continuous infiltration of inflammatory cells in SCCVII.

Conclusions: Tumor growth assays revealed that two murine tumors, which have different radiosensitivity to gamma irradiation, kept their intrinsic radiosensitivity to carbon-ion irradiation. Transcriptional profiling of two tumors identified a number of carbon-ion irradiation response genes in murine tumors. We have also identified genes as being candidates for predictive markers of radiosensitivity to carbon-ion therapy.

Correlation between single nucleotide polymorphisms and jejunal crypt cell apoptosis after whole body irradiation

To identify loci concerned with radiosensitivity in a mouse model using SNP markers. We subjected 276 second filial generation (F2) mice descended from two inbred mouse strains, radiation-induced apoptosis sensitive C57BL/6JNrs (B6) and radiation-induced apoptosis resistant C3H/HeNrs (C3H), to 2.5 Gy whole-body irradiation. We quantified jejunal crypt apoptosis, performed a genome-wide survey, and identified quantitative trait loci (QTL) associated with radiation sensitivity. We expressed apoptosis levels as an apoptotic score (AS), which was equal to the number of apoptotic bodies divided by the number of crypts. We genotyped the mice for 109 SNP markers. AS values were 97.7+/-32.9 in B6 mice and 49.0+/-24.9 in C3H mice ($p < 0.01$). Genome-wide analysis revealed 8 markers (2 on chromosome 9, 4 on 15, 1 on 17, and 1 on 18) affecting radiation-induced jejunal apoptosis with log odds (LOD) scores ranging from 2.11+/-3.91. We found a significant locus on chromosome 15, which was previously reported by Weil and colleagues. These findings support the view that the radiosensitivity of clinically normal tissue depends on variations in several genes.

Human RAD18 is involved in S phase-specific single-strand break repair without PCNA monoubiquitination

Switching from a replicative to a translesion polymerase is an important step to further continue on replication at the site of DNA lesion. Recently, RAD18 (a ubiquitin ligase) was shown to monoubiquitinate proliferating cell nuclear antigen (PCNA) in cooperation with RAD6 (a ubiquitin-conjugating enzyme) at the replication-stalled sites, causing the polymerase switch. Analyzing RAD18-knockout (RAD18-/-) cells generated from human HCT116 cells, in addition to the polymerase switch, we found a new function of RAD18 for S phase-specific DNA single-strand break repair (SSBR). Unlike the case with polymerase switching, PCNA monoubiquitination was not necessary for the SSBR. When compared with wild-type HCT116 cells, RAD18-/- cells, defective in the repair of X-ray-induced chromosomal aberrations, were significantly hypersensitive to X-ray-irradiation and also to the topoisomerase I inhibitor camptothecin (CPT) capable of inducing single-strand breaks but were not so sensitive to the topoisomerase II inhibitor etoposide capable of inducing double-strand breaks. However, such hypersensitivity to CPT observed with RAD18-/- cells was limited to only the S phase due to the absence of the RAD18 S phase-specific function. Furthermore, the defective SSBR observed in S phase of RAD18-/- cells was also demonstrated by alkaline comet assay.

Major Publications :

1. Y. Michikawa, K. Fujimoto, K. Kinoshita, S. Kawai, K. Sugahara, T. Suga, Y. Ootsuka, K. Fujiwara, M. Iwakawa, T. Imai: Reliable and Fast Allele-Specific Extension of 3'-LNA Modified Oligonucleotides Covalently Immobilized on a Plastic Base, Combined with Biotin-dUTP Mediated Optical Detection, *Anal Sci, 22,* 1537-1545, 2006
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3. S. Nakajima, M. Mori, T. Shiomi, A. Yasui, et. al: Replication-dependent and -independent responses of RAD18 to DNA damage in human cells, *J Biol Chem,* 281, 34687-34695, 2006
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5. M. Iwata, M. Iwakawa, S. Noda, T. Ohta, Y. Minfu, T. Kimura, H. Shibuya, T. Imai: Correlation between single-nucleotide polymorphisms and jejunal crypt cell apoptosis after whole body irradiation, *Int J Radiat Biol, 83*: 181-186, 2007

3.5. Biological Research Concerning the Improvement of Radiation Therapy

Ryuichi Okayasu, Ph. D.
Director

Outline of Research Career :

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

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Objectives :

There are three mid-term plans for this group. These are 1) To provide biological experimental data for analyzing clinical data with regard to tumor control ratio and normal tissue responses for various radiation therapy protocols, 2) 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. To propose more efficient radiation therapy regimen by comparing heavy ion radiotherapy and other radio-therapy protocols such as use of X-rays, and 3a) To explore radio-sensitizers and protectors which could be used with heavy ion radiotherapy, 3b) To elucidate the mechanism of effective heavy ion treatment for hypoxic tumor cells which show strong resistance to radiation, 3c) To study the indirect (bystander) effects of radiation which occur in non-irradiated cells adjacent to irradiated cells, 3d) To integrate the above proposals to improve radiation therapy and accumulate the biological data resources for a new cancer therapy. These objectives are studied by four teams including 1) Biophysics Team, 2) Experimental Therapy Team, 3) Cellular and Molecular Biology Team and 4) Radiation Modifier Team. Each team has different objectives, however, co-operations among four teams are sought in order to accomplish the goals of this group.

Progress of Research :

Biophysics Team :

Concerning the modification of RBE values, we found that the repair efficiencies with and without existence of oxygen are different in DNA double strand breaks (DSB) induced by X-rays or carbon ions. These data indicate that there are indirect effects of radiation damage even in cells irradiated with high-LET radiation. The RBE spectra for chromosome aberrations and remaining DNA damage after repair process are not only LET dependent but also dependent on the kinds of accelerated ions. The RBE of cell killing at very high-dose region that could not be estimated by calculation was obtained experimentally. We investigated the radiosensitivity and the remaining number of chromatin breaks using cells derived from a cervical cancer patient. These studies eventually lead to the undertaking of carbon therapy for a patient with osteosarcoma and genomic instability. This is a good example of application of radiation biology for tumor treatment. Experiments on bystander effects with micro beams were started at TIARA/JAERI, PF/KEK, and Spring-8/JASRI. We found bystander effects in normal human cells irradiated with low energy carbon ions. These effects seem to depend on the number of particles of accelerated ions. Experiments concerning the inter-comparison of RBE among domestic and/or international ion-beam radiotherapy facilities were completed.

Experimental Therapy Team :

The mouse legs were locally irradiated once with carbon ions with various LET values, and the effect of LET on tumor incidence was studied. Life time observations indicated that there was no difference in the induction of tumors between gamma-ray and carbon irradiated mice. Our data also demonstarted the higher tumor inductions with the higher radiation doses. Furthermore, to our surprise, the tumor induction with 15 KeV/μm carbon irradiation is lower than that with gamma-irradiation.

New studies on tumor heterogeneity were started using the mixture of two tumor types with varying radio-sensitivity. These mixed tumors were implanted on the leg of mice and the tumor sensitivities were

compared with those of mice implanted with one tumor type. Among three mixed tumor groups, one showed a different sensitivity when compared to the control with single tumor type. These studies indicate the importance of tumor heterogeneity and warrant further studies.

Cellular and Molecular Biology Team :

Biological differences between X-ray and heavy ion particle (C, Fe, Ne) irradiation were investigated using some quantitative assays (H2AXγand PCC), focusing on the molecular mechanism in the early responses of DNA damage at the therapeutic level radiation doses. Comprehensive gene expression techniques were employed to several human cell lines which were irradiated with X-rays and carbon ion particles at the doses of therapeutic relevance. Both DNA microarrays and HiCEP, a novel gene expression profiling technique developed in our institute, successfully demonstrated some characteristic feature of the molecular signatures to those different types of ionizing radiation (IR).

One of the potent radio-sensitizers, 17-AAG was intensively studied in our laboratory. We demonstrated that 17-AAG could enhance the radio-sensitivity in some cancer cell lines irradiated with X-rays as well as carbon ions. In this fiscal year, we obtained significant evidence that 17-AAG inhibits the repair of DNA DSBs, especially homologous recombination repair, induced by IR. Yeast extract is a potential radio-protector whose effect was ever shown in vivo (mice). In order to find out the cellular and molecular mechanism for this protective effect, in vitro study has just started in our lab using cell lines treated with the yeast extract. We also studied the function of specific DNA DSB repair proteins using RNA interference strategy. For example, BRCA siRNA was found to enhance the radiation sensitivity in HeLa cells by inhibiting repair of DSBs.

Radiation Modifier Team :

The radiation modifier team has studied three subjects and obtained following results.

1) In order to develop better compounds for free radical scavenging, several novel compounds of vitamin E analog, containing (-chromane ring structure as well as basic pyridine moiety, were synthesized. By the kinetic study of their *in vitro* free radical scavenging reaction, we found that one of these compounds has a scavenging rate constant three times larger than that of natural vitamin E.

2) For the study of radioprotector, two vitamin E analogs were examined. Both tocopherol monoglucoside (TMG) and γ-tocopheryl-N, N-dimethylglycine (γ-TDMG) showed significant *in vivo* radioprotection activity against the lethal dose of whole body X-irradiation (7.0-7.5 Gy). It is interesting that both compounds showed the radiation protection effect even by post-irradiation administration. Another compound, α-Lipoic acid, was found to be a good protector for brain. The cognitive dysfunction of mice caused by X-irradiation was ameliorated by the administration of α-lipoic acid before irradiation.

3) For the study of redox- and oxygen-mapping, the resolution and signal to noise ratio of EPR imaging and T1-weighted MRI were compared using an identical phantom. Several solutions of nitroxyl contrast agents with different EPR spectral shapes were tested. T1-weighted MRI can detect nitroxyl contrast agents with a complicated EPR spectrum easier and quicker ; however, T1-weighted MRI has less quantitative ability especially for lipophilic nitroxyl contrast agents, because T1-relaxivity, i. e. accessibility to water, is affected by the hydrophilic/hydrophobic micro-environment of a nitroxyl contrast agent. The less quantitative ability of T1-weighted MRI may not be a disadvantage of redox imaging, which obtains reduction rate of a nitroxyl contrast. Therefore, T1-weighted MRI has a great advantage to examine the pharmacokinetics of newly modified and/or designed nitroxyl contrast agents.

Major Publications :

1) K. Ando, S. Koike, A. Uzawa, N. Takai, T. Fukawa, Y. Furusawa, M. Aoki, R. Hirayama : Repair of Skin Damage During Fractionated Irradiation with Gamma Rays and Low-LET Carbon Ions. *J. Radiat. Res., 47,* 167-174 (2006).

2) M. Suzuki, C. Tsuruoka, T. Nakano, T. Ohno, Y. Furusawa, R. Okayasu, The PCC assay can be used to predict radiosensitivity in biopsy cultures irradiated with different types of radiation. *Oncol. Rep., 16,* 1293-1299 (2006).

3) M. Noguchi, D. Yu, R. Hirayama, Y. Ninomiya, E. Sekine, N. Kubota, K Ando, R. Okayasu : Inhibition of Homologous Recombination Repair in Irradiated Tumor Cells Pretreated with Hsp90 Inhibitor 17-Allylamino-17-demethoxy geldanamycin. *Biochem Biophys Res Commun.* 351, 658-663 (2006).

4) K. Anzai, M. Ueno, A Yoshida, M. Furuse, W. Aung, I Nakanishi, T. Moritake, K. Takeshita, N. Ikota, "Comparison of Stable Nitroxide, 3-Substituted 2,2,5,5-Tetramethylpyrrolidine-N-oxyls, with Respect to Protection from Radiation, Prevention of DNA Damage, and Distribution in Mice", *Free Radic. Biol. Med., 40,* 1170-1178 (2006).

5) K. Manda, M. Ueno, T. Moritake, K. Anzai, "Radiation-induced cognitive dysfunction and cerebellar oxidative stress in mice : Protective effect of ? -lipoic acid", *Behav Brain Res. 177,* 7-14 (2007).

3.6 Transcriptome Research for Radiobiology

Masumi Abe, Ph. D.
Director

Objectives :

Long-range objectives of the 2nd 5-year project (2007-2011)

1) Establishing a high throughput system of HiCEP analysis for dealing with a large number of samples such as clinical samples.
2) Developing a HiCEP protocol for blood analysis.
3) Developing an assay system for genome reprogramming.
4) Functional study using gene knockout mice, in which genes identified by transcriptome analysis were disrupted.

Progress of Research :

For 1), we developed an automatic HiCEP reaction machine (designated as HiCEPer), which achieves simultaneous 96 reactions with 3 days. This enables us to perform 10,000 reactions per year and to apply the analysis for many applications such as diagnosis, human molecular epidemiology and so on. In addition, we improved the system of capillary electrophoresis, so that 48 simultaneous runs for HiCEP analysis became possible.

For2), our proposals for medical use of HiCEP have been discussed by the ethical committee of our institute. Then, that for esophageal cancer was just authorized and the other for blood use is under consideration.

For3), genome reprogramming occurs some particular situations such as when the oocyte nucleus was replaced by the nucleus of differentiated cell, or when differentiated cells were fused with stem cells such as ES cells. In both cases, the genome status underlying the differentiated cell converts to that underlying undifferentiated cells, which have a pluripotency.

In order to establish an assay system for genome reprogramming, we attempted to prepare a differentiated cell line in which reporter gene is existed just downstream of stem-cell specific promoter. The reporter will express only when their genome was reprogrammed by certain stimulus such as gene transfection. More details, we generated lacZ-knockin ES cells by means of the homologous recombination technique, in which reporter gene is controlled by stem-cell specific promoter that was identified by us. With this ES cells, we generated a knockin mice, from which we generated fibroblast cell lines. Thus, this system allows us to assess candidate genes, because if the fibroblast cells were reprogrammed by the candidates, the reporter gene would be expressed.

In addition, we performed functional analyses of the four genes utilizing their knockout mice, which were g enerated last year. Two lines out of the four strains, abnormal chromosome integrity, radiosensitivity, oncogenesis and rapid aging have been suggested. One out of the four, defects of circadian rhythm and carcinogenesis have been also suggested. The remaining one showed a male infertility. Detail analysis of their testis suggested a severe defect in spermatogensis.

HiCEP Project : Development of a Next-generation Gene Expression Profiling Technology

Progress of Research

We have developed a new gene expression profiling method called HiCEP (High Coverage gene Expression Profiling), whose principle is different from that of DNA micro-array technology. So far fundamentals of the technology have been achieved; now, we are currently focusing on the development of a high throughput system for the analysis and of the protocol for the analysis using a small amount of starting materials. This project has been supported by Japan Science and Technology (JST) for 5 years.

Aims in 2006 were :

1) Developing an automatic HiCEP reaction machine (designated as HiCEPer)

2) Developing a procedure for the analysis using a small amount of starting materials : 0.5-1.0 ng of total RNA which is corresponded to 50 to 100 eukaryotic cells.

Results

1) We have been developed an automatic HiCEP reaction machine. This year we finally achieved the expected performance. 96 reactions can be performed simultaneously with 3 days by HiCEPer, enabling us to conduct 10,000 reactions per year. A durability test showed some problems but all of them have been overcome.

2) Developing a procedure for the analysis using a small number of cells :

We succeeded in HiCEP analyses using 0.5-1 ng of total RNA. During this study, we faced a contamination of other unknown organisms into the reaction mixture. Especially under 100 cells analysis, this problem became severe. Even without any RNA, we detected the peak pattern clearly. Cloning of the peaks and following sequencing of them disclosed that these peaks come from microorganism like psuedemonus. We checked all reagents in the HiCEP reaction and replaced some reagents in which contamination was suggested. Now, we overcome the contamination problem ; therefore it became possible to examine the reaction condition for the HiCEP analysis using less than 100 cells. 100-cells HiCEP analysis allows us to conduct transcriptome analysis following FACS sorting or LMD (Laser Microdissection).

4. Molecular Imaging Center

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

Outline of Research Career :

Iwao Kanno started his professional job at Akita Research Institute of Brain and Blood Vessels in 1970, where his major activities were carried out until 2006 for 36 years. He firstly developed a custom radionuclide emission tomography using handmade rotational dentist chair in 1977. Then, he developed the hybrid type emission tomography which enabled to assess positron emission tomography (PET) and single photon emission computed tomography (SPECT) in collaborating with medical company in 1979. His efforts were also paid to develop methodology for quantitative assessment of physiological and biochemical parameters from PET and SPECT images. He developed quantitative method for cerebral blood flow and cerebral oxygen metabolism from Oxygen-15 PET images in mid 1980's. His interests were gradually turned to the brain physiology of circulation and metabolism mechanism to adapt to the neurovascular coupling during neuronal activation, which is essential to understand functional brain mapping using magnetic resonance imaging and near infrared topography.

Objectives :

Progress in molecular biology has opened the field to understanding the molecular mechanism of living healthy and diseased organs. Molecular imaging is a new interdisciplinary field that integrates imaging technology and molecular biology to help visualize molecular behavior spanning the microscopic to macroscopic scales. Positron emission tomography (PET), magnetic resonance imaging (MRI) and optical imaging will provide clear and comprehensive images demonstrating molecular function. Molecular Imaging Center consists of four research groups, Diagnostic Imaging Group, Molecular Neuroimaging Group, Molecular Probe Group and Biophysics Group, and Research Promotion Unit. Molecular Imaging Center aims to image molecular function of living animals in health and diseases. Of several methodologies for imaging molecular functions, this center covers in vivo molecular imaging from rodents to humans. Molecular Imaging Center is already a world leader in the development of PET probe and technology, and also invested in other promising technologies such as MRI. Our final goal is understanding mechanism of brain function and cancer pathology and use these knowledge in clinical applications.

Overview :

Diagnostic Imaging Group started clinical PET study with FLT, a marker of cell proliferation, in the evaluation of effectiveness of carbon ion radiotherapy in lung cancer patients in collaboration with the Research Center for Charged Particle Therapy. Multi-center study of PET with ^{62}Cu-ATSM, a marker of tumor hypoxia, has also been stated. Functional analysis of cancer-related genes such as radiation susceptibility genes in cells and model animals in search of specific targets of molecular imaging was performed using an RNA interference library targeting 200 genes in human cells. Novel targets of imaging by means of gene expression analysis and metabolome analysis was investigated. Mass screening for genes related to the proliferation of mesothelioma cells was performed using RNA interference. Animal models for the evaluation of imaging probes were developed. PET/SPECT tumor imaging using antibody probes was developed. Investigation on the use of anti-c-kit monoclonal antibody in imaging c-kit-positive tumors such as gastrointestinal stromal tumors (GIST) has started. Novel reporter gene imaging was developed. In vitro experiments demonstrated that cells transiently expressing ferritin heavy chain (FHC) gene showed increased cellular uptake of iron resulting in the decreased T2 weighted (T2W) MR signal in the cell pellets. Search for specific molecular target of asbestos-induced mesothelioma imaging through investigation of the mechanism of carcinogenesis was investigated.

Molecular Neuroimaging Group carried out mapping of peripheral benzodiazepine receptors in Alzheimer's disease. Normal database for the pre- and postsynaptic dopaminergic functions in the living human brain using PET was constructed. Dopamine transporters in schizophrenia using [^{11}C] PE2I were measured and no significant difference was observed between schizophrenia patients and controls in any brain regions. Regional differences in receptor occupancy by antipsychotic drugs were investigated and found no regional difference in occupancy of dopamine D2 receptors by atypical antipsychotic drug. Clarification of molecular mechanisms linking imaging-based biomarkers and psychiatric symptoms by behavioral analyses was carried out. Further investigations of transgenic

mouse models using PET and [^{18}F] fluoroethyl-DAA1106 also revealed deleterious roles of activated microglia in the Alzheimer's disease pathogenesis (Neuron, 2007). In vivo studies of monkeys and rats using PET and [^{11}C] MNPA, a novel agonistic PET tracer for dopamine D2 receptor, indicated that changes in the release of endogenous dopamine after pharmacological challenges is measurable in the living brains. Functional roles played by the central substance P neurotransmission system by in vivo imaging of substance P receptors were elucidated. [^{18}F] fluoroethyl-SPA-RQ, delineated consistency in the distribution of the central substance P receptors across species and potential utility of these animals for preclinical assessments of pharmaceutical agents targeting the substance P neurotransmission (Synapse, 2007).

Molecular Probe Group was carried out the probe study for assessment of glutathione S-transferase activity, a key enzyme related with GSH maintenance, in the brain. Targeting multidrug resistance-associated protein (MRP), 6-halo-purine derivatives were designed on the basis of a metabolite extrusion method. On the probe imaging tumors, a novel thymidine analog, 4'- [methyl-^{14}C] thiothymidine ([^{14}C] S-dThd), was further evaluated to assess DNA synthesis in tumor cell proliferation. The resulted in that [^{14}C] S-dThd is a promising marker of DNA synthesis. A novel ligand (PTBN), a selective antagonist of mGluR5, was designed and evaluated on PET probes to assess brain glutamate receptor. Probes for protein-kinase C and for ^{18}F-alternative to assay AChE were evaluated. A practical route for preparing [^{18}F] ligand containing [^{18}F] fluorobenzene moiety was developed by employing a reaction of diphenyliodonium salt with [^{18}F] F-. [^{11}C] Acetyl chloride ([^{11}C] AcCl) as a labeling precursor was synthesized using a loop method by reacting methylmagnesium bromide with [^{11}C] CO_2, followed by treatment with thionyl chloride or oxalyl choride. A new labeling method generating^{11}C-C bond was developed by using [^{11}C] nitromethane. In vitro binding of [^{11}C] raclopride with ultra-high specific activity (SA) in the striatum and cerebral cortex of rat brain was characterized. Novel ligand, [^{11}C] AC-5216, was synthesized and evaluated as a PET ligand for imaging PBR in primate brain. A new irradiation system using vertical beams was developed for the production of positron emitters. A new production unit using [^{18}F] F2 as a synthetic precursor was developed for the versatile PET radiopharmaceutical production apparatus. The radionuclide ^{62}Zn was produced by the nuclear reaction ^{63}Cu (p, 2n) ^{62}Zn with the big cyclotron at NIRS. The ^{62}Zn/^{62}Cu generator was prepared remotely and distributed to 3 PET facilities (Fukui Univ., Yokohama City University, National Cancer Center). Sensitive and rapid high-performance liquid chromatographic methods were developed. Six new PET radiopharmaceuticals ([^{11}C] BF227, [^{18}F] FLT, [^{18}F] NaF, [^{18}F] FMeNER-d2, [^{18}F] FEtSPARQ and [^{61}Cu] ATSM) were released for the clinical use and approved by the Institutional Review Board at NIRS.

Biophysics Group carried out ^{19}F high sensitivity imaging for in vivo drug dynamics performed in mice at 7T with 5-FU. Imaging most of ^{19}F metabolites of 5-FU in mice is successful at 7T by using minimal TE of FISP and FSE under the dose of 2 mmol 5-FU/kg, p. o. Imaging using MRI high sensitive quadrature and 4ch phased-array RF coils were prepared for rat brain imaging on high field 7T MRI system. Biosignal Physiology Team covers two kinds of signals, human MRI data and animal two-photon microscopy data. Long-term monitoring of in vivo [1-13C] glycogen storage/degradation in the liver was achieved in healthy volunteers (n=5) and diabetic patients (n=5). T2 measurement was performed in an oblique coronal plane, which was passed through the center of the femoral head, was acquired using a 3.0 Tesla system. The ADC value of Pca increases after radiation therapy, becoming close to those of intact inner gland (IG) and peripheral zone (PZ). Although fraction anisotropy is not useful for distinguishing Pca because of the overlaps among Pca, intact IG and PZ, DTI is able to show changes in the prostatic structure. Magnetic resonance elastography (MRE) methods deform the sample using external vibration system. The healthy young subjects continuously performed the two- or three-back (N-back) working memory task. Image Analysis Team aims to calculate accurate and quantitative biological parametric images of brain functions from dynamic PET images following administration of the radioactive probes. Imaging Physics Team demonstrated the capability of 8-layer depth-of-interaction (DOI) encoding on a PET detector.

4.1. Research on Molecular Imaging of Cancer

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

Outline of Research Career :

Dr. Saga received a Ph. D. from Kyoto University in 1991 for his investigations on cancer targeting of radiolabeled monoclonal antibodies. He continued his research on antibody targeting at 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 researches covering wide area of cancer imaging. Since 2006, he has been the group leader of Diagnostic Imaging Group at NIRS to further advance the basic and clinical researches on molecular imaging of cancer.

Contact Point : saga@nirs.go.jp

Objectives :

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

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

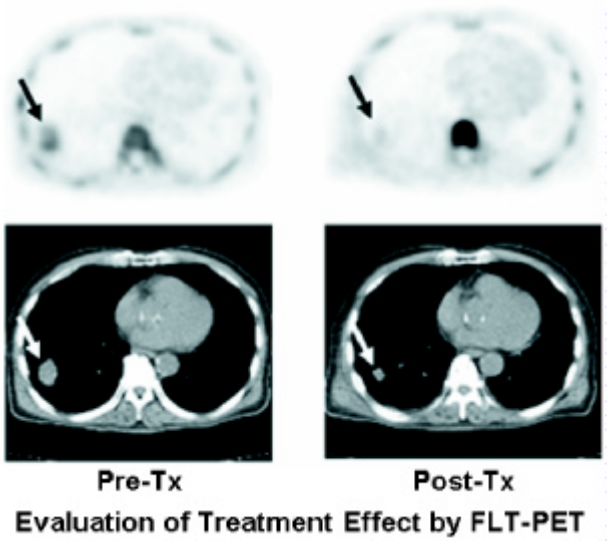
Molecular Diagnosis Team conducts basic molecular imaging research focusing on design and evaluation of PET probes that capture and depict the changes of biomolecules specifically associated with cancer and other diseases to realize effective non-invasive diagnosis. We also are developing novel *in vivo*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

Biomolecule Team focuses on the elucidation of genetic/molecular events occurring during carcinogenesis, searching for suitable targets of molecular imaging of cancer. By means of functional screening of genes related to cell growth or radiation susceptibility, and by proteome analysis of the blood and tissue samples of cancer patients, we select the genes and proteins specifically expressed in cancers. Through the exploration of the targets with high specificity, we are at development of a novel molecular imaging system which can non-invasively depict the characteristics of each cancer.

Progress of Research :

1) Clinical studies on cancer imaging using various PET probes

We started clinical PET study with FLT, a marker of cell proliferation, to evaluate effectiveness of carbon ion radiotherapy in lung cancer patients in collaboration with the Research Center for Charged Particle Therapy. Preliminary data showed that, although significant reduction of FLT tumor uptake was observed three months after the treatment, accurate evaluation of the treatment effect was difficult if FLT-PET was performed immediately after the treatment. In addition, slight uptake of FLT was observed in the area of radiation induced pneumonitis, probably reflecting the activity of fibroblasts related to the remodeling of the irradiated lung tissue.



Evaluation of Treatment Effect by FLT-PET

A multi-center study of PET with ^{62}Cu-ATSM, a marker of tumor hypoxia, has also been stated in collaboration with the Research Center for Charged Particle Therapy. By comparing the therapeutic outcome of radiation therapy and the tracer uptake in a lesion (i. e. the grade of hypoxia), we are expecting to know whether carbon ion therapy is effective irrespective of the presence of tumor hypoxia.

2) Functional analysis of cancer-related genes such as radiation susceptibility genes in cells and model animals in search of specific targets of molecular imaging

We performed cell-based functional screening using an RNA interference library targeting 200 genes in human cells. We identified nine new radiation susceptibility genes, eight of which are linked with cell cycle progression. Cell cycle analysis on four of the genes not previously linked to cell cycle progression demonstrated that one was associated with the G2/M checkpoint in response to DNA damage. Further study of new radiation susceptibility genes should help to elucidate the molecular mechanisms of cell cycle progression, DNA repair, cell death, cell growth and genomic instability, all tightly related to carcinogenesis and cancer progression.

3) Investigation of novel targets for imaging by means of gene expression analysis and metabolome analysis

Mass screening for genes related to the proliferation of mesothelioma cells was performed using RNA interference and it was found that inhibition of 390 genes by corresponding siRNA reduced the proliferation of mesothelioma cells by more than 50%. Many of these genes were related to nucleotide binding factors or receptors and possible targets in imaging and therapy.

Metabolome analysis of various cultured cancer cell lines showed that cancer cells produce more acetate into culture medium than normal cells and that the acetate production in cancer cells further increased under the hypoxic condition, which was not observed in normal cells. Measurement of the mRNA for acetyl-CoA syntase, one of the enzymes involved in acetate production, showed that the mRNA expression of this enzyme in cancer cells was coincided well with the acetate production pattern. The tumor specific acetate metabolism pathway may provide a possible target of cancer imaging.

4) Development of animal models for the evaluation of imaging probes

To facilitate the evaluation of imaging probes, mesothelioma cell lines expressing red fluorescent proteins were established. *In vivo* optical imaging was performed for mice bearing heterotopic (subcutaneous) and orthotopic (pleural) transplant of red fluorescent cells, which gave positive images of the tumor. In addition, the measured fluorescent intensity correlated well with the size of the subcutaneous tumor.

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

Investigation on the use of anti-c-kit monoclonal antibody in imaging c-kit-positive tumors such as gastrointestinal stromal tumors (GIST) was started. Basic *in vitro* characteristics of two radiolabeled antibodies having separate specificity and function were evaluated and it turned out that these antibodies were internalized after binding to the cell surface antigen. For *in vivo* evaluation of radiolabeled antibodies, tumor xenograft model highly expressing c-kit has been established.

In vitro evaluation of radiolabeled monoclonal antibodies recognizing mesothelioma related antigen (ERC/mesothelin) has also been started.

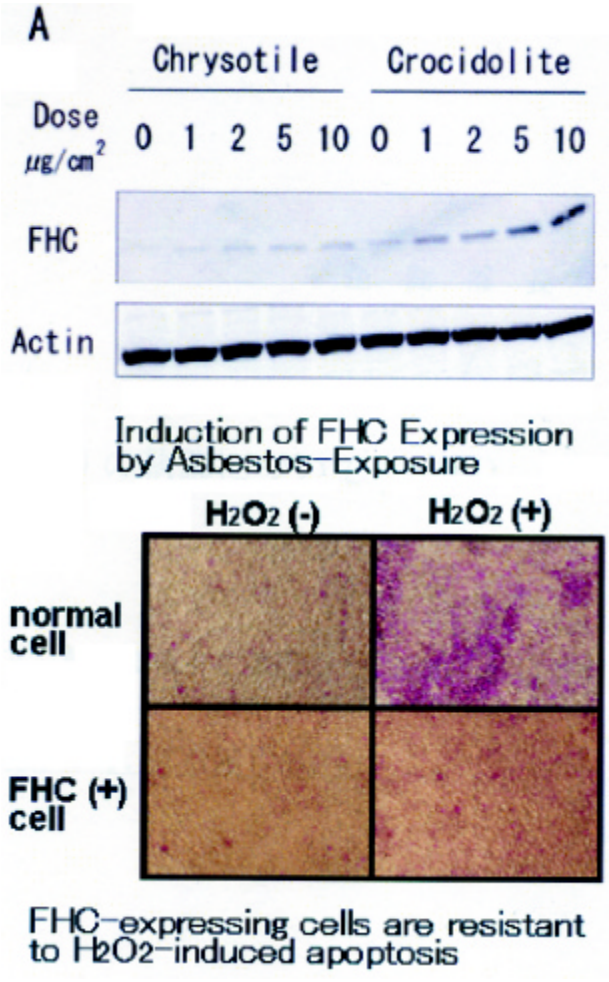
6) Development of novel reporter gene imaging

In order to develop a novel PET/MRI dual modality reporter gene imaging system, various cell lines were established which constitutively or inducibly express ferritin heavy chain (FHC) gene. *In vitro* experiments demonstrated that cells transiently expressing FHC gene showed increased cellular uptake of iron resulting in the decreased T2 weighted (T2W) MR signal for cell pellets. *In vivo* MR imaging of mice transplanted with these cells is now being done.

7) Search for specific molecular target for asbestos-induced mesothelioma imaging through investigation of the mechanism of carcinogenesis

For the early detection of asbestos-induced mesothelioma, we investigated the mechanism of carcinogenesis associated with asbestos exposure. Our

investigation has shown that exposure of normal mesothelial cells to asbestos caused the increased expression of ferritin heavy chain gene. Furthermore, some mesothelioma cell lines also showed an increased level of FCH expression. Mesothelial cells highly expressing FHC were resistant to apoptosis related to asbestos exposure because of the decreased production of reactive oxygen species induced by the exposure. We proposed that the acquired resistance to apoptosis caused mesothelial cells to survive under additional carcinogenic stimuli which led to mesothelioma formation.



Major Publications :

1) Saga T, Kawashima H, Araki N, Takahashi JA, Nakashima Y, Higashi T, Oya N, Mukai T, Hojo M, Nobuo Hashimoto N, Manabe T, Hiraoka M, Togashi K. Evaluation of primary brain tumors with FLT-PET: usefulness and limitation. Clin Nucl Med 31 : 774-80, 2006.

2) Tanaka T, Furukawa T, Fujieda S, Kasamatsu S, Yonekura Y, Fujibayashi Y. Double-tracer autoradiography with Cu-ATSM/FDG and immunohistochemical interpretation in four different mouse implanted

4.2. Molecular Neuroimaging Research

Tetsuya Suhara , M. D., Ph. D.
Director of Molecular Neuroimaging Group, Molecular Imaging Center, NIRS

Outline of Research Career :

Dr. Suhara received the Ph. D. from Jikei University School of Medicine in 1991 for his study of dopamine receptor binding *in vivo.* He joined NIRS in 1989. In 1992-1993, he studied in the PET group of Department of Clinical Neuroscience, Karolinska Hospital, Sweden. He has done research on brain functional imaging for many years. He has served as a visiting professor in the Department of Neuropsychiatry, Nippon Medical School since 2004, and in the Graduate school of Medicine, Yokohama City University since 2006.

Contact point : suhara@nirs. go. jp

Objectives :

1. Clinical Neuroimaging
   1) Mapping peripheral benzodiazepine receptors in Alzheimer's disease
   2) Constructing a normal database for the pre- and post-synaptic dopaminergic functions in the living human brain using PET
   3) Measuring dopamine transporters in schizophrenia using [^{11}C] PE2I
   4) Investigating regional differences in receptor occupancy by antipsychotic drugs

2. Molecular Neurobiology
   1) Clarifying molecular mechanisms linking imaging-based biomarkers and psychiatric symptoms by behavioral analyses and *in vivo* imaging of transgenic mice showing abnormal monoaminergic neurotransmission
   2) Molecular imaging of mice modeling Alzheimer's disease in search of biomarkers useful for diagnosis and treatment of Alzheimer's disease
   3) Measuring endogenous neurotransmitters and their pathophysiological alterations using quantitative PET techniques
   4) Elucidating functional roles played by the central substance P neurotransmission system by *in vivo* imaging of substance P receptors
3. System Neurochemistry
   1) Further understanding of human brain function by investigating the relevant organization of functional localization for higher- cognitive function in underlying neurochemical mechanisms

Progress of Research :

1. Clinical Neuroimaging
   1) Mapping peripheral benzodiazepine receptors in Alzheimer's disease

By applying a wavelet method for reduction of image noise, parametric images of peripheral benzodiazepine receptors could be obtained with [^{18}F] FEDAA1106. Binding potential of [^{11}C] DAA1106 was increased in the brain of Alzheimer's disease patients compared with controls in all measured regions, suggesting a widespread and diffuse existence of glial reactions in early-stage Alzheimer's disease.

   2) Constructing a normal database for the pre- and post-synaptic dopaminergic functions in the living human brain using PET

This database allows the comparison of regional distributions of striatal and extrastriatal dopamine D1 and D2 receptors, dopamine trans porter, and endogenous dopamine synthesis capability. These distributions were in good agreement with those from human postmortem studies.

   3) Measuring dopamine transporters in schizophrenia using [^{11}C] PE2I

No significant difference in binding potential of [^{11}C] PE2I was observed between schizophrenia patients and controls in any brain regions. Although the dopaminergic system is of central interest in schizophrenia, dopamine transporter which is one of the presynaptic functions did not change in schizophrenia.

   4) Investigating regional differences in receptor occupancy by antipsychotic drugs

No regional difference was observed in occupancy of dopamine D2 receptors by atypical antipsychotic drug. This finding does not support the concept of "limbic selectivity" of atypical antipsychotic drug.

2. Molecular Neurobiology

1) Clarifying molecular mechanisms linking imaging-based biomarkers and psychiatric symptoms by behavioral analyses and *in vivo* imaging of transgenic mice showing abnormal monoaminergic neurotransmission

Autoradiography of Ca^{2+}/calmodulin-dependent kinase IIα heterozygous knockout mice, done in collaboration with Dr. Miyakawa, Kyoto University, demonstrated notable abnormalities in the monoaminergic receptors which were tightly correlated with neurobehavioral phenotypes of these animals.

2) Molecular imaging of mice modeling Alzheimer's disease in search of biomarkers useful for diagnosis and treatment of Alzheimer's disease

High-resolution PET scans of transgenic mice exhibiting brain amyloidosis were performed using [^{11}C] PIB, a widely utilized radiotracer for amyloid imaging in humans. These scans were the first successful demonstration that Alzheimer's disease pathology in small animals can be captured by *in vivo* PET systems. By applying this imaging technique, distinct properties of [^{11}C] PIB and [^{11}C] BF-227, a new amyloid probe developed by researchers at Tohoku University, were clarified. Further investigations of transgenic mouse models using PET and [^{18}F] fluoroethyl-DAA1106 also revealed deleterious roles of activated microglia in the Alzheimer's disease pathogenesis (Neuron, 2007).

3) Measuring endogenous neurotransmitters and their pathophysiological alterations using quantitative PET techniques

In vivo studies of monkeys and rats using PET and [^{11}C] MNPA, a novel agonistic PET tracer for dopamine D2 receptor, indicated that changes in the release of endogenous dopamine after pharmacological challenges is measurable in living brains. This system was also proven to be useful for elucidating interactions between glutamatergic and dopaminergic neurotransmissions.

4) Elucidation of functional roles played by the central substance P neurotransmission system by *in vivo* imaging of substance P receptors

PET imaging of rhesus monkeys, marmosets and gerbils with a newly developed radioligand, [^{18}F] fluoroethyl-SPA-RQ, delineated consistency in the distribution of the central substance P receptors across species and potential utility of these animals for preclinical assessments of pharmaceutical agents targeting the substance P neurotransmission was demonstrated (Synapse, 2007).

3. System Neurochemistry

1) Further understanding of human brain function by investigating the relevant organization of functional localization for higher-cognitive function in underlying neurochemical mechanisms

From a PET activation study with O-15 labeled water we elucidated the neural organization for executive function including the prefrontal cortex, parietal cortex, and cerebellum.

We could visualize the anatomy in monkey brain using 7-tesla, high-field MRI by improving the head coil for macaques.

An accident in which an experimenter was bitten by a monkey resulted in the interruption of all monkey studies in our laboratory. The interruption continued for 8 months, during which we carried out a risk management assessment for monkey studies, and considered such points as establishing security checks for all kinds of experiments dealing with awake monkeys. We also decided how to guarantee the reliance quality of PET data, and established a SOP (Standard Operating Procedure) for our institute to prepare for preclinical studies in the future.

Major Publications :

1. Haneda E., Higuchi M., Maeda J., Inaji M., Okauchi T., Ando K., Obayashi S., Nagai Y., Narazaki M., Ikehira H., Nakao R., Zhang M. R., Suzuki K., Suzuki H., Suhara T., In vivo mapping of substance P receptors in brains of laboratory animals by high-resolution imaging systems. *Synapse,* 61 : 205-15, 2007
2. Higuchi M., Saido T. C., Suhara T., Animal models of tauopathies. *Neuropathology*, 26 : 491-7, 2006
3. Ikoma Y., Takano A., Ito H., Kusuhara H., Sugiyama Y., Arakawa R., Fukumura T., Nakao R., Suzuki K., Suhara T., Quantitative analysis of 11C-verapamil transfer at the human blood-brain barrier for evaluation of P-glycoprotein function. *J Nucl Med*, 47 : 1531-7, 2006
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4.3. Studies on Molecular Probes and Radiopharmaceuticals

Kazutoshi Suzuki, Ph. D.
Director, Molecular Probe Group

Objectives :

Molecular probes are playing important roles in the rapidly developing field of molecular imaging. The purposes of this research group are 1) to develop novel probes to assess *in vivo* biological and physiological functions (Probe Research Team), 2) to develop new labeling methods to widen production for a variety of probes for high yield and high quality (Radiochemistry Team), 3) to develop a new integrated system for the production of safe probes considering the GMP standard, without radiation exposure to personnel by automation (Production System Team), and 4) to establish production methods and quality control methods of developed probes for clinical application (Radiopharmaceutical Production Team).

The Probe Research Team is developing novel probes for quantitative assessment of oxidative stress and/or disruption of homeostasis and brain efflux function targeting multidrug resistance-associated protein (MRP). This team also is taking part in the development of novel tumor imaging probes to assess DNA synthesis in tumor cell proliferation and a novel receptor ligand to function as a selective antagonist of mGluR5 for assessment of brain glutamate receptor. The Radiochemistry Team is developing new labeling methods with PET radionuclids ; special focus is on a direct fluorination method with $^{18}F^-$ of a benzene ring in unstable compounds and achieving higher specific activity for various kinds of PET probes. The Production System Team and Radiopharmaceutical Production Team have not only the above objectives but also have the missions to support research activity on PET molecular imaging in collaboration with the Planning and Promotion Unit. The research activities performed in FY 2006 were as follows.

1) Probe Research Team

We have addressed the development of novel probes assessing *in vivo* biological and physiological functions by approaches with a rationale-based design, as well as modification of potent probes. Our targets are molecules and/or functions involved in the bio-defense system, judgment of malignancy and therapeutic response in tumors, and neurotransmission.

In the research on probes assessing oxidative stress and/or disruption of homeostasis, two subjects have been investigated. The probe study for assessment of glutathione S-transferase activity, a key enzyme related with GSH maintenance, in the brain was launched. A series of compounds were designed based on a metabolic trapping principle and their reactivity to GSH was examined to evaluate properties as a probe. The other study was on the probe for quantitative assessment of brain efflux function. Multidrug resistance-associated protein (MRP) was targeted and 6-halo-purine derivatives were designed on the basis of a metabolite extrusion method and some of them were found to be promising.

Regarding probe imaging tumors, a novel thymidine analog, 4'- [methyl-^{14}C] thiothymidine ([^{14}C] S-dThd), was further evaluated to assess DNA synthesis in tumor cell proliferation. The result provided us the evidence that [^{14}C] S-dThd is a promising marker for DNA synthesis. A novel ligand (PTBN), a selective antagonist of mGluR5, was designed and evaluated on PET probes to assess brain glutamate receptor. The result showed the potential in a specific binding property.

In addition, probes for protein-kinase C and for 18F-alternative to assay AChE were evaluated, and a SPECT probe, single strand Fv of anti-tenascin-C antibody, was further examined to assess tissue-remodeling in myocardial disorders. In collaboration with a clinical-research group ^{11}C-MP4A/PET (for AChE) and ^{11}C-PIB/PET (for amyloid) were investigated for application to diseases with dementia.

2) Radiochemistry Team

1. Labeling Technique

A practical route for preparing [^{18}F] ligand containing [^{18}F] fluorobenzene moiety was developed by employing a reaction of diphenyliodonium salt with [^{18}F] F-. Diphenyliodonium tosylate, a labeling precursor for the radiosynthesis, was prepared by reacting tributylphenylstanne with a novel reagent (hydroxy) tosyliodoanisol. Using this method, [^{18}F] DAA1106, a PET ligand for imaging peripheral-type benzodiazepine receptor (PBR), was synthesized.

[^{11}C] Acetyl chloride ([^{11}C] AcCl) as a labeling precursor was synthesized using a loop method by reacting methylmagnesium bromide with [^{11}C] CO2, followed by treatment with thionyl chloride or oxalyl choride. After reaction, [^{11}C] AcCl was purified by distillation as a radiochemically pure product. It can be used for highly efficient acylation of nucleophilic substrates such as phenol and amine.

A new labeling method generating ^{11}C-C bond was developed by using [^{11}C] nitromethane. C-carboxylation of [^{11}C] nitromethane was accomplished from [^{11}C] methyl nitronate and 1-ethoxycarbonylbenzotriazole to afford [2-^{11}C] ethyl nitroacetate in a radiochemical yield of 75±6%. [2-^{11}C] Glycine ethyl ester was synthesized as a simple application of [2-^{11}C] ethyl nitroacetate.

2. Specific Activity

In vitro binding of [^{11}C] raclopride with ultra-high specific activity (SA) in the striatum and cerebral cortex of rat brain was characterized. The *in vitro* homogenate assay demonstrated that high SA [^{11}C] raclopride (>2500 GBq/μmol) had two affinity binding sites in the striatum and cerebral cortex of rat brain. By contrast, using low SA [^{11}C] raclopride (44 GBq/μmol), only one binding site was found in the striatum and no binding site was identified in the cerebral cortex.

3. Novel PET Ligand

[^{11}C] AC-5216 was synthesized and evaluated as a PET ligand for imaging PBR in primate brain. PET study on the monkey brain determined that [^{11}C] AC-5216 had relatively high uptake in the occipital cortex, a PBR-rich, dense area in the primate brain. Pretreatment with non-radioactive AC-5216 and PK11195 reduced the radioactivity of [^{11}C] AC-5216 in the occipital cortex significantly, suggesting its high specific binding with PBR in the brain.

3) Production System Team

A new irradiation system using vertical beams and a new production unit using [^{18}F] F_2 as a synthetic precursor for the NIRS versatile apparatus were developed for effective production of radionuclides and radiopharmaceuticals. The ^{62}Zn/^{62}Cu generators were prepared and distributed to 3 other PET facilities once a month regularly, to promote collaboration for cancer diagnosis with PET.

1. A new irradiation system using vertical beams was developed for the production of positron emitters. The system has 4 target chambers for gas target (^{11}C), liquid target (^{18}F) and two metal targets (^{76}Br and ^{124}I). A dry distillation apparatus and a remote system to handle the irradiated target were also installed and coupled with the same irradiation system. All these apparatus were installed in a convenient hot cell in the irradiation room. Tubes for water and compressed air were also connected to the irradiation system to cool the target during irradiation.
2. A new production unit using [^{18}F] F_2 as a synthetic precursor was developed for the versatile PET radiopharmaceutical production apparatus. Using the unit, [^{18}F] fluoro-m-Tyrosine, which is a tracer for evaluation of dopaminergic presynaptic function, was produced in satisfactory yield (ca 15% EOS).
3. The radionuclide ^{62}Zn was produced by the nuclear reaction ^{63}Cu (p, 2n) ^{62}Zn with the big cyclotron at NIRS. The ^{62}Zn/^{62}Cu generator was prepared remotely and distributed to 3 PET facilities (Fukui Univ., Yokohama City University, National Cancer Center). The generators were shipped from NIRS in the midnight, accepted at the partner's facility and used for tumor imaging in the chemical form of ^{62}Cu-ATSM to visualize hypoxia. These shipping were performed once a month from October, 2006.

4) Radiopharmaceutical Production Team

Sensitive and rapid high-performance liquid chromatographic methods were developed and validated for the quality control analysis of PET radiopharmaceuticals. These methods made it possible to determine the chemical mass of the PET probes with ultra high specific radioactivity (>3.7 TBq/μmol) and to perform ultra high-throughput analysis (<1 min) for a wide variety of pharmaceuticals.

Regarding support for researche conducted in the Molecular Imaging Center, the production and quality assurance of short-lived PET radiopharmaceuticals have been performed both for clinical and animal experiments. Six new PET radiopharmaceuticals ([^{11}C] BF227, [^{18}F] FLT, [^{18}F] NaF, [^{18}F] FMeNER-d_2, [^{18}F] FEtSPARQ and [^{61}Cu] ATSM) were approved by the Institutional Review Board at NIRS and released for the clinical use.

Contracts for the analysis of FDG solutions were made with four private companies. Under the contracts, 197 samples from 86 PET facilities in Japan were accepted for analysis.

Major Publications :

1) Toyohara, J., Kumata, K., Fukushi, K., Irie,

T. and Suzuki, K. : Evaluation of [methyl-14C] 4 ¢ -thiothymidine for DNA synthesis imaging.
J. Nucl. Med., 47, 1717-1722, 2006

2) Hirano, S., Shinotoh, H., Kobayashi, T., Tsuboi, Y., Wszolek, Z. K., Aotsuka, A. Tanaka, N., Ota, T., Fukushi, K., Tanada, S. and Irie, T. : Brain acetylcholinesterase activity in FTDP-17 studied by PET.
Neurology, 66, 1276-1277, 2006

3) Zhang M. -R., Ogawa M., Maeda J., Ito T., Noguchi, J., Kumata K., Okauchi T., Suhara, T., Suzuki, K. [2-11C] Isopropyl-, [1-11C] ethyl- and [11C] methyl- labeled phenoxyphenyl acetamide derivatives as positron emission tomography ligands for peripheral benzodiazepine receptors : radiosynthesis, uptake and in vivo binding in brain. *Journal of Medicinal Chemistry* ; 49, 2735-2742, 2006.

4) Zhang M. -R., Ogawa, M., Yoshida Y., Suzuki K. Selective synthesis of [2-11C] 2-iodopropane and [1-11C] iodoethane using the loop method by reacting methylmagnesium bromide with [11C] carbon dioxide. *Applied Radiation and Isotope*s 64, 216-222, 2006.

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6) Ryuji Nakao, Kenji Furutsuka, Masatoshi Yamaguchi and Kazutoshi Ssuzuki : Development and Validation of a Liquid Chromatographic Method for the Analysis of Positron Emission Tomography Radiopharmaceuticals with Ru (bpy) $_3^{2+}$-$KMnO_4$ Chemiluminescence Detection., *Analytical Sciences*, 23(2), 151-155. 2007.

4.4. Research and development of the next-generation technology of the molecular imaging.

Iwao Kanno, Ph. D.
Director of BIOPHYSICS GROUP

Outline of Research Career

Iwao Kanno started his professional job at Akita Research Institute of Brain and Blood Vessels in 1970, where his major activities were carried out until 2006 for 36 years. He firstly developed a custom radionuclide emission tomography using handmade rotational dentist chair in 1977. Then, he developed the hybrid type emission tomography which enabled to assess positron emission tomography (PET) and single photon emission computed tomography (SPECT) in collaborating with medical company in 1979. His efforts were also paid to develop methodology for quantitative assessment of physiological and biochemical parameters from PET and SPECT images. He developed quantitative method for cerebral blood flow and cerebral oxygen metabolism from Oxygen-15 PET images in mid 1980's. His interests were gradually turned to the brain physiology of circulation and metabolism mechanism to adapt to the neurovascular coupling during neuronal activation, which is essential to understand functional brain mapping using magnetic resonance imaging and near infrared topography.

(Same as above)

Objectives :

Biophysics Group intends to develop the methodologies and technologies for watching, detecting, analyzing and understanding the molecular and physiological signals emerged from the living animals and humans by means of the kinetics of radioactive molecular probes, magnetic resonances signals of proton interacting with molecular probes, multi-photon laser microscopy and engineering physics for detection and imaging of the positron annihilation. The Group consists of four research teams. The Imaging Physics Team covers software and engineering physics involved in the PET instrument system. The Biosignal physiology Team combines molecular information and physiological information measured from MRI and the microcirculation facilities on hemodynamic signals relating to neurovascular coupling during neuronal activation. The Data Analysis Team aims to extract quantitative parameters from dynamic PET images taken from patients and healthy subjects after radioactive ligand administrations. The Magnetic Resonance Molecular Imaging Team develops methods for detecting the variable signals from the high tesla (7T) MRI. These four teams collaborate to assess quantitative molecular mechanisms from in vivo animals and humans. The Biophysics Group is thus supporting the other groups of application for diagnosis and neuropsychiatry in the Molecular Imaging Center.

Progress of Research (Achievements, prospect) :

Magnetic Resonance Molecular Imaging Team carried out ^{19}F high sensitivity imaging for in vivo drug dynamics performed in mice at 7T with 5-Fluoroaracil. Imaging of 19F metabolites of 5-FU in mice is successful at 7T by using minimal TE of Fast imaging with steady-state precession and Fast Spin Echo under the dose of 2 mmol 5-FU/kg, p. o. The image quality by FISP was excellent even in mice if the target organ is surrounded by the homogeneous tissues such as bladder and some case of the stomach. Single shot FSE was successfully applied to the study of 5-FU catabolic and excretion processes at 7T giving stable results as in the previous work at 9.4T irrespective of rather long TE due to large bore gradient system. For the imaging of fluolo-nucleotides by FSE, however, single line selection mode or 2-shot was required to obtain reliable image especially in the liver. Reduction of TE was essential for this drug, and the use of smaller gradient system is waited. At this field strength, FSE is the first choice as a standard method. The dynamical study of 5-FU is successful by FSE at 7T under the dose of 2mmol/kg. Cellular and molecular imaging using MRI high sensitive quadrature and 4ch phased-array RF coils were prepared for rat brain imaging on high field 7T MRI system. Although sensitivity of the phased array coil was higher than the quadrature coil in the cortical area, the homogeneity was not enough for rat whole brain especially at the brainstem. In addition, anesthetic circuits, automatic temperature control systems, monitoring systems for animal physiologic condition, respiratory gating system, data server, RAID systems, and animal preparation system were developed and installed for continuous in-vivo MRI measurement. Furthermore, relaxabilities of novel/ functional MRI contrast agents such as manganese and iron oxide particles were measured and evaluated in-vitro.

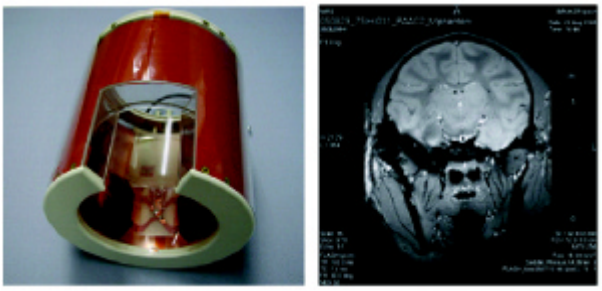

Figure caption : Development of the quadrature coil for imaging large animal and the coronal sectiona of the head of macaque measured using this coil.

Biosignal physiology Team covers two kinds of signals, human MRI data and animal two-photon microscopy data. 1) It is shown that the signal can be decomposed into contributions from intravascular, fast-diffusion and slow-diffusion compartments. After decomposition the post-stimulus undershoot seems to be confined to the fast-diffusion phase, while the slow-diffusion response may closely reflect the neural response. 2) In order to explore the feasibility of a clinical 3.0 T MR system, long-term monitoring of in vivo [1-13C] glycogen storage/degradation in the liver was achieved in healthy volunteers (n=5) and diabetic patients (n=5). The correlation between the fasting levels of plasma glucose and the increasing rate of glycogen in the liver was statistically significant (Spearman: $r=-0.758$, $p<0.05$, $n=10$). This indicates that improvement in glycogen synthesizing ability may be beneficial for reducing the blood glucose level. 13C MR spectroscopy is useful for monitoring glycogen synthesis in vivo. 3) The variation of T2 for normal femoral cartilage in hip joint was studied. T2 measurement was performed in an oblique coronal plane, which was passed through the center of the femoral head, was acquired using a 3.0 Tesla system. Our results demonstrate the existence of topographic variation of femoral cartilage T2 in young healthy volunteers which might be due to the variation of cartilage matrix composition in the joint as well as the relationship between the collagen network and orientation of the static magnetic field. These findings can be a comparative standard to evaluate degeneration of hip cartilage in patients. 4) In addition to diffusion weighted image (DWI) and apparent diffusion coefficient (ADC) values, diffusion tensor imaging (DTI) is a new, promising technique for detecting prostate cancer (Pca). We assessed the changes of ADC values and DTI between pre- and post-radiation. The ADC value of Pca increases after radiation therapy, becoming close to those of intact inner gland (IG) and peripheral zone (PZ). Although fraction anisotropy is not useful for distinguishing Pca because of the overlaps among Pca, intact IG and PZ, DTI is able to show changes in the prostatic structure. These results may help to estimate the prediction of the effect of radiation therapy. 5) Magnetic resonance elastography (MRE) methods deform the sample using external vibration system. We have been used transverse driver, which generates shear waves at surface of the object. One of the problems is that shear waves rapidly attenuate at surface of the tissue and not propagate into deep inside of the body. In this research, we compared the shear waves generated by transverse driver and longitudinal driver. By the in-vitro porcine liver phantom study, the longitudinal driver was induced shear waves into deep inside. These results suggest the longitudinal driver makes it possible to measure the shear modulus of deep inside of the body. 6) We examined the influence of chewing on brain activities during a working memory task using fMRI. The healthy young subjects continuously performed the two- or three-back (N-back) working memory task. The subjects chewed gum, without odor and taste components, between N-back tasks. Chewing increased the BOLD signals in the dorsolateral prefrontal cortex during N-back tasks. In addition, there were more prominent activations in the posterior portion of the hippocampus in the right hemisphere during after chewing trial. These results suggest that gum chewing may accelerate or recover the process of working memory, besides inducing an arousal effect, consequently enhancing cognitive performance.

Image Analysis Team aims to calculate accurate and quantitative biological parametric images of brain functions from dynamic PET images following administration of the radioactive probes. PET images include massive statistical noises in the radioactive concentration information. To obtain quantitative physiological parameters, mathematical engineering and image processing are necessary in image analysis. Major targets of the image analysis are to obtain parameters of neurorecepter functions from images of neurotransmitters and transporters. In order to reduce effect of the statistical noise in dynamic PET, the wavelet algorithm was introduced in calculating the biding potential from the kinetics of the dopamine ligand.

Imaging Physics Team demonstrated the capability of 8-layer depth-of-interaction (DOI) encoding on a PET detector. The detector is expected to reduce parallax error effectively because of its short data-sampling interval in depth direction. It would be advantageous to use in a high sensitive PET system of large solid angle and a PET system dedicated to breast or prostate cancer, MRI-PET, and optical-PET, which all need a close detector setting to the object. Previously, we

proposed an 8-layer DOI encoding method for a PET detector and proved its validity. The layer of interaction is identified by hybrid method: scintillation light control by the original reflector arrangement for 4-layer DOI encoding and pulse shape discrimination for 2-layer DOI encoding. In the 8-layer DOI detector, four layers then consist of the scintillator of different pulse shape from another scintillator for the other four layers. The two kind crystal layers can be arranged in two ways: stacked alternately (LSLS) or set in the upper and lower four layers (LLSS). Here"L"and "S" represent longer and shorter decay time in the pulce shape. Since the two crystal arrangements are expected to show different detector performance, we investigated the difference to understand the characteristics of the DOI detector for its optimization. Gd_2SiO_5 (GSO) crystals of 0.5 mol% Ce dopant and 1.5 mol% Ce dopant were used for the measurement. The former is in dimensions of 2.9 mm × 2.9 mm × 3.75 mm and the latter is 2.9 mm × 2.9 mm × 3.6 mm, respectively. The experimental results show better performance of the LLSS arrangement in pulse shape discrimination, while inferior in the 4-layer DOI encoding. There was no particular difference between the two crystal arrangements in light output and energy resolution of each layer.

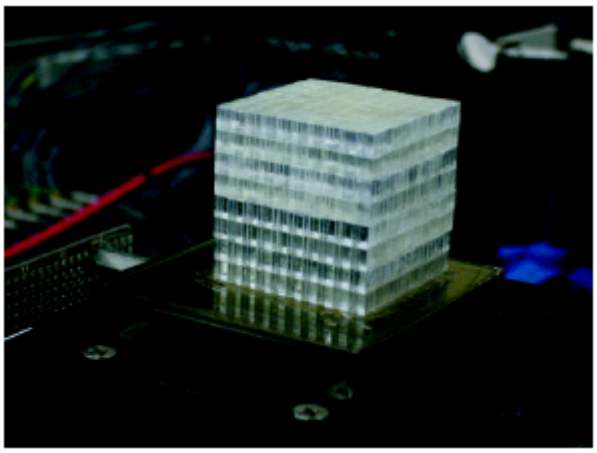

Figure caption : Prototype of an 8-layer DOI detector for a PET detector. The 8-layer DOI encoding is performed by scintillation light control with the original reflector arrangement for 4-layer DOI encoding and pulse shape discrimination (PSD) for further 2-layer DOI encoding. For PSD, four layers consist of the scintillator of different pulse shape from another scintillator for the other four layers. The two kind crystal layers can be arranged in two ways: stacked alternately or set in the upper and lower four layers.

Major Publications :

1. Taiga Yamaya, Naoki Hagiwara, Takashi Obi, Tomoaki Tsuda, Keishi Kitamura, Tomoyuki Hasegawa, Hideaki Haneishi, Naoko Inadama, Eiji Yoshida, Hideo Murayama. : Preliminary Resolution Performance of the Prototype System for a 4-Layer DOI-PET Scanner: jPET-D4. IEEE Transactions on Nuclear Science 53 (3), pp1123-1128, 2006.
2. Takayuki Obata, Koji Uemura, Hiroi Nonaka, Mitsuru Tamura, Shuji Tanada, Hiroo Ikehira : Optimizing T2-weighted magnetic resonance sequences for surface coil microimaging of the eye with regard to lid, eyeball and head moving artifacts. Magnetic Resonance Imaging 24, pp. 97-101, 2006.
3. Youko Ikoma, Akihiro Takano, Hiroshi Ito, Hiroyuki Kusuhara, Yuichi Sugiyama, Ryosuke Arakawa, Toshimitsu Fukumura, Ryuji Nakao, Kazutoshi Suzuki, Tetsuya Suhara : Quantitative analysis of 11C-verapamil transfer at the human blood-brain barrier for evaluation of P-glycoprotein function. Journal of Nuclear Medicine 47 (9), pp. 1531-1537, 2006.
4. Naoko Inadama, Hideo Murayama, Manabu Hamamoto, Tomoaki Tsuda, Yusuke Ono, Taiga Yamaya, Eiji Yoshida, Kengo Shibuya, Fumihiko Nishikido : 8-Layer DOI Encoding of 3-Dimensional Crystal Array. IEEE Transactions on Nuclear Science 53 (5), pp. 2523-2528, 2006.
5. Eiji Yoshida, Keishi Kitamura, Yuichi Kimura, Fumihiko Nishikido, Kengo Shibuya, Taiga Yamaya, Hideo Murayama : Inter-crystal scatter identification for a depth-sensitive detector using support vector machine for small animal PET. Nuclear Instruments & Methods in Physics Research Section A 571, pp. 243-246, 2006.

5. Research Center for Radiation Protection

Kazuo Sakai, Ph. D., Director

Outline of Research Career :

In 1982, Dr. Sakai got 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 was a Lecturer in the Department of Radiation Oncology, Graduate School of Medicine, University of Tokyo (1989-1999). The main subjects of his research at the University of Tokyo were radiation-induced DNA damage and its repair, and mechanisms of radiation induced cell death. While he worked for the University of Tokyo, he visited the Genetics Division, Children's Hospital, Harvard Medical School from 1983 to 1985. The research subject there was gene amplification and cloning of genes responsible for radiosensitivity. He moved to the Central Research Institute of Electric Power Industry in 1999 to research biological effects of low dose radiation. He joined NIRS in 2006.

Objectives :

The Research Center for Radiation Protection was newly established in 2006. The aim of the Center is to provide 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 activities are not limited to Japan. The Center has been appointed a collaborating center by the International Atomic Energy Agency.

Overview :

The Research Center consists of 4 Research Groups (Regulatory Sciences Research Group, Experimental Radiobiology for Children's Health Research Group, Radiation Effect Mechanisms Research Group, and Environmental Radiation Effects Research Group), the Nakaminato Laboratory for Marine Radioecology, and the Department of Advanced Technologies for Radiation Protection Research.

The activities of the Research Groups and the Nakaminato Laboratory are described in their own sections of this Report.

The Department of Advanced Technologies for Radiation Protection Research consists of 4 sections. In the Advanced Analytical Technology Section cooperative studies with other research groups in the Center were carried out to measure trace elements in environmental and biological samples. Also, the effect of rhenium concentration on environmental Tc-99 analysis, and a separation and concentration method for uranium isotope ratio measurements for terrestrial and rain samples were studied. In The Animal Pathology Section provided histopathological and diagnostic support for analyses of radiation-induced murine tumor model and tumor-xenograft murine model, and some genetically-engineered mice. Moreover, ultra-high resolution real time CT imaging techniques was established for experimental animal research. The Advanced Animal Research Section has supported integrated research of molecular and genetic studies with physiological studies in whole animals. Although remarkable progress in radiation biology has been made at genetic, molecular and cellular levels, physiological analysis of whole animal models is necessary for extrapolation to human health. The section has contributed in this area through production of "gene-modified mice" in which specific radiation-related gene (s) were introduced or deleted. The Environmental Radioactivity Survey Section initiated three collaborative research programs with three universities. These have involved development of an ultra sensitive radon decay products measuring system, establishment of a calibration procedure for radon and its decay products concentrations and development of a new technique (detection of Cherenkov radiation) for radon measurements. In addition to the above, other seven commissioned projects were given to this section.

In the Research Center 64 permanent and 85 temporary members, together with 69 visiting scientists have actively conducted research. They produced 123 original papers, of which 42 represented the principal contribution and 81 were supportive. The Center held 3 symposia on timely subjects : modeling in radiation research, Medaka biology in radiation research, the other on the effects of the Chernobyl accident.

As of April 1, Dr. Kazuo Sakai was appointed as the Director of the Research Center ; Dr. Masahiro Doi as the Director of the Regulatory Sciences Research Group ; Dr. Yoshiya Shimada as the Director of the

Experimental Radiobiology for Children's Health Research Group ; Dr. Mitsuru Nenoi as the Director of the Radiation Effect Mechanisms Research Group ; and Dr. Satoshi Yoshida as the Director of the Environmental Radiation Effects Research Group. After Dr. Doi's untimely demise, Dr. Hidenori Yonehara was appointed as the Director of the Regulatory Sciences Research Group.

5.1. Regulatory Sciences Research for Radiation Safety and Protection

Hidenori Yonehara, Ph. D.
Dierector, 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 issues of exposure due to residential radon. He joined to NIRS in 1996 and began working on the studies related to dose evaluation from environmental radiation. From 2003 to 2006 he worked on development of radiation safety standards as Director for Radiation Protection Policy in Ministry of Education, Culture, Sports, Science and Technology (MEXT). After returning to NIRS, he has studied dose evaluation from natural radiation sources as well as issues related to radiation safety regulation. Since March 2007, he has been working as Director of the Regulatory Sciences Research Group.

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Objectives :

"Regulatory science" can be considered to be an integrated science of uniting views of rationality in science and society. The main objectives of the group is to summarize scientific based information for radiation safety regulation and to exchange the information among different stakeholders to bridge the gap between science and society. The research programs are focused on four points :

1) Summarizing radiation protection issues

The group aims to summarize scientific information on radiation protection provided by NIRS, universities and other research institutes in order to contribute to activities of relevant international organizations such as UNSCEAR, OECD/NEA, and ICRP. The group also summarizes the information on radiation protection for dissemination to regulatory authorities and the public. To share the information with scientific organizations, regulatory authorities and the public, the group has constructed a research information network.

2) Construction of information databases for radiation risk assessment

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, and on the exposures and health effects of radiation among different human populations, and on environmental effects of radiation from the epidemiological studies are collected for the databases.

3) Development of mathematical models

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

4) Development of method for risk communication

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

Progress of Research :

1) Summarizing radiation protection issues

Recently new scientific findings related to the effects of low dose radiation exposures have been provided by some epidemiological studies. New reports on the effects were also published by some committees such as the BEIR Committee and the French Academy of Sciences. New scientific information is considered to be important for discussion of the direction to be taken for new Safety Standards of radiation protection. The information will be summarized comprehensively in the report of UNSCEAR. The group took a key role in collection of scientific comments on the UNSCEAR draft from the members of an expert panel committee in Japan and submitted the comments to the UNSCEAR. The group also took part in summarizing the comments from experts in various fields for drafting the new ICRP Recommendation.

2) Construction of information databases for radiation risk assessment

The information from recent studies on the dose-response relationship of low dose radiation was summarized. The information on status for industrial use of naturally occurring radioactive materials (NORM) was also summarized. Specific radioactivities of ores and stone materials for industrial use were investigated in the literature or measured to summarize the information into a database. The studies on dose evaluation by means of chromosome aberration in people who are living in a high background radiation area in Iran were carried out. Epidemiological studies were started on possible health effects associated with

medical exposures during childhood and on lung cancer associated with residential radon in China.

3) Development of mathematical models

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

In FY v2006, we focused on a model of carcinogenesis. Tumorigenesis often involves exposure to multiple carcinogens. We constructed a two- stage model, which consisted of individuals in three states : normal, intermediate, and malignant. We considered a population exposed to two carcinogens and examined two exposure scenarios : [1] separately exposed to two carcinogens exposed and [2] simultaneous exposure to two carcinogens. We calculated the incidence rate of the malignant state, introducing a "synergy index" to quantify the interaction between the two carcinogens. We confirmed the results of previous analyses, but we also calculated a more general situation in which each carcinogen affected both steps. (a) The carcinogen R which is exposed first affects the first step, and carcinogen C which is exposed second affects the second step. (b) The exposure order is the same with (a), but effect of carcinogens on the mutation steps is exchanged. In this case, the effect is qualitatively the same if the order is reversed. (c) Two carcinogens are exposed identically. Two carcinogens shows the synergistic effect in (a) and (c), and the effect is additive in (b) (Fig. 1)

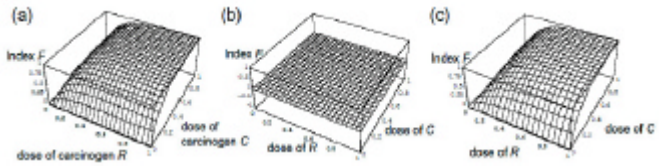

Fig. 1 Analysis of synergy effects of multiple carcinogens by means of two-stage model

4) Development of method for risk communication

The surveys on risk perception of medical radiation exposure were carried out. In FY 2006, the surveys for the general public and hospital nurses were performed and the results were compared with those from the previous studies. A series of meetings called a "Dialog Seminar" on themes of the effects from the Chernobyl accident, the new ICRP recommendation, and cosmic-ray exposure of aircrews was held to communicate information on risk among scientists, persons in regulatory authorities, those in relevant companies, and the public. Educational material for airplane crews was developed based on the results of the dialog seminar with the crews (Fig. 2).

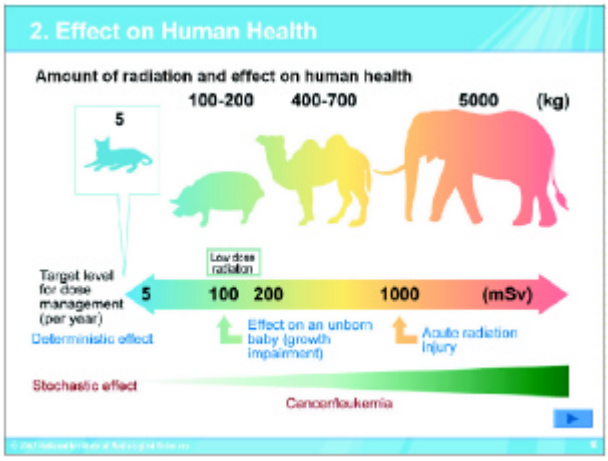

Fig. 2 A page from the educational material prepared for airline crews.

Major Publications :

1. R. Kanda, M. Minamihisamatsu, S. Tsuji, Y. Ohmachi, T. Hiraoka, Y. Shimada, T. Ogiu, T. Ohno, I. Hayata : Investigation of new cytogenetic biomarkers specific to high-LET radiation using in vivo and in vitro exposed human lymphocytes, *International Journal of Radiation Biology*, 82 (7), 483-491, 2006
2. Y. Fujikawa, M. Shimo, H. Yonehara, et. al : On the Optimal Regulation Of Technologically-Enhanced Naturally Occurring Radioactive Materials, *Japanese Journal of Health Physics*, 41 (2), 99-108, 2006 (in Japanese)
3. I. Kawaguchi, M. Doi, S. Kakinuma, Y. Shimada: Combined effect of multiple carcinogens, and synergy index., *Journal of Theoretical Biology*, 243 (1), 143-151, 2006
4. I. Kawaguchi, A. Sasaki, The wave speed of intergradation zone in two-species lattice Muellerian mimicry model., *Journal of Theoretical Biology*, 243, 594-603, 2006
5. R. Kanda, S. Tsuji, M. Doi, How should be Made the Planning ofStakeholder Participation for Decision-making Process-Case Study Report on Stakeholder Involvements in Japan-, *Japanese Journal of Risk Analysis*, 17 (1), 95-104、2007 (in Japanese)

5.2. Experimental Radiobiology for Children's Health Research Group

Yoshiya Shimada, Ph. D.
Director

Outline of Research Career :

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

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Objectives :

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

Progress of Research :

1) Age dependency of life shortening by irradiation in B6C3F1 mice

Fifty female and male B6C3F1 mice per each group, which have been used in a wide variety of toxicological studies such as the National Toxicology Program (NTP) in USA, were exposed to gamma-rays 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. With the same protocol, the mice were irradiated at 0.2 and 2 Gy of carbon ion beams at 13 keV/um. These mice are now kept under observation. Preliminary observation indicated that carbon ions were more potent in reducing lifespan than gamma-rays. Female mice appeared more susceptible to radiation-induced lifespan shortening than male mice at the dose of 2 Gy, but not at 0.2 Gy. The total number of mice exposed is 2,334 so far.

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

It is reported that risks for breast cancer is somewhat higher than those for many other sites and that they depend markedly on age-at-exposure. In order to see the age effect on mammary tumors, female Sprague-Dawley (821 in number) rats, which have been used as a suitable model of human breast carcinogenesis, were irradiated with gamma-rays and carbon ions at doses of 0.2 and 1 Gy. In addition, mammary tumorigenesis in $Apc^{Min/+}$ mice was also examined. We found an enhancement of tumor incidence with increasing age at exposure. The lung is one of the important organs for radiological protection of workers and the public because of its high radiation-associated cancer risks. To elucidate the age dependence of its dose-effect relationship, 1, 5 and 15 week-old female Wistar rats (total 760 animals) were irradiated with X-rays (200kVp, 20mA) at the thoracic region at doses of 0, 1, 3 and 5 Gy. For the age effect on induction of myeloid leukemia, we started gamma-ray irradiation of postnatal male C3H/Nrs mice at doses between 0.2 and 3Gy. Preliminarly, neonatally irradiated mice with 3Gy developed thymic lymphoma, which was rarely induced in adult exposure of C3H mice. The age-effect of tumor induction of liver, Harderian gland, pituitary, and ovary will be obtained from the study on lifespan shortening in B6C3F1. We also introduced mutant and knockout animals such as the Eker rats, and *Ptc*$^{+/-}$, *Apc*$^{Min/+}$, and *Mlh1*$^{-/-}$ mice for the research on the age effect on tumor development of kidney, brain and intestine. Detailed histopathological analysis in all animals has been just started.

Dose and energy distribution of 2MeV fast neutron-

exposure field in the low-dose radiation effect research building were characterized and optimized.

3) Combined effect of radiation with chemical carcinogens on lung, uterine and liver tumors

In order to investigate the age effect of combined exposure of radiation and a chemical carcinogen on pulmonary carcinogenesis, a total of 250 female Wistar rats were irradiated at infant (1 weeks of age), pubertal (5 weeks of age) and adult (15 weeks of age) stages and then received a peritoneal injection (1.0 g/kg body weight) of N-bis (2-hydroxypropyl) nitrosamine. These animals will be kept for lifetime. Uterine corpus cancer, a typical fatal tumor in women, is increasing in many developed countries. For the age-dependent effects of irradiation on the uterine carcinogenesis, Donryu rats, which is a highly-susceptible strain of uterine cancer, were exposed to gamma-rays at doses of 0.2 and 2 Gy with or without N-ethyl-N'-nitro-N-nitrosoguanidine treatment during juvenile (2 weeks after birth) and adulthood (10 weeks after birth) stages. To see the combined effect on liver cancer development, B6C3F1 female mice were irradiated with 2 Gy at 2- and 7-weeks after birth followed by i.p. injection of diethylnitrosoamine 2 weeks later. All animals used for combined effect are now under observation and will be subjected to analysis of tumor incidence and carcinogenic mechanisms. These results will provide the information of the relative risk and the age-weighting factor for radiation-induced carcinogenesis.

4) Establishment of the methods for quantification of gpt-delta and Aprt mutation rate and chromosome aberration

We introduced and established the methods for determining mutation frequency using *gpt*-delta transgenic mice and *Aprt*$^{+/-}$ mice. The former mouse system detects small (i. e., point and frameshift) mutations, while the latter is suitable for detection of large deletions and mitotic recombinations. The chromosome painting method for mouse T-cell lymphomas has been also established.

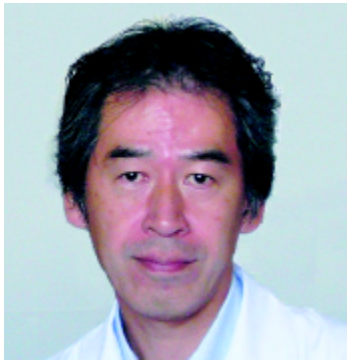
5) Detrimental effect of uranium on the childhood kidney

Health effects for children in depleted uranium-polluted areas and uranium mining areas are of recent concerns. Uranium and its compounds have the potential to cause nephrotoxicity. We attempted to apply synchrotron radiation X-ray fluorescence analysis (SR-XRF) with nano-probe for determination of precise distribution of uranium in the kidney. Clear images of uranium in the epithelium of the proximal tubules, a toxic target site of uranium, were obtained in the kidney of rats exposed to uranium.

Major Publications :

1. Shizuko Kakinuma, Youtarou Kodama, Yoshiko Amasaki, Yi Shang, Yutaka Tokairin*, Masami Arai*, Mayumi Nishimura, Manami Monobe, Shuji Kojima*, Yoshiya Shimada : *Ikaros* is a mutational target for lymphomagenesis in *Mlh1*-deficient mice, *Oncogene, 26*, 2945-2949, 2007.
2. Kazuki Taniguchi, Shizuko Kakinuma, Yutaka Tokairin*, Masami Arai*, Hiroyuki Kohno*, Keiji Wakabayashi*, Tatsuhiko Imaoka, Eisaku Ito*, Morio Koike*, Hiroyuki Uetake*, Mayumi Nishimura, Kazumi Yamauchi, Kenichi Sugihara*, Yoshiya Shimada : Mild inflammation accelerates colon carcinogenesis in *Mlh1*- deficient mice, *Oncology, 71 (1-2)*, 124-130, 2007
3. Takashi Takabatake, Fujikawa Katsuyoshi, Satoshi Tanaka*, Tokuhisa Hirouchi*, Shingo Nakamura, Igunasya Tanaka*, Kazuaki Ichinohe, Mikio Saitou, Shizuko Kakinuma, Mayumi Nishimura, Yoshiya Shimada, Yoichi Oghiso*, Kimio Tanaka*, et. al : Array-CGH analyses of murine malignant lymphomas : Genomic clues to understanding the effects of chronic exposure to low-dose-rate gamma rays on lymphomagenesis, *Radiation Research,* 166, 61-72, 2006
4. Tatsuhiko Imaoka, Mayumi Nishimura, Yukiko Nishimura, Shizuko Kakinuma, Yoshiya Shimada : Persistent cell proliferation of terminal end buds precedes radiation-induced rat mammary carcinogenesis, *In Vivo, 20*, 353-358, 2006
5. Yamada Daisuke, Yoshida Midori, Williams N. Yuko, Fukami Takeshi, Kikuchi Shinji, Masuda Mari, Murayama Tomoko, Ohta Tsutomu, Nakae Dai, Maekawa Akihiko, Kitamura Tadashi, Murakami Yoshinori : Disruption of spermatogenic cell adhesion and male infertility in mice lacking *TSLC1/IGSF4*, an immunogloblin superfamily cell adhesion molecule, *Molecular and Cellular Biology, 26*, 3610-3624, 2006

5.3. Studies on Radiation Effect Mechanisms



Mitsuru Nenoi, Ph. D.
Director, Radiation Effect Mechaisms 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 regulation mechanisms of gene transcription after exposure to DNA damaging agents.

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 necessarily have the scientific evidence to support this assumption. We do not have sufficient scientific data on the effects of low-dose radiation on developmental and differentiational anomaly either. Because it is now considered to be difficult to assess the risk of low-dose radiation from animal experiments or in epidemiological data, this research group conducts studies on the mechanism of radiation effects caused by low-dose radiation. The purpose of this research group is to derive findings useful in the risk assessment of low-dose radiation which can be used as a basis for the development of appropriate regulatory framework. The following study items are separately investigated by the four teams.

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

Progress of Research :

1) Radiation Carcinogenesis Research Team

Chromosomal rearrangements are implicated in the etiology of T-cell lymphomagenesis and *Rag*-dependent and independent pathways participate in mouse thymic lymphomagenesis. However, their underlying mechanisms and the connection between these pathways and the causes of rearrangements of cancer-related genes remain unknown. We showed molecular mechanisms for the pathways by clarifying susceptibility of *Rag2*$^{-/-}$, *Atm*$^{-/-}$, scid, and doubly mutated mice to thymic lymphomagenesis and abnormalities of *Notch1* oncogene in thymic lymphomas. *Rag2*$^{-/-}$ mice per se developed thymic lymphomas via *Rag2*-independent pathway. *Atm*$^{-/-}$ mice developed them via both pathways. Scid mice developed radiation-induced thymic lymphomas mainly via *Rag2*-independent pathway. Analyses of *Notch1* rearrangements showed that *Rag2*-dependent mechanisms were the illegitimate V(D)J recombination and the Rag2-mediated pathway where *Rag*-cleaved DNA end and another DNA break were involved. *Rag2*-independent mechanisms included the microhomology-mediated end-joining, the nucleotide addition in deletion, the insertion of intracisternal A particle, inversion, duplication, and translocation. These mechanisms functioned properly according to the defects of mutants in repair and V (D) J recombination. Total abnormalities of *Notch1* including rearrangements and mutations exceeded 80% in thymic lymphomas, making *Notch1* as the most important oncogene for thymic lymphomagenesis. There was no difference in mutation types among mutants, indicating that *Notch1* mutations occurred independently of *Rag2*, *Atm*, and *Prkdc* genes. High

susceptibility of *Rag2*$^{-/-}$ mice to lymphomagenesis suggested the existence of another *Rag2* deficiency-driven pathway for thymic lymphomagenesis.

2) DNA Repair Gene Research Team

Our chief aim of this project is to clarify the induction mechanism of mutation by radiation. In particular, the identification of the modulatory factor (s) for a low-dose radiation risk in non-homologous end-joining (NHEJ) and the elucidation of the molecular mechanism (s) involved with those factor (s) are the focus of our interest. DNA double strand breaks (DSBs) can arise from multiple sources including ionizing radiation (IR), and are the most serious DNA damage. NHEJ, which is a simple mechanism to piece together the broken DNA ends, can function in all phases of the cell cycle and it appears as the major repair pathway in mammalian cells. In the current study, we carried out the generation and characterization of NHEJ-related gene deficient human cell lines to define the biological roles of NHEJ-related genes on DNA damage induced by IR.

We have produced cells that bear a disrupted NHEJ-related gene, such as *XRCC4*, *Artemis* and *MDC1*, by using a gene-targeting technique in a human colon tumor cell line (HCT116). Proliferation rates were slightly slower in all of the cell lines deficient for NHEJ-related genes than in the wild type cells, although no morphological difference was observed between the cell lines. The highest survival rate was exhibited in the wild type cells (D_{10} = 3.9 Gy) and the lowest was in *XRCC4*$^{-/-}$ cells (D_{10} = 1.2 Gy) in the cell survival assay after X-ray irradiation, while *MDC1*$^{-/-}$ cells (D_{10} = 1.5 Gy) and *Artemis*$^{-/-}$ cells (D_{10} = 2.2 Gy) showed intermediated radio-sensitivities between the wild and *XRCC4*$^{-/-}$ cells. Formation of γ-H2AX foci, which appear to be true markers of DSBs, increased in a dose-dependent manner for X-rays and the number of foci peaked at 30 min after X-ray-exposure in all cell lines. In the wild type cells, γ-H2AX foci, then, disappeared gradually as time passed and returned to the basal level within 4 hr. On the other hand, a slower disappearance of the induced foci was shown and a number of foci still remained at 4 hr after X-ray irradiation in *XRCC4*$^{-/-}$ and *MDC1*$^{-/-}$ cells. These results suggested that deficiencies of NHEJ-related genes caused deteriorations of the γ-H2AX foci-associated events, probably a DNA DSB repair process and in turn became a significant reason for the radio-sensitivity of these cells. The NHEJ-related gene deficient human cell lines established in this study should contribute to further understanding of the profile of DNA damage and repair in radiation biology.

3) Developmental Anomalies Research Team

The purpose of our team is to investigate the threshold of the definitive effects of low-dose radiations by studying their effects on the development of neural crest-derived cells. In addition, we aim to elucidate the mechanism of the effects of low-dose radiations on the development of neural crest-derived cells at cellular and molecular levels.

Pregnant females of C57BL/10JHir mice at 9 days of gestation were whole-body irradiated with a single acute dose of silicon ion radiation. The effect was studied by scoring changes in the prenatal and postnatal development of the mice as well as in their pigmentation in prenatal hair follicles and cutaneous coats 22 days after birth. The frequency of abnormalities in the fore and hind legs, tails and eyes as well as of hemorrhage was increased as dose increased and the number of embryos as well as the body weight of the 18-day-old embryos decreased. The percentage of births, the survival to day 22 and the body weight at day 22 were also reduced. By comparing the survival to day 22 for silicon ion radiation with that of γ-rays, the former was more than twice as effective. In 18-day-old embryos, the development of hair follicles was delayed as dose increased. The frequency and the size of the white spots in the mid-ventrum increased in the irradiated mice. Silicon ion radiation was more effective than γ-ray radiation and the former seemed to have a greater effect on prenatal and postnatal development of mice as well as on the melanocyte development.

4) Radioadaptive response research team

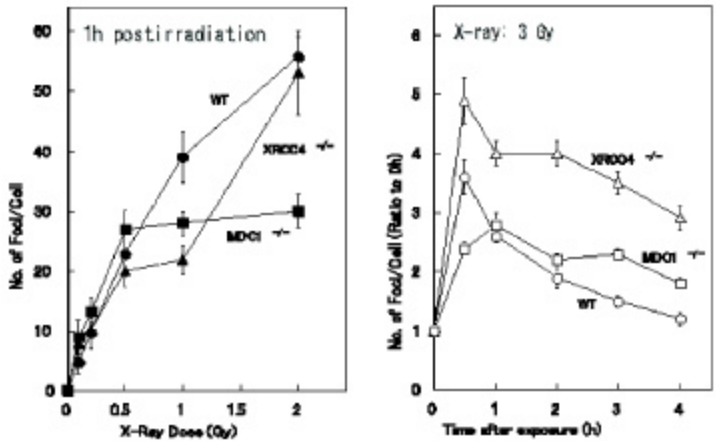
Exposure to sublethal doses of ionizing radiation can induce protective mechanisms against a subsequent higher dose irradiation. This phenomenon, called radiation-induced adaptive response (AR), has been described in a wide range of biological models. We previously demonstrated the existence of AR in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

effects.

Major Publications :

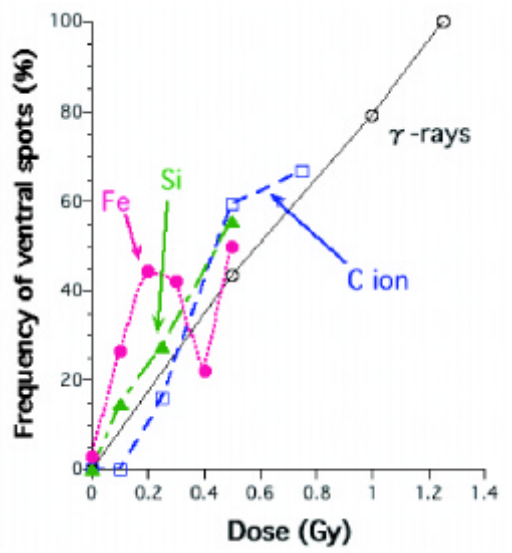
1. Takahagi, M. and Tatsumi, K. Aggregative organization enhances the DNA end-joining process that is mediated by DNA-dependent protein kinase. *FEBS J.*, 273, 3063-3075, 2006.
2. Hirobe, T. and Abe, H. The slaty mutation affects the morphology and maturation of melanosomes in the mouse melanocytes. *Pigment Cell Research*, 19, 454-459, 2006.
3. Sugaya, K., Hongo, E., Ishihara, Y. and Tsuji, H. The conserved role of Smu1 in splicing is characterized in its mammalian temperature-sensitive mutant. *Journal of Cell Science*, 119, 4944-4951, 2006.
4. Wang, B., Murakami, M., Eguchi-Kasai, K., Nojima, K., Shang, Y., Tanaka, K., Watanabe, K., Fujita, K., Moreno, S. G.., Coffigny, H. and Hayata, I. Effects of prenatal irradiation with an accelerated heavy-ion beam on postnatal development in rats : II. Further study on neurophysiologic alterations. *Advances in Space Research*, 39, 994-1003, 2007.
5. Nenoi, M., Daino, K., Ichimura, S., Takahashi, S. and Akuta, T. : Low-dose radiation response of the $p21^{WAF1/CIP1}$ gene promoter transduced by adeno-associated virus vector. *Exp. Mol. Med.*, 38, 553-564, 2006.

Figure 1, Studies on Radiation Effect Mechanisms



Formation and disappearance of g-H2AX foci in NHEJ-related gene deficient cells after X-irradiation. Cells received X-irradiation with various doses (0-2 Gy) indicated, and g-H2AX was visualized with a specific 1st antibody and a fluorescein-conjugated 2nd antibody at 30 min after the irradiation (Left panel). g-H2AX was also visualized in the cells at the indicated time after the exposure to X-rays (3 Gy) (Right panel).

Figure 2, Studies on Radiation Effect Mechanisms



Dose dependence of the frequency of ventral white spots of the 22-day-old mice. Pregnant females were treated with a single irradiation of gamma-rays, carbon-ions, silicon-ions, and Fe ions at different doses on 9 days of gestation

5.4. Studies on Environmental Radiation Effects

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

Outline of Research Career :
Education : 1983, Yokohama National University (BE in safety engineering) ; 1985, Tokyo Institute of Technology (ME in environmental chemistry) ; 1989, Tokyo Institute of Technology (Ph. D. in environmental chemistry)
Professional Activities : 1989-present, National Institute of Radiological Sciences
Research Interests : Radioecology, environmental chemistry, and ecotoxicology.
Contact point : s_yoshid@nirs. go. jp

Objectives :

The recent rapid changes in energy production systems and life styles of people worldwide have made the environmental radiation research even more important. In order to satisfy the needs for radiation safety and regulations, this research group aims to investigate three subjects related to environmental radiation and radioactivity, i. e. 1) effects of radiation on organisms and ecosystems, 2) exposure of public to natural radiation, and 3) marine dynamics of important radionuclides. The group consists of five research teams : Terrestrial Radiation Ecotoxicology Research Team, Aquatic Radiation Ecotoxicology Research Team, Natural Radiation Exposure Research Team, Cosmic Radiation Exposure Research Team, and Marine Radioecology Research Team. The following describes the progress of each of these teams during FY 2006.

Progress of Research :

1) Effects on organisms and ecosystems

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

Terrestrial Radiation Ecotoxicology Research Team (*Team Leader* : Yoshihisa Kubota)

Among terrestrial organisms, plants (particularly cedar tree), fungi, earthworms and collembolans were selected to study. Cedar and pine trees are known to be radiosensitive and the latter experienced excessive radiation damage in the Chernobyl accident. Fungi, earthworms and collembolans are all soil organisms and have been recognized to play very important roles in the maintenance of the terrestrial ecosystem. The accumulation of data on the radiation effects of these organisms should be useful to understand the impact of radiation on ecosystems. The study on the radiation effect of collembolans had the most progress. Dose-effect relationships of gamma radiation on the survival, growth, and reproduction of *Folsomia candida* (one species of collembolans) were studied in a standard laboratory test for chemical toxicity. *Folsomia candida* was acutely irradiated, and subsequent survival, growth in body length, and number of neonate juveniles produced by irradiated specimens were examined. The 50% lethal dose (LD50) was 1360 Gy, and the 10% and 50% effective doses (ED10 and ED50) for growth were 32 and 144 Gy, respectively. The ED10 and ED50 values for reproduction were 7 and 22 Gy, respectively, indicating that the reproductive damage was most sensitive radiation effect seen in collembolans. The same trend was also observed in earthworm, *Eisenia fetida*.

Aquatic Radiation Ecotoxicology Research Team (*Team Leader* : Hiroshi Takeda)

The studies on the radiation effects of aquatic ecosystems at various end points were carried out by using some selected organisms and experimental model ecosystems.

The radiation effects on developing brains of Medaka (*Oryzias latipes*) were examined under a stereomicroscope in living embryos until hatching. Medaka embryos at 25 - 26 and 28 - 30 stages were irradiated with a single acute dose of 10 Gy of X-ray,

which is lower than the 50% lethal dose (LD50) of the embryos. All the irradiated embryos survived; however, from 6 to 35 h after X-ray irradiation, massive clusters of dead cells were observed either in the entire brain region or mainly in the optic tectum. These dead cells disappeared thereafter, and the irradiated embryos continued to develop apparently normally. The grown irradiated embryos, however, had smaller brains and eyes than the non-irradiated control embryos. At hatching, the irradiated embryos exhibited histological abnormalities in the brain, particularly in the torus longitudinalis, and in the retina, although most of them hatched normally. The results indicate that brain cell death and a reduced brain size can be observed in living irradiated embryos, and suggest that the Medaka embryo is useful for screening the developmental neurotoxicity effects of various hazardous factors.

In order to investigate the radiation effects on ecosystem functioning, paddy soil samples flooded with well water were exposed to gamma rays with a dose rate of 1 Gy day^{-1} for 10 days. After day 5 of the exposure, a brownish discoloration was observed in the supernatants and its presence continued until day 10. To determine the factor causing the discoloration, minerals in the supernatants were analyzed by the droplet PIXE system. The results showed that the amount of dissolved iron in the irradiated samples was significantly smaller compared to that in the non-irradiated control samples. It was demonstrated that irradiation reduced the concentration of dissolved iron in the soil ecosystem. Iron is an essential trace nutrient for plants, and thus the amount of dissolved iron is one of the aspects of ecosystem functioning. Effects of irradiation on the dissolved iron could give a change in soil ecosystem through the depression of iron flux in the long term.

2) Exposure to natural radiation

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

Natural Radiation Exposure Research Team (*Team Leader*: Shinji Tokonami)

The team aims to investigate exposure aspects of natural radiation sources and to develop a method to control their exposures. The team was especially active in making radon and thoron measurements in Hungary because the country has some naturally high radon areas. Hungarian detectors modified and developed by NIRS were placed at different sites, including in village dwellings and in a manganese mine in Hungary, in order to gain information on the average radon and thoron concentration levels. This was the first time parallel measurements of radon and thoron made in Europe. The radon and thoron concentrations in the village dwellings in the summer were found 154 (17 - 1083) and 98 (1 - 714) Bq m^{-3}, respectively. Considering the results of other radon measurements during the winter (814 Bq m^{-3}) and summer (182 Bq m^{-3}), the thoron concentrations were also expected to be higher in winter. In the manganese mine, radon and thoron were measured at 20 points for 6 months, changing the detectors each month. The averages were 924 (308 - 1639) and 221 (61 - 510) Bq m^{-3} for radon and thoron, respectively. These results showed significant variance with the date and place of the measurement. Further investigation is required.

Cosmic Radiation Exposure Research Team (*Team Leader*: Hiroshi Yasuda)

More than 16 million Japanese people go abroad every year using aircraft and about 20 thousand members are working as aircraft crew in Japanese airline companies. At high altitude, they are exposed to enhanced cosmic radiation, and additional radiation dose can exceed 1 mSv per year. However, the situation and the health effects of cosmic radiation exposure are still uncertain. The team thus makes efforts to collect scientific information on dose and effects of cosmic radiation and also to provide them in an easy-to-understand way by the general public. Major tasks are (1) calculation of route doses (effective doses received in aircraft) using the most up-to-date method, (2) development of new detectors to verify calculation results, and (3) improvement of dosimetry system for radiological protection of aircraft crew. Some results obtained by the team are open to public from the NIRS web site "Japanese Internet System for Calculation of Aviation Route Doses (JISCARD) ". In 2006, space weather information (RSS data) from National Institute of Communication Technology was put into JISCARD and also the mobile-phone version of JISCARD was developed and provided for the public.

3) Marine dynamics of important radionuclides

Because many 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 (*Team Leader* : Masatoshi Yamada)

The highly sensitive isotope dilution SF-ICP-MS method combined with two-stage chromatographic separation and purification was developed in order to obtain precise plutonium (Pu) isotope composition in seawater samples. Irish Sea water reference material (IAEA-381) was analyzed for the activities of ^{239}Pu and ^{240}Pu and for the atom ratio of ^{240}Pu/^{239}Pu. The experimentally established values were in good agreement with the certified ones. For the ^{240}Pu/^{239}Pu atom ratio, a value of 0.2315 ± 0.0008 with a high precision (RSD, 0.35 %) was obtained, which was much more precise than the information value of 0.22 ± 0.03 (RSD, 13.6 %) provided by the IAEA certification report. It is our conviction that the precise determination of Pu isotopes in this seawater reference material will be useful for the validation of analytical method for the study of radionuclides in the marine environment.

The $^{239+240}$Pu activities and ^{240}Pu/^{239}Pu atom ratios were determined for the surface waters in the western North Pacific Ocean, the Sulu and Indonesian Seas and the South China Sea. The samples were collected by using a built-in pumping system from an inlet at the bottom of a research vessel (5 - 6 m below sea level). The ^{240}Pu/^{239}Pu atom ratios ranged from 0.199 ± 0.026 to 0.248 ± 0.027, and were significantly higher than the global stratospheric fallout ratio of 0.18. The contributions of the North Pacific Proving Grounds close-in fallout Pu were estimated to be 20 % for the western North Pacific Ocean, 39 % for the Sulu and Indonesian Seas and 42 % for the South China Sea by using the two end-member mixing model. The higher ^{240}Pu/^{239}Pu atom ratios could be attributed to close-in fallout Pu delivered from the Enewetak and Bikini Atolls by ocean currents of branches of the North Equatorial Current to the Southeast Asian seas.

Major Publications :

1) T. Ban-nai, Y. Muramatsu, S. Amachi : Rate of iodine volatilization and accumulation by filamentous fungi through laboratory cultures, *Chemosphere*, 65, 2216-2222, 2006.
2) T. Yasuda, K. Aoki, A. Matsumoto, K. Maruyama, Y. Taguchi, S. Fushiki, Y. Ishikawa : Radiation-induced brain cell death can be observed in living Medaka embryos, *Journal of Radiation Research*, 47, 295-303, 2006.
3) H. Yasuda, M. Takami, T. Ishidoya : Changes in optical transmission caused by gamma ray induced coloring in photoluminescence dosimeter, *Health Physics*, 90, 565-568, 2006.
4) Y. Yasuoka, T. Ishikawa, S. Tokonami, et al. : Evidence of precursor phenomena in the Kobe earthquake obtained from atmospheric radon concentration, *Applied Geochemistry*, 21, 1064-1072, 2006.
5) J. Zheng, M. Yamada : Plutonium isotopes in settling particles : Transport and scavenging of Pu in the western Northwest Pacific, *Environmental Science and Technology*, 40, 4103-4108. 2006.

5.5. Office of Biospheric Assessment for Waste Disposal

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

Outline of Research Career :

Dr. Uchida received his B. S., M. S. and Ph. D. degrees in Agricultural Science from Kyoto University. The title of his Ph. D. thesis was "Studies on radioiodine (^{129}I) transfer paths to agricultural plants". He has been interested in the behaviors of long-lived radionuclides in the environment, e. g., ^{63}Ni, ^{79}Se, ^{90}Sr, ^{99}Tc, ^{129}I, ^{137}Cs, Th and U. He has over twenty years' experience in the fields of radioecology and environmental radiochemistry. Through his research, he has also improved models and parameters in soil-to-crop systems.

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Objectives :

The biospheric assessment of radiation dose to human beings related to the releases of long-lived radionuclides from underground nuclear waste disposal sites is very important for the peaceful use of atomic energy. For this 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 need to have our own data in Japan.

In this office, environmental transfer parameters, such as soil-to-crop transfer factors (TFs) and soil-soil solution distribution coefficients (K_ds), have been collected throughout Japan. Analyses of stable isotopes and some natural radioisotopes in crops and their associated soils have been carried out in order to obtain TFs under equilibrium conditions, while radiotracer experiments have been applied for K_ds in various soils. Since rivers are one of the most important paths of radionuclide transfer from waste disposal sites to agricultural fields, chemical components of major Japanese rivers have also been determined and we published a data book entitled "Elemental concentrations of Japanese rivers (NIRS-M-200) ". In addition, the transfer model for predicting the radionuclide behavior in atmosphere-paddy soil-rice plant systems has been developed.

Progress of Research :

1) Comparison of transfer factors between Cs-137 and stable Cs

The soil-to-plant transfer factor (TF), which is defined as the concentration of an isotope in a crop (in Bq kg^{-1} or mg kg^{-1} dry weight [DW]) divided by the concentration of the isotope in soil (in Bq kg^{-1} or mg kg^{-1} DW), is important for long-term radiation dose assessment.

It is necessary to obtain TF data for long-lived radionuclides under equilibrium conditions ; some naturally occurring radionuclides in the environment such as ^{226}Ra, ^{232}Th, and $^{235,\ 238}U$, and fallout radionuclides derived from atmospheric nuclear weapons testing such as ^{90}Sr and ^{137}Cs have been present in the environment for more than 40 years. However, many long-lived radionuclides generated in nuclear power plants do not exist in the natural environment and there is a general lack of knowledge on their environmental behavior over decades. To fill these gaps, measurement of TF values of naturally existing elements rather than radioactive nuclides can be a powerful tool to obtain TF values under equilibrium conditions. It has been reported that the TF values of fallout ^{137}Cs are 3-6 times higher than those of native Cs suggesting that physico-chemical forms of global fallout ^{137}Cs differ slightly from naturally occurring stable Cs TF data for fallout ^{137}Cs and stable Cs for crops collected from the 2002 to 2005 are plotted for comparison in Fig. 1. The values were similar but the TF for ^{137}Cs was usually higher than that the TF for stable cesium ($p<0.01$).

The phenomenon can be explained as follows. Fallout ^{137}Cs is more mobile and more easily adsorbed by plants than stable Cs in the soil. Stable Cs is present in the interlayer lattice of clays where it is relatively non labile compared with ^{137}Cs. However, ^{137}Cs and stable Cs have reached an approximately isotopic equilibrium in the bioavailable fraction in the soils ; therefore, the TF value for stable Cs can be used to evaluate long-term transfer of ^{137}Cs in the environment. The same reasoning can be adopted for other elements. For several radioisotopes, there is/are stable isotope (s), such as ^{88}Sr for ^{90}Sr, ^{127}I for ^{129}I and ^{133}Cs for $^{135,\ 137}Cs$,

so that the stable isotopes can serve as analogues.

2) Measurements of TFs of naturally existing elements for brown rice

To obtain local TFs of long-lived radionuclides under natural/equilibrium conditions, we used above mentioned hypothesis, and thus analyses of stable isotopes and natural radioisotopes in rice and wheat grains and their associated soils collected throughout Japan were carried out. We focused on rice, because the consumption of rice is high in Japan and other Asian countries. About 50 elements such as Cs, Sr, Th and U in plant and soil samples were measured by ICP-MS and ICP-OES.

TF values of 36 elements (Li, Na, Mg, Al, Si, P, K, Ca, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, As, Se, Rb, Sr, Mo, Cd, Sn, Cs, Ba, La, Ce, Pr, Nd, Eu, Tb, Ho, Pb, Th and U) obtained for brown rice samples are listed in Table 1. TFs of C (most of which is accumulated from the atmosphere) and N, and Ga, Hf and W (numbers of measured samples were less than 50% of total sample numbers) are not listed. The probability distributions of TFs for Mn, Co, Sr, Cs, La, Th and U were recognized as log-normal type distributions. Other elements showed a similar trend. Thus the arithmetic mean was not used, but GM and 95% lower and upper confidence limits were calculated as reported in TRS-364.

The highest GM of TF (TF-GM) for brown rice was observed for P followed by Mo, Zn, Mg, K and Rb. In upland field crops, the highest TF-GM was observed for K followed by P, Rb, Mo, Mg and Zn as reported previously. From these results, TF-GMs had the same tendency for these crops, however, TF-GMs were usually low in brown rice and white rice.

The TFs for brown rice for selected elements, Mn, Co, Ni, Zn, Sr, Cs, Pb, and U were compared with those for cereals in TRS-364. We used 'expected' values in TRS-364, which were essentially best estimates ; the compiled data were analyzed to estimate an expected value for TFs so that the value is considered typical or most likely to occur, and GM calculated from compiled data is called an expected value. The expected values of Mn, Co, Ni (wheat), Zn (wheat), Sr, Cs, Pb, and U listed in TRS-364 were 3.0E-3, 3.7E-3, 3.0E-2, 8.8E-1, 1.2E-1 (clay, loam pH=6), 1.0E-2 (clay, loam pH=6), 4.7E-3, and 1.3E-3, respectively, while TF-GMs of these elements obtained in this study were 4.6E-2, 9.3E-4, 1.3E-2, 2.4E-1, 3.1E-3, 9.5E-4, 2.8E-4, and 5.6E-5, respectively. The present TF values were lower than the expected values in TRS-364. Thus, when TFs compiled in TRS-364 were used, it would be necessary to consider that the values were higher than observed in the natural environment. It is likely that differences of plant species, water management practices and amounts of elements in plant available fractions in soil affect the TFs.

3) Studies on selenium sorption behavior on humic acid

We have collected K_d values using several radionuclides, such as ^{137}Cs, ^{75}Se, and ^{85}Sr. Among these isotopes, Se is of great interest because it takes anionic forms under the natural soil environment. Its long-lived radioisotope, ^{79}Se, a fission product from ^{235}U, is a major radionuclide that must be considered in long-term environmental dose assessment due to its long half-life (1.1 million years). In addition, Se is an essential element, but it is also toxic to animals including humans when ingested excessively. Soil contamination with Se will become a bigger problem in the future because Se consumption for industrial purposes is increasing. Therefore, it is important to have knowledge about the mobility of Se in surface soils. Thus, further studies on Se sorption mechanisms in soil were carried out.

There have been some reports about the mobility of Se in soil. Compared to metallic elements, Se mobility is higher ; however, its mobility is lower than that of anionic elements, such as technetium and iodine. The mobility of Se in soil would be affected by various factors, such as active Al content and active Fe content. Also, soil pH is recognized as an important factor affecting Se sorption on soil. However, sufficient studies detailing Se sorption kinetics on soil organic matter are lacking. Humic substances, one of the main forms of soil organic matter, can be classified into humic acid (HA), fulvic acid (FA), and humin. The present study dealt with HA because it is present in greater amounts than FA in some Japanese soil types, and it is an important factor influencing Se sorption. In this study these two kinetic models were discussed as a function of the initial Se concentration and solid/liquid ratio to show Se sorption mechanisms on HA.

Se sorption on HA was investigated as a function of initial Se concentration and solid/liquid ratio using the batch sorption test. It was found that the kinetics of Se sorption on HA was described by the pseudo-second order reaction model, and the sorption mechanism on HA was not a single process one, but it would be explained as specific sorption and/or non-specific sorption due to ionic strengths. Additionally, the relationships of the amount of sorbed Se on HA as a function of initial Se concentration or solid/liquid ratio were obtained. With these empirical equations, the 3-D empirical equation of the amount of sorbed Se as a function of initial Se concentration and solid/liquid ratio was described. The results showed that the equation fitted well, and thus, Se sorption mechanism would be

expected to be multiple processes. By using the 3-D empirical equation, environmental assessments of soil contamination would be done more accurately for some contaminant types.

Major Publications :

1) K. Tagami, S. Uchida: Sample storage conditions and holding times for the determination of total iodine in natural water samples by ICP-MS, *Atomic Spectroscopy*, 26, 209-214, 2005
2) K. Tagami, S. Uchida, I. Hirai, H. Tsukada, H. Takeda: Determination of chlorine, bromine and iodine in plant samples by inductively coupled plasma-mass spectrometry after leaching with tetramethyl ammonium hydroxide under a mild temperature condition, *Analytica Chimica Acta*, 570, 88-92, 2006
3) N. Wakae, N. Ishii, S. Shikano, S. Uchida: The influence of paddy soil drying on Tc insolubilization by bacteria, *Chemosphere*, 63, 1187-1192, 2006
4) K. Tagami, S. Uchida: Concentrations of chlorine, bromine and iodine in Japanese rivers, *Chemosphere*, 65, 2358-2365, 2006
5) N. Ishii, S. Uchida: Removal of techentium from solution by algal flagellate Euglena gracilis, *Journal of Environmental Quality*, 35, 2017-2020, 2006.

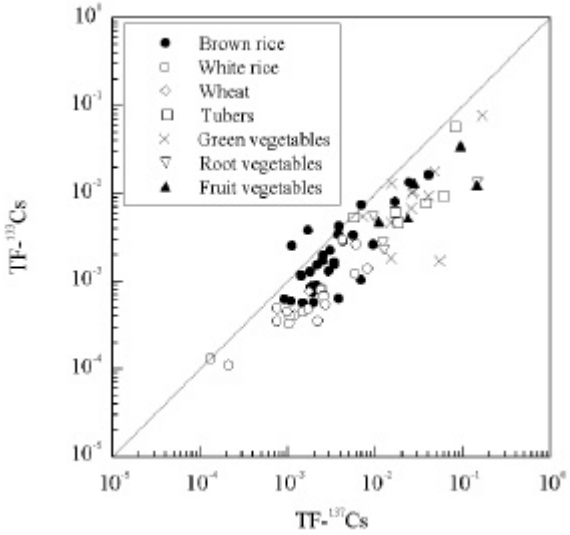

Fig. 1 Relationship between TF-137Cs and TF- stable native 133Cs for various crops.

Table 1 Soil-to-brown rice transfer factors of 36 elements on dry weight basis

	Li	Na	Mg	Al	Si	P	K	Ca	Ti	V	Cr	Mn
N*1	44	50	50	36	50	50	50	50	42	50	50	50
Minimum	1.8E-5	3.2E-4	8.8E-2	2.3E-6	9.3E-5	3.7E-1	8.7E-2	2.2E-3	3.5E-5	2.1E-6	2.3E-4	1.7E-2
Maximum	3.6E-4	6.9E-3	2.4E+0	2.5E-4	2.7E-3	9.4E+0	7.8E-1	4.6E-2	4.2E-4	3.2E-4	1.9E-2	1.2E-1
Max. /Min.	19	21	27	109	29	25	9	21	12	149	81	7
Median	7.2E-5	9.9E-4	2.0E-1	2.0E-5	5.1E-4	2.5E+0	2.0E-1	8.4E-3	1.4E-4	5.0E-5	1.8E-3	4.9E-2
Geometric Mean	6.2E-5	9.8E-4	2.4E-1	2.2E-5	5.2E-4	2.4E+0	2.2E-1	8.8E-3	1.4E-4	4.6E-5	2.0E-3	4.6E-2
Lower 95% confidence limit	1.6E-5	2.6E-4	5.8E-2	3.8E-6	1.3E-4	7.5E-1	7.5E-2	2.1E-3	5.9E-5	9.3E-6	1.6E-4	1.8E-2
Upper 95% confidence limit	2.4E-4	3.7E-3	9.6E-1	1.3E-4	2.2E-3	7.9E+0	6.2E-1	3.7E-2	3.4E-4	2.3E-4	2.4E-2	1.2E-1
	Fe	Co	Ni	Cu	Zn	As	Se	Rb	Sr	Mo	Cd	Sn
N*1	50	49	50	50	50	50	41	50	48	50	50	43
Minimum	7.5E-5	2.4E-4	3.4E-3	3.2E-2	7.3E-2	3.0E-3	9.5E-3	8.8E-3	9.6E-4	2.8E-1	9.0E-3	1.0E-3
Maximum	1.3E-3	6.4E-3	8.7E-2	3.5E-1	6.8E-1	3.4E-2	2.9E-1	2.2E+0	1.0E-2	3.4E+0	1.1E+0	1.7E-1
Max. /Min.	17	27	26	11	9	11	30	251	11	12	127	172
Median	2.9E-4	9.1E-4	1.2E-2	1.0E-1	2.5E-1	9.1E-3	7.0E-2	1.2E-1	3.1E-3	7.0E-1	7.8E-2	5.0E-3
Geometric Mean	2.9E-4	9.3E-4	1.3E-2	1.0E-1	2.4E-1	9.2E-3	6.7E-2	1.2E-1	3.1E-3	7.6E-1	9.4E-2	6.4E-3
Lower 95% confidence limit	9.8E-5	2.7E-4	2.8E-3	3.5E-2	1.0E-1	2.6E-3	1.7E-2	1.2E-2	1.1E-3	2.3E-1	8.8E-3	5.6E-4
Upper 95% confidence limit	8.4E-4	3.2E-3	6.1E-2	3.1E-1	5.7E-1	3.3E-2	2.6E-1	1.1E+0	9.1E-3	2.5E+0	1.0E+0	7.3E-2
	Cs	Ba	La	Ce	Pr	Nd	Eu	Tb	Ho	Pb	Th	U
N*1	50	50	45	33	29	37	27	32	27	50	40	32
Minimum	1.3E-4	3.4E-4	1.8E-5	1.9E-6	1.7E-5	1.8E-5	7.5E-5	5.1E-5	2.4E-5	8.8E-5	2.2E-5	8.6E-6
Maximum	1.6E-2	7.8E-3	4.2E-4	3.4E-4	4.9E-4	4.1E-4	1.7E-3	2.4E-3	1.4E-3	3.5E-3	8.3E-4	3.1E-4
Max. /Min.	122	23	24	180	29	23	22	46	58	39	37	36
Median	7.1E-4	2.0E-3	4.7E-5	3.5E-5	6.1E-5	4.7E-5	2.4E-4	2.4E-4	1.7E-4	2.4E-4	9.4E-5	4.9E-5
Geometric Mean	9.5E-4	1.8E-3	4.9E-5	3.3E-5	6.4E-5	5.0E-5	2.6E-4	2.8E-4	1.8E-4	2.8E-4	1.0E-4	5.6E-5
Lower 95% confidence limit	9.9E-5	4.4E-4	1.3E-5	3.9E-6	1.1E-5	1.3E-5	6.2E-5	5.8E-5	2.6E-5	6.6E-5	1.9E-5	9.8E-6
Upper 95% confidence limit	9.1E-3	7.2E-3	1.8E-4	2.8E-4	3.7E-4	1.9E-4	1.1E-3	1.3E-3	1.2E-3	1.2E-3	5.7E-4	3.2E-4

*1 : Numbers of samples for which concentrations were determined.

6. Research Center for Radiation Emergency Medicine

Outline of Research Career :

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

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Objectives :

This Research Center had the unique experience of receiving three victims heavily exposed 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 by the nuclear disaster prevention plan of the Japanese government since 1980. The Center is responsible for, and has established a solid system for dealing with a radiation emergency from a medical viewpoint. Our required aims are as follows :

To accept victims exposed to radiation who require specialized diagnosis and treatment,

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

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

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

To promote technical development and research on radiation emergency medicine, and

To develop skilled manpower for dealing with a radiation emergency.

Other objectives are to carry out research on radiation emergency medicine. Details are given elsewhere ; only subjects are presented here.

1. Research for diagnosis and treatment of high-dose exposure to radiation,

1-1 Studying mechanisms of radiation injuries leading to developing new agents for treatment, with the focus on skin and gastrointestinal tract,

1-2 Studying indicators for dose of radiation exposure from biological specimens, and

2. Research on dose assessment for victims in radiation accidents.

Overview :

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

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

1) Network System

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

1-1. NIRS Radiation Emergency Medicine Network Council

This is a group of experts and medical organizations from which NIRS asks for help to treat the victims at the time of a nuclear or a radiological accident. The cooperation involves dispatch of an expert in the specific field in an emergency, arrangement of

acceptance of patients at medical facilities affiliated with the expert's organization, and provision of advice. Such collaboration is expected to reinforce the functions of NIRS. NIRS will call the Radiation Emergency Medicine Network Council to solicit cooperation when it is requested by authorities (or when NIRS thinks the necessity arises) to respond to radiation emergencies. This council worked effectively at the time of the JCO criticality accident in 1999.

1-2. Chromosome Network Council

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

1-3. Physical Dosimetry Network Council

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

Topic : Investigation on WBC in the secondary levels of hospitals for radiation emergency

The whole body counter (WBC) is used for measurement of internal contamination. However, it cannot provide meaningful measurements without calibration . The secondary levels of hospitals for radiation emergency have WBCs and victims internally contaminated with radionulides are transported to them. The committed effective dose is important for deciding whether these victims should be transferred to NIRS. We checked WBCs in four hospitals by using BOMAB phantom containing the standard radioactivity source of either ^{137}Cs, ^{60}Co, ^{133}Ba or ^{40}K which NIRS had developed based on the ANSI standard. Using the phantom with ^{137}Cs, we found that the deviation from the standard ranged from -87.5% to + 35%. One of the main reasons for this variation is that the methods of calibration were different among makers of WBCs ; phantoms used by these makers were too small for calibration of these WBCs. Thus, a committee has been constructed for establishment of a standard calibration method in Japan.

1-4. Local Medicine Network Council

In Japan, medical systems are currently being constructed in accordance with disaster prevention plans of local governments that have nuclear facilities in their territories. Within the framework of each local nuclear disaster prevention plan, set up of a specific collaboration system with NIRS is mandatory and it must specify the steps to be performed in the prompt transfer of patients from a site to a hospital, including radiation protection management at the hospital.

2) Training

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

(A) Radiation emergency medicine course (hospital course)
The course is held three times a year with 20 participants in each course. More than 320 participants have been trained so far. Many of them are working actively in primary or secondary levels of radiation emergency hospitals and playing an important role in local radiation emergency exercises.

(B) Emergency rescue training course (pre-hospital course)
The course is held four times a year with 30 participants in each course. The duration of the course is 3days.

(C) Training course for the "whole body counter" measurement
The persons who are responsible for estimation of internal exposure dose in the case of a radiation emergency are trained to be able to measure and estimate internal dose by themselves.

3) Emergency Exercises

National and local governments in Japanese regularly organize emergency exercises to which we send our staff to take roles in emergency medicine and radiation protection. On 25-26 October 2006 the Japanese government conducted a nuclear disaster prevention exercise in Ehime prefecture. Our staff participated in this. Moreover we conducted an additional exercise to simulate emergency handling, especially dose assessment.

4) Follow-up Studies

The center also carries on follow-up clinics for the victims of the thermonuclear weapons test on the Bikini Atoll, patients with thorotrastosis and the surviving JCO accident victim.

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

During the nuclear test on Bikini Atoll on 1 March, 1954, 23 crew members (18 to 39 years old at the time)

of the Lucky Dragon (Dai-go Fukuryu-maru) out of Yaizu City, Shizuoka Prefecture, were exposed to radiation. This follow-up survey aims to examine the physical states of these patients over a long period of time to study late radiation injuries. The follow-up examinations that have been conducted for 50 years provide precious data. The type of exposure was external and also internal, and the estimated dose was 1.7 to 6.0 Gy. A physical checkup of still living survivors was conducted at NIRS and Yaizu City General Hospital this year.

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

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

5) Database

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

6) Special topic : Polonium-210 analysis in urine samples of Japanese involved in the UK Po-210 incident

The first-ever nuclear terrorism event occurred in November 2006 in London, UK. A former Russian spy was killed using 210Po and some areas were contaminated with 210Po. The Health Protection Agency (HPA) in UK found that there were some Japanese travelers in the contaminated area at London, and informed us of their addresses. We tried to contact these travelers and could question three of them. Among them, two agreed to checking levels of ^{210}Po contents of in their 24-hr urine samples. They were admitted to the NIRS hospital and 24-hr urine samples were collected. Three smokers and three non-smokers, all Japanese men living in Chiba, were also analyzed as control. After decomposing a portion of urine sample (200 ml) with a spiked tracer (^{209}Po) using mineral acid, ^{210}Po and ^{209}Po were deposited on a silver disk spontaneously in diluted hydrochloric acid. The isotopes were analyzed by α-spectrometry. Daily ^{210}Po excretion in controls was found to be in the range of 12 to 85 mBq. Mean value was 33 mBq. The values of the two tourists were lower than the maximum value of control. It was concluded, therefore, that there was no contamination of the tourists. In general, an intake of ^{210}Po in smokers was higher than that of non-smokers. However, the reason for the difference was not clear due to this small sample numbers. Dietary intake of ^{210}Po has been reported to be 600 mBq per day person in Japanese, being higher that average groups in the world. Excretion, 72 mBq in 24-hr urine was estimated from the dietary intake of 600 mBq.

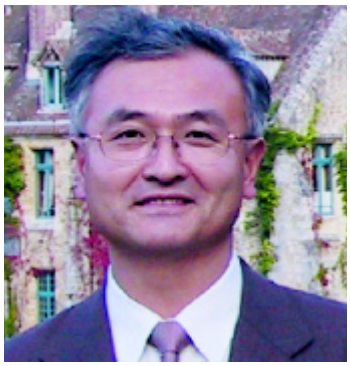
7) International Cooperation

1. Six professionals from Beijing Institute of Radiation Medicine visited our facility and discussed a future cooperative project for radiation emergency medicine with NIRS staff on 29 June 2006.
2. Invited lectures
   Staff members were invited to give lectures in the following meetings and training courses.
   (1) A training course held in Jakarta, Indonesia from 6 to 11 November 2006 sponsored by the JAEA.
   (2) Global Health Security Action Group Working Group on Radionuclear Threat Health Implications of Radiological Terrorist Incidents Workshop and Simulation Exercise held in Paris, France on 19 and 20 June 2006 supported by the Ministry of Health, Labour and Welfare, Japan.
   (3) International Symposium " Emergency Medical Response for Radiation Accidents " held in Ulsan, Korea from 18 to 20 April 2006.
   (4) A lecture regarding " Internal Dosimetry in Inhalation Intakes " held at Fudan University in

Shanghai, China on 28 June 2006.

3. Organization of meetings
   (1) International Workshop on Radiation Emergency Medical Preparedness within the Framework of the Asian Nuclear Safety Network collaborated with IAEA and NEAT held on 17 November 2006.
   (2) Meeting on Radiation Emergency Medical Preparedness and Response in Asian countries was organized from 30 January to 1 February and from 27 February to 1 March 2007. The former was held with 4 participants from South Korea, and the latter was held with 16 participants from Indonesia, South Korea, Mongolia, Philippines, Thailand, and Vietnam.
4. Staff members attended the International Conference on Polonium 210 : The public health response held in London, England on 27 and 28 March 2007.
5. Members of international committees
   (1) IAEA Assistance Work Group (AWG) and Expert Groups (EG) meetings held in Milan, Italy on 6-8 June and in Vienna, Austria on 6 - 8 June 2006.
   (2) The 11th Coordination and Planning Meeting of the WHO REMPAN Collaborating Centers and Liaison Institutions held in Kiev, Ukraine on 25-28 April 2006.
   (3) Meeting for medical database of radiation accidents held Beijing and Xiamen, China from 29 November to 1 December 2006.

6.1. The Study for Medical Treatment for High Dose Exposure



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

Outline of Research Career :

Dr. Akashi started his medical career at Jichi Medical School (Tochigi Prefecture) as a junior resident of internal medicine in 1981. He worked as a senior resident at the Division of Hematology of Jichi Medical School and moved 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 activities 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 :

Study on injuries and therapeutic measures in high-dose radiation exposure

This group conducts studies that are usually not performed by other research institutions, emphasizing the diagnosis and treatment of radiation injuries due to high-dose exposure.

1) Research for mitigation of radiation injuries caused by high-dose exposure

The group tries to clarify the mechanism of injuries in cells and tissues exposed to high doses of radiation and dose effects on survival, repair, and maintenance of function. It evaluates candidate substances for therapeutic drugs particularly for gastrointestinal and skin injuries. Regarding gastrointestinal injuries due to radiation, the group uses experimental animals, primary cultured cells, and tissues to develop quantitative evaluation systems. For the study of skin injuries, cultured skin cells and the skin model system using feeder and epithelial cells are used to explore basic mechanisms of injury and fibrosis due to high-dose radiation exposure.

2) Research on diagnostic measurements for high - dose exposure

To develop diagnostic measurements in high-dose exposure to radiation, this group tries to find markers for radiation exposure from bio-molecules contained in samples which can be collected less invasively, such as cells and blood. The group tries to determine genes, proteins, and other constituents of the living body that can provide a guide to treatment for radiation exposure.

Progress of Research :

1) Research for mitigation of radiation injuries caused by high-dose exposure

1-1. Study on treatment of skin in high-dose radiation exposure

Recently, it has been found that fibroblast growth factors (FGFs) protect and enhance repairing radiation-induced tissue damage. They need the binding of heparan sulfate proteoglycan (HSPG) to activate their target receptors. We investigated the effect of ionizing radiation on the biosynthesis of HSPG in human HaCaT keratinocytes. Levels of two sulfotransferases, HS2ST1 and HS6ST1, were significantly increased in the HaCaT cells 24 hr after X-ray irradiation. Addition of hydrogen peroxide decreased the levels of these enzymes in HaCaT cells. Transfection of the catalase gene also induced an increase of HS2ST1 and HS6ST1 expression in the cells. In addition, Western blot analysis showed that the smeared bands of HSPG were clearly shifted to higher-molecule-weight in the transfectants owing to glycosylation. These enzymes are known to play a critical role in the formation of binding complexes of HSPG with FGFs and their receptors. Indeed, siRNA-mediated repression of catalase or HS2ST1 significantly inhibited FGF7-inudced proliferation of HaCaT cells. These findings suggest that hydrogen peroxide inhibits sulfation of specific sites in HSPG in irradiated cells. Thus, hydrogen sulfate may play a role as a negatively signaling molecule to promote the regeneration of irradiated skin.

1-2. Study on mitigation of gastrointestinal tract (GIT) injuries by high-dose radiation exposure

Exposure to high dose radiation causes lethal GIT injuries. This is largely due to apoptosis of intestinal epithelial cells and subsequent depletion of the stem cells. We found that lysophosphatidic acid (LPA) and ginsenosides Rd and Rg1 prevent and rescue radiation-induced apoptosis *in vivo* and *vitro*.

LPA, a biogenic phospholipid, is linked to a variety of cellular responses including differentiation, proliferation, migration, or inhibition of apoptosis. Pretreatment

of the rat small intestinal epithelial IEC-6 cells with LPA significantly inhibited apoptosis by radiation. Addition of LPA to these cells after radiation also blocked the apoptosis. Inhibition of either PI3K/Akt or MEK pathway significantly attenuated anti-apoptotic effect of LPA. In contrast, treatment with an inhibitor of p38 MAPK pathway did not affect the apoptosis. LPA activated phosphorylation of Akt and ERK1/2 but not p38 MAPK in irradiated cells. Moreover, LPA inhibited activation of caspase-3 and -9 in irradiated cells. LPA increased levels of Bcl-2 and Bcl-xL without affecting Bax levels. Thus, these results suggest that LPA protects and rescues IEC-6 cells from radiation-induced apoptosis through activation of a pathway involving PI3K/Akt and ERK. We also show that the mitochondrial pathway is important for anti-apoptotic effects of LPA.

Ginsenosides are the main pharmacoactive molecules of ginseng, the root of Panax ginseng C. A. Meyer. Ginsenosides Rd and Rg1 have been identified as two of the most effective compounds responsible for pharmaceutical actions of ginseng. Rg1 blocked radiation-induced apoptosis of these cells in a dose-dependent manner. Inhibitor of either MAP kinase kinase (PD98059) or p38 mitogen-activated protein kinase (SB230580) significantly decreased the number of apoptotic cells, whereas an inhibitor of the phosphoinositide-3 kinase (LY294002) pathway, attenuated the anti-apoptotic effects of Rg1. Radiation activated phosphorylation of the extracellular signal-regulated protein kinase (ERK), p38, and Akt proteins. Treatment with Rg1 either before or after irradiation inhibited phosphorylation of ERK and p38 MAPK, but enhanced phosphorylation of Akt. Rg1 also decreased levels of Bax and caspase 3, and increased Bcl-2 expression. Studies of immuno-histochemistry found that Rg1 significantly improved recovery of crypt architecture and also reduced the number of apoptotic bodies in the crypt of irradiated mice. In conclusion, Rg1 protects and rescues intestinal injuries *in vitro* and *in vivo* through activation of the PI3K/Akt pathway and, via inhibition of the MEK/p38 MAPK pathway.

1-3. Study on the mechanism for radiation-induced GIT injuries

The mechanisms of GIT injuries by radiation was studied using mice. Mouse intestinal epithelial cells were obtained subsequently along the crypt to villus axis by the modified method of Weiser. Western blot analysis showed that proteins of the proliferating cell nuclear antigen (PCNA), Bax and Bcl2 were constitutively expressed in the crypt and their levels were reduced toward the villus axis. On the other hand, active form of caspase 3, and cytochrome c were accumulated in the villus tip. Radiation increased levels of Bax, active form of caspase 3, and cytochrome c with concomitant reduced levels of PCNA and Bcl2 in the crypt. In contrast, radiation did not affect the caspase 3 and cytochrome c in the villus tip. The p53 and p21 proteins were not detected in intestinal epithelial cells without radiation. However, radiation increased the levels of these proteins toward the crypt but not in the villus. On the other hand, the p27 protein was constitutively expressed in the crypt, and radiation decreased its level in the crypt. Our results suggest that the cell proliferation and response to radiation is differentially regulated in the crypt from the villus ; p53 may play an important role in the crypt.

Tumor necrosis factorα (TNFα) has both apoptotic and anti-apoptotic properties depending on the activation of signaling pathways. The human T cell line Jurkat cells were transfected with TNFα short interfering (si) RNA (siRNA). Studies of competitive PCR showed that an increased level of TNFα mRNA was observed immediately after irradiation in control cells. However, the knock-down of TNFα using siRNA significantly abolished the irradiation-induced accumulation of TNF? mRNA. We also investigated the mRNA levels of Bax, Bcl-2, and Bcl-XL. Levels of Bcl-2 and Bcl-XL mRNA were similar in control cells and siTNFα cells. However, the level of Bax mRNA was apparently higher in siTNFα than control cells but radiation failed to increase the level in both cell lines. On the other hand, staining with Annexin-V and detection of DNA fragmentation showed that irradiation at a dose of 10 Gy induced apoptosis more frequently in the control cells than TNFα siRNA cells. These results indicate that irradiation induces apoptosis through a pathway requiring TNFα production. Our results also suggest that apoptosis by irradiation occurs independent of the Bax expression.

1-4. Study on endothelial cells exposed to high-dose radiation

The balance between survival and cell death of vascular endothelial cells is regulated by a homeostatic mechanism. This homeostatic mechanism is deregulated by exposure to radiation. It is known that vascular endothelium is a principal target for radiation injury to the GIT, lung, brain, and skin. Thus, vascular damage is a key mechanism in radiation injuries, and death and proliferation of the vascular endothelial cells are the primary lesion leading to stem cell dysfunction.

We examined the effects of vascular endothelial growth factor (VEGF) and copper/zinc superoxide dismutase (Cu/ZnSOD) on cell growth in radiation using human primary umbilical vein endothelial cells (HUVEC). Studies of cell growth and proliferation showed that radiation suppressed the cell growth in a dose-dependent manner. Moreover, assays of WST1 and colony formation showed that treatment of these

cells with VEGF or Cu/ZnSOD before or after radiation, rescued the cell growth suppression and both factors activated the phosphorylation of ERK1/2 in irradiated cells. We also found that VEGF or CuZnSOD restored endothelial damage caused by radiation. Thus, our results indicate that VEGF and Cu/ZnSOD may be candidates of therapeutic agents for radiation-induced injury.

VEGF or fibroblast growth factor-2 (FGF-2) significantly increased viability, up-regulated telomerase activity, and inhibited apoptosis in irradiated HUVECs. VEGF synergistically suppressed apoptosis with FGF-2 in irradiated cells. VEGF was more effective than FGF-2 in inhibition of radiation-induced apoptosis. This anti-apoptotic effect of VEGF occurred through up-regulation of telomerase activity and subsequent activation of PI3K/Akt pathway.

1-5. Functional analysis of PIDD protein as a drug target for protection from ionizing radiation-induced cell death

PIDD (p53-induced protein with a death domain) plays a critical role in the activation of caspase 2 to trigger DNA damage-induced apoptosis through the formation of a so-called PIDDosome, which contains the adaptor protein RAIDD and caspase 2. PIDD also plays an essential role in DNA damage-induced activation of the anti-apoptotic transcription factor NF-κB through the formation of an alternative PIDDosome, consisting of PIDD, RIP1 and NEMO. We found that transcription of PIDD was induced after exposure to ionizing radiation in rat epithelial cell line (IEC6) cells, suggesting that PIDD might be a drug target for protection from radiation-induced gastrointestinal cell death. When IEC6 cells were exposed to radiation, ubiquitinated and SUMO-modified NEMO was observed, which is required for the activation of NF-κB. The modification of NEMO was also observed even in the unirradiated cells when full-length human PIDD cDNA was overexpressed in IEC6 cells. Yeast two-hybrid analysis indicated that the death domain of PIDD interacts with RAIDD. In order to inhibit the PIDD-mediated apoptosis with designed synthetic peptides, we are currently pursuing fine mapping of regions involved in the interaction of PIDD with RAIDD using yeast two-hybrid analysis.

1-6. Study on agents affecting the survival of irradiated mice

The aim of this study is to establish the treatment for damage following high-dose radiation exposure. We studied molecular mechanisms of the effects of chemicals, medicines, natural substances and genes on mice or cells that were irradiated with high doses.

Heat-inactivated Saccharomyces containing metals were injected intraperitoneally to C3H/He inbred mice before or immediately after whole-body irradiation of lethal dose (7.5Gy) of X-ray and 30-day survivals were estimated. Under the 7.5Gy irradiation without any treatment, 30-day survival rates was 6% (n=334). When the Saccharomyces containing zinc, copper, manganese or selenium were administrated at 100mg/kg immediately after irradiation, 30-day survival rates were 90% (n=73), 91% (n=33), 81% (n=37) and 75% (n=47), respectively. Similarly, the increase in the survival rate of 98% (n=42) was also found by the administration of gamma-tocopherol N, N-dimethylglycine ester hydrochloride at 100mg/kg immediately after irradiation.

2) Research on diagnostic measurement for high-dose exposure patients

The aim of this project is to establish the methods for evaluating the effective dose and other radiation effects using biological samples based on the molecular and biochemical technology. It is already known that the parasites such as endogenous viruses in the microorganisms are activated by lethal damage of the host microorganisms. Since mammalian genome possesses thousands of copies of DNA elements that encodes endogenous retrovirus-like transposon, we focused on retrotransposon, intracisternal A-particle (IAP) DNA element in mouse. To distinguish from the endogenous IAP, synthetic IAP DNAs that possess nucleotide sequence markers, were constructed and stably introduced into the RAW264.7 mouse cells. Based on the real-time PCR method to quantitate very low levels (approx. 0.001 copy/ haploid) of reverse-transcripts that are generated by the activation of IAP, a method was established. When the cells were irradiated at 3 to 5 Gy of X-ray, the levels of these reverse transcripts were significantly increased. This suggests that the effective dose of radiation at the cellular level is measurable by specific quantification of a trace amount of nucleic acid.

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2) W Dobrowsky, NG Huigol, S Ranapala, H Tatsuzaki, et. al : AK-2123 (Sanazol) as a radiation sensitizer in the treatment of stage III cervical cancer : results of an IAEA multicentre randomised trial., Radiotherapy and Oncology, 82, 24-29, 2007
3) K Suzuki, I Tanaka, I Nakanishi, A Kurematsu, H Yakumaru, N Ikota, H Ishihara : Drastic effect of several caffeic acid derivatives on the induction of

heme oxygenase-1 expression revealed by quantitative real-time RT-PCR., BioFactors, 28, 151-158, 2006
4) H Wan, H Ishihara, I Tanaka : Immediate-early Inducible Function in Upstream Region of junB Gene, Biomedical and Environmental Sciences , 19, 210-213, 2006
5) K Yoshida, Y Hirabayashi, F Watanabe, T Sado, T Inoue : Caloric restriction prevents radiation-induced myeloid leukemia in C3H/HeMs mice and inversely increases incidence of tumor-free death : implications in changes in number of hemopoietic progenitor cells, Experimental Hematology, 34, 274-283, 2006
6) L Huang, M Watanabe, M Chikamori, Y Kido, M Shibuya, N Tsuchida, T Yamamoto : Unique role of SNT-2/FRS2beta/FRS3 docking/adaptor protein for negative regulation in EGF receptor tyrosine kinase signaling pathways, Oncogene, 25, 6457-6466, 2006
7) M Chikamori, J Fujimoto, N Nishizumi, T Yamamoto: Identification of multiple SNT-binding sites on NPM-ALK oncoprotein and their involvement in cell transformation, Oncogene, in press.

6.2. Research on Radiation Dose Assessment for Radiation Emergency Medicine

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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 28 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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Objectives :

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

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

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

Progress of Research :

Development of ESR dosimetry using human nail clippings

Electron spin resonance (ESR) dosimetry is a method to measure radical numbers produced by radiation in substances and to estimate exposure dose. This method is useful for dose estimations when workers are exposed while not wearing personal monitors and when the general public is exposed accidentally. Tooth enamel is typically used for this purpose. However, teeth cannot be extracted easily from the persons in all cases. It is necessary to find other human tissues or substances around exposed persons that can be used to estimate personal exposures. Nail samples are more easily obtained from exposed persons than tooth enamel samples. Therefore, nail samples were applied to ESR dosimetry in the case of γ-irradiation. Stability of free radicals in nail clippings was found to differ among individuals. Decreasing of radicals (fading) produced in the nail sample after irradiations of 3.75, 7.5, 11.3, and 15 Gy was measured by ESR for one week. A linear relationship between ESR sensitivity and absorbed dose (Gy) was obtained to be linear by curve-fitting of the fading conditions. Unknown dose of γ-exposed nail clipping was estimated within 30% errors using the obtained calibration curve. However, analysis time was too long for radiation emergency purpose. A more rapid method must be developed for practical use.

Chromosome aberration analysis

For cytogenetic dosimetry in radiological emergencies, it is important to keep the quality level of the chromosome analysis in the biological dosimetry laboratory. Therefore, we analyzed the chromosome abnormality of human lymphocytes irradiated at the doses of 0, 0.2, 0.5, 1.0, 2.0, 3.0, 4.0, 5.0Gy. The frequencies of dicentric chromosomes at each dose points in these analyses were almost identical with those previously obtained by other investigators.

The Metaphase Finder, one part of the chromosome analysis system, has been developed. It consists of a motorized microscope, camera and computer. The finder scans the slide glass and finds metaphase cells in which chromosomes can be seen, records their positions and relocates them to be seen by the

cytogenetists or machine analyzer. New features of the software for the Metaphase Finder were added this year as follows :

a) The metaphase position converter was added to adjust inter-microscope difference.
b) Digital cameras were found to be usable for image processing.
c) A new algorithm for binarizing the cells was developed.
d) A new metaphase finding program was tested for fluorescent images.

In the protocol for the chromosome analysis, it is important to distinguish clearly the centromere. From this viewpoint, we have also analyzed the relationship between the degree of chromosome condensation, the treatment period and the concentration of Colcemid. There were no differences in the chromosome condensation at the concentration of 0.02 - 0.1 μg/ml for 48 hrs treatment. In the present project, we also analyzed the chromosome abnormality in the embryonic fibroblasts, because of the preparedness of the biological dosimetry in persons who had been irradiated partially. Unfortunately, the metaphases suitable for the analysis were not obtained in the experiment, because there are some problems in the timing of slide preparation after irradiation of cells.

Nose swab for alpha emitters

Alpha emitters are the most dangerous materials for internal exposure. A nose swab method is a useful way to detect lung contamination just after accidental inhalation of alpha emitters. It is quite difficult to determine the quality of an inhaled radioactive volume yet. Filter paper or cotton swab is used for the nose swab method. For determine the quality of nose swab samples, detection efficiency for alpha radiation was tested on several filter papers. Plutonium oxide suspension or plutonium nitrate solution was dropped onto the filter paper as simulated nose swab. Detection efficiency was calculated from the alpha activity measured by an alpha scintillation counter. The detection efficiencies for some filter papers were compared with that of stainless steel disk. All detection efficiency for filter paper showed lower than that for stainless steel disk. This result indicates that the activity of nose swab is underestimated when counting efficiency is determined by the standard calibration method using a stainless steel disk source. The detection efficiency for plutonium oxide was higher than that for plutonium nitrate. This indicated that plutonium oxide stayed on the surface of the filter paper as aerosol particle. This result suggested that physical and chemical forms for plutonium affected determination of the quantity needed for nose swab.

Development of integrated WBC and basic study on phantoms for calibration

Instead of the conventional whole body counter (WBC) using the 8"Φ×4" NaI (Tl) scintillator which has a scanning bed geometry, an integrated WBC was developed. This integrated WBC is intended for use in identifying nuclides in multiple contamination cases. This counter has ten detectors which are located just above the target organ in order to improve the identification of nuclides. Two sets of p-type arrayed planar Ge detectors composed of two crystals are used for lungs and two sets of p-type high efficiency coaxial Ge detectors are used for intestine. Similarly, the n-type coaxial detector is used for thyroid and other p-types are used for skull, liver and gastrointestinal tract, respectively. An electric cooling system based on adiabatic expansion was adopted as the cooling apparatus for all detectors with the objectives of preventing asphyxia and operating continuously.
In the case of lung measurement, the chair is set at a locus position to prevent deformation of lungs. All other measurements are performed at a decubitus position to reduce a burden of a patient.

As for the efficiency calibration, a JAERI phantom with newly-designed tissue equivalent lungs which contain ^{241}Am homogeneously was applied to lung detector and a BOMAB phantom regulated by ANSI was also applied to detectors for trunk. This system shows 2.55 times improvement of MDA compared to that of previous NaI (Tl) system for ^{137}Cs. It demonstrates the new system is a considerable improvement in radiation emergency preparedness.

We also investigated LLNL phantom for the lung monitor. When a transuranic element such as ^{239}Pu is inhaled, we must measure the low energy LX-rays which are difficult to measure accurately with the lung monitor. However, LX-rays are influenced strongly by properties of the medium which they passed through. The LLNL phantom which is referenced to Westerner was used to calibrate the lung monitor. That phantom was very different from Japanese. So, we developed the phantom for calibrating the lung monitor which was fitted to the Japanese physical size. Now, we confirm the phantom was agreed with the formation which was designed. The formation of the lung models in the phantom agreed with MRI data for individual lung as well, and the characteristics for radiation penetration also had good agreement. One of the lung models was sliced, and the uniformity of the internal structure was actually confirmed, and a chemical composition analysis was done. Additionally, the uniformity of the distribution of ^{241}Am (LX-rays and γ ray sources) was confirmed by imaging plate analysis as well as the structure of polyurethane.

A rapid analysis technique of uranium in urine samples

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

In this study, the strontium specific resin column, microwave digestion (MW) technique and inductively coupled plasma mass spectrometry (ICP-MS) were combined to develop a rapid urine analysis of ^{238}U in human urine samples. An aliquot of ^{238}U standard solution was added to get final concentrations of 1.2-10 μg per fresh urine samples of 20ml (63-500ng/ml-urine). The spiked urine samples were digested by the MW technique. A good recovery (above 86-99 %) was obtained. The total analysis time was ca. 8 hr. This would be an effective bioassay method in a radiation emergency and also a good way to prevent a detector contamination of ICP-MS instrument by the high matrix urine samples.

Computer code for internal dose evaluation

Computer code MONDAL3 has been released for all users including non-specialists to estimate committed effective dose based on measurement results of individual monitoring. Also the preparation for database update was performed on the basis of a new human alimentary tract model and revision of the ICRP recommendations for radiological protection. On the assumption that the characteristics of the intake pathway, chemical form or AMAD (Activity Median Aerodynamic Diameter) of inhaled aerosols would be unidentified at an early stage in radiation emergency medicine, the committed effective doses were calculated for various conditions under a certain monitoring measurement quantity. The doses for radio-cesium or iodine with *in vivo* measurement were consistent with previous values. However, the dose for radio-cobalt in the worst case was found to be overestimated compared with that in the default condition.

Clinical diagnostic indicators for uranium toxicity, and tests of chelating agents on removal of uranium, comparison of acute toxicities of plutonium and uranium for radiation emergency medicine

The first work was carried out to clarify the usefulness of clinical diagnostic indicators of renal and bone damages in rats intravenously injected with 0.2-2.0mg/kg depleted uranium. The serum and urinary biochemical markers of renal function, such as N-acetyl-b-D-glucosanidase, blood urea nitrogen and creatinine increased, but might not distinguish the chemical safety limit of 3mg/g of kidney weight from that of control group. Also, the bone marker, osteocalcin responded sensitively to the lowest dose, compared with TRAP, pyridinoline, and PTH. The second work was to examine the effects of deferipone, an iron chelator, on removal of uranium. The result indicated that the deferiprone was effective in increasing initial excretion of uranium in urine, suggesting that this drug may possibly to excrete uranium little by little in a long-term treatment. The third work was to examine the effects of chelating agents, CBMIDA (catechol-3,6-bis (methyleneiminodiacetic acid) and EHBP (ethan-1-hydroxy-1,1-bisphosphonate) on removal of uranium in rats when the chemical forms of uranium were varied by pH. The results indicated that CBMIDA was more effective in excreting uranium that EHBP, particularly preventing damages. The fourth work was carried out to compare the acute toxicity of plutonium with that of depleted uranium in mice, to prepare the assessment of mixed plutonium and uranium induced-chemical toxicities and the method of treatment. The results indicated that, in the ranges of 2-32mg/kg, plutonium was more toxic than uranium.

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2) S. Kimura, S. S. Kumar, K. Shiraishi, Y. Watanabe, T. Ban-nai, et. al: Radiation monitoring using imaging plate technology : A case study of leaves affected by the Chernobyl nuclear power plant and JCO criticality accidents, Nuclear Technology & Radiation Protection, 21, 41-47, 2006
3) S. Ko, K. Shiraishi, S. S. Kumar, K. Ayama, Y. Muramatsu, I. P. Los, V. N. Korzun, N. Y. Tsigankov, P. V. Zamostyan : Contribution of milk to daily intakes of iodine and bromine in northwestern Ukraine, Journal of Radioanalytical and Nuclear Chemistry, 267, 575-579, 2006
4) T. Suzuki, M. Matsumoto, E. Kim, K. Yajima, M. Akashi, K. Fujimoto: Dose Estimation of a Soft X-Ray Exposure Incident, Health Physics Operational Radiation and Safety, 91, S35-S38, 2006
5) S. Fukuda, M. Ikeda, M. Nakamura, X. Yan, Y. Xie : Effects of pH on DU intake and DU removal by CBMIDA and EHBP, Health Physics, 92, 10-14, 2007

7. Fundamental Technology Center

—Supporting various studies of the NIRS with fundamental technology—

Yoshikazu Nishimura,
D. V. M., Ph. D.
Director of Fundamental Technology Center

Outline of Research Career :

Dr. Nishimura received a Ph. D. from the University of Tokyo in 1984 for his study on the biokinetics of radiocobalt in rats. He has 30 years of experience in research on biokinetics of radionuclides in experimental animals. He also has studied how to reduce radionuclide concentrations in animals and humans using natural chelating agents such as chitin and chitosan. He was a group leader of the Environmental Radiation Protection Research Group from 2005 to 2006. Since April 2006 he has been a Director of the Fundamental Technology Center.

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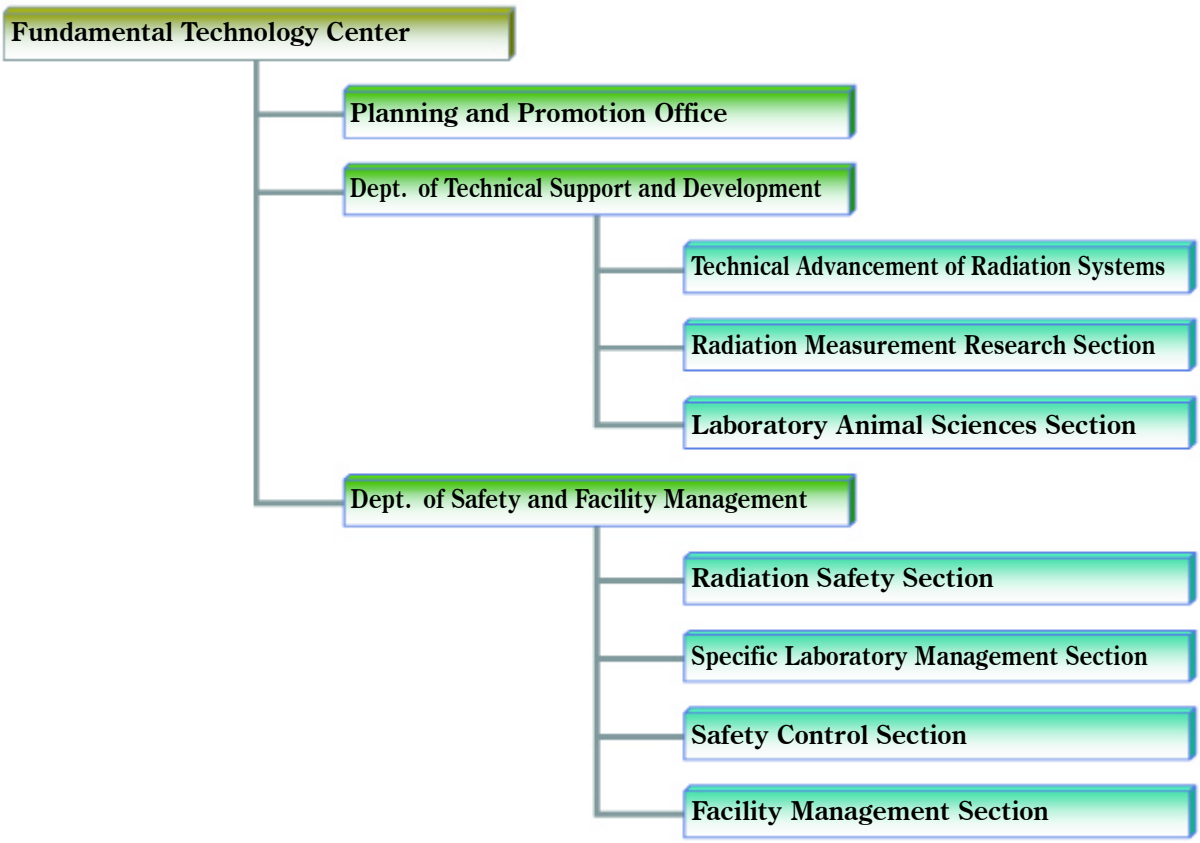
Overview :

The Fundamental Technology Center performs advanced research and development necessary for the support of the activities of NIRS. It manufactures major pieces of research equipment for the Institute and ensures the safety of laboratory apparatuses. The center consists of one office, two departments and seven sections. The office is the Planning and Promotion Office which besides planning and promotion, also supports the infrastructure for the studies carried out at NIRS, and encourages the shared use of facilities. The office sponsors technical report meetings to combine and improve the technical foundations of NIRS.

As for the departments, the first is the Department of Technical Support and Development. This department consists of three sections ; (1) technical advancement of radiation systems section, (2) radiation measurement research section and (3) laboratory animal sciences section. The second department is the Department of Safety and Facility Management and consists four sections ; (1) radiation safety section (2) specific laboratory management section, (3) safety control section and (4) facility management section. This department promotes : improvements in the handling of radioactive substances and nuclear materials, safety measures used in the control of radiation generators such as HIMAC, control of radioactive wastes and dangerous substances, and a safe working environment for NIRS employees. It also maintains the facilities and equipment necessary for safety assurance. This department also institutes a plan for the facilities and equipment to be set up and used over the next 10 years and implements the effective use of the facilities and equipment over the planned timeframe.

Organization of Fundamental Technology Center



7.1. Study of Radiation Measurements

Yukio Uchihori
Member the Radiation Measurement Research Section

Research Interests : Measurements of cosmic-rays and space radiation ; developments of active radiation detectors.
Contact Point : (E-mail) uchihori@nirs. go. jp

Objectives :

One of the objectives of our group is support of radiation measurements and characterization of radiation fields for researchers in NIRS. For examples, neutron fields in the Low-Dose Radiation Effects Research Building and in the medical synchrotron facility has been characterized by neutron detectors. And, in the biological exposure room (BIO) in HIMAC, exposures for biological samples with low dose (1 mGy) for long period (about 8 hours) were supported.

Other objectives are developments of new detectors and measurement techniques in various radiation fields like accelerators and in space. For these complex radiation fields, advanced, highly accurate and reliable detectors are required and, several new detectors and analyzing devices have been developed. These detectors are calibrated and characterized by radiation from several radiation sources and beams from several accelerators.

The international intercomparison programs of space radiation detectors, the ICCHIBAN Project, have been executed in a well-characterized neutron field (CERN-CERF) and the International Space Station (ISS) in a space environment. About 10 institutes worldwide participated in both experiments and these experiments will contribute to standardization of space radiation detectors in world space agencies including NASA in USA, Institute of Bio-Medical Problem (IMBP) in Russia and Japan Aerospace Exploration Agency (JAXA) in Japan.

Progress of Research :

Passive detectors (Nakahiro Yasuda)

Atomic force microscopy with CR-39 for neutron study Atomic force microscopy (AFM) has been applied to the analysis of CR-39 nuclear track detectors for high-dose neutron dosimetry. As a feasible study to extract the neutron dose, we have employed a ^{239}Pu-Be neutron source with the traditional track density measurement of recoil proton etch pits from a high density polyethylene (CH2) radiator. After very short etching (~ 1 μm), etch pit densities were measured as a function of neutron fluence (neutron dose) up to 1.4×10^{10} cm^2 (6.6 Sv). Neutron sensitivity was also measured as 6.6×10^4. Maximum measurable neutron dose was estimated to be ~ 200 Sv by measuring the fraction of the total image area occupied by the etch pits.

Development for exposure system for radiobiology A system to expose biological specimens to medium-energy (2.6-6.0 MeV/u) irradiation has been developed at NIRS-HIMAC. In order to determine the beam energy or LET at the irradiation position in air, the dose distribution for 6.0 MeV/u carbon beam has been obtained using a secondary electron monitor and a flat-type ionization chamber by using air as the energy absorber. Imaging plates were applied to assess the beam profile distribution. The intensity of photo-stimulated luminescence (PSL) was found to be almost proportional to the energy deposited within the sensitive layer of the imaging plate. It has been confirmed that a uniform irradiation field can be produced (about ±5 % within 20 mm in diameter) at low-intensity exposure from 10^1 to 10^4 ions/cm^2/s. Long-term beam stability in the low-intensity condition has also been demonstrated. As a consequence, the methodology for uniform, stable and low-intensity beam exposure has been established, and the continuously variable linear energy transfer (LET) values have also been obtained by changing the distance from the endcap of beamport, for biological studies.

Development for new microscope system for CR-39 study Automated digital imaging optical microscopy is widely used for diagnostic applications in health care and biology fields and for routine inspection in industrial

applications such as semiconductor fabrication. These applications require the imaging of large areas at high speed in order to obtain sufficient data for image processing with good statistics. Track detector analysis also benefits from the rapid acquisition of large areas on the detector surface. We have developed a new microscope system, the HSP-1000, for high speed image acquisition that uses a line sensor camera in place of a traditional CCD camera. Continuous, automatic focusing of the microscope is achieved by means of an optical pick-up system that provides fast feedback for control of distance between the objective and the image surface. Using transmitted light illumination, the microscope is able to digitize a 1cm^2 area at 0.35μm /pixel resolution in ~ 20 s. As a result of continuous stage motion and continuous focusing, we have attained image acquisition speeds that are 50-100 times faster than conventional CCD-based microscope systems.

Neutron detectors (Masashi Takada)

The measurement of high energy neutrons in air and space crafts is complicated in mixed fields of neutrons, gamma rays and protons. A phoswich-type neutron detector was developed in order to discriminate high-energy neutrons from gamma rays and protons. In this study, the neutron phoswich detector was improved for onboard neutron measurements. The liquid scintillator was covered with the EJ-299-15 plastic scintillator and coupled with a single photomultiplier tube. For safe use in air and space crafts, a biodegrable liquid scintillator (EJ-399-06) was used in place of the liquid one (NE213). For neutrons, short signals from the liquid scintillator are acquired; however, summed signals from the liquid and plastic scintillators are obtained for charged-particle detection. Based on different signals, identification between charged and uncharged particles can be thus obtained. The characteristics of particle discriminations were measured at HIMAC. The gamma-ray, neutron and proton events were separated by selecting events each particle in the scatter plot of the peak and tail of the signals. The neutron response functions were evaluated both with measurements and calculations. The detector responses were measured in the NIRS cyclotron and in HIMAC. The MCNPX code was applied to simulate the neutron response functions. Calculated response functions were compared with the measurements. The shapes of calculated response functions agreed well with the measurements except for some discrepancies. Some events were found in the calculated pulse heights above the maximum proton energies, equal to the incidence neutron energies. Particle light outputs were measured in the NIRS cyclotron by direct incidence of particles in the liquid scintillator, EJ-399-06. The light outputs of the EJ-399-06 are a few percent smaller than those of the BC-501A.

Scintillation Detector (Hidehito Nakamura)

Sintillation detectors have been widely used for radiation detection. To achieve high sensitivity, key elements for the scintillation detector performance are the photon production rate of the scintillator, the photon collection efficiency, the photo-electron efficiency and the energy resolution. It is well known that the energy resolution depends on the statistical fluctuation of scintillation photons. To obtain good energy resolution, consideration must be made not only for the statistical fluctuation component but also the non-statistical component.

Therefore, energy resolution of a scintillation detector was studied from the viewpoints of the two components. The statistical fluctuation component is caused mainly by fluctuation of the number of photo-electrons, N, collected at the anode of the photo-detector and the non-statistical fluctuation component comes from an intrinsic property of the scintillator.

A new method identifying these two components was developed to study the resolution of a beta camera detector. The beta camera consisted of a 6 cm × 6 cm × 1 cm plastic-scintillator plate (BC-408 provided by Saint Gobain) and 4 photomultiplier tubes which covered each side face of the plastic-scintillator plate. (Fig. 13) The statistical fluctuation component was found to be well reproduced by *1/sqrt (N)*. The non-statistical fluctuation component of the plastic-scintillator plate was Sigma *(nonstat)* = 4.0 ± 0.3 % (dE/E = 9.3 ± 0.8 % in FWHM) at the 976 keV region.

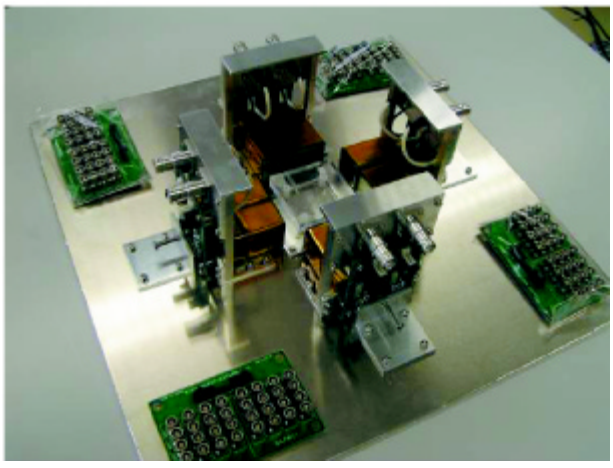


Fig. 13. The beta camera detector.

The present method is useful for investigating statistical and non-statistical fluctuation components of the resolution, and thus to improve and monitor them.

ICCHIBAN Program (Hisashi Kitamura)

As the inter-comparison campaign for space radiation dosimeters (ICCHIBAN Project), the 1st CERF-ICCHIBAN experiment was held on 26th - 27th October, 2006 (Fig. 14). The CERF (CERN-EU Reference Field) facility is a reference neutron field of characteristics similar to the field encountered at commercial flight altitudes (10 - 20 km). This is the first inter-comparison experiment with neutral particles (gamma-rays and neutrons), so differs from the former ICCHIBAN experiments with charged ions. The main purpose of the present experiment was the comparisons of responses of the dosimeters to neutron field at high altitudes. During the 24-hour machine time, the passive dosimeters were irradiated with about 3 mSv. Additionally, the active detectors also were irradiated with about 0.1 mSv. We will summarize the data measured by each participating institute which will be valuable for dosimetry in space and high altitudes.

Fig. 14. Photograph in the 1st CERF-ICCHIBAN experiment.

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2. N Yasuda, Y Koguchi, M Tsubomatsu, et al. : Extremely high dose neutron dosimetry using CR-39 and atomic force microscopy, Radiation Protection Dosimetry, 120 (1-4), 470-474, 2006
3. H Nakamura : MOON for spectroscopic studies of double beta decays and the present status of the MOON-1 prototype detector, Journal of Physics. Conference Series, 39, 350-352, 2006
4. D Broggio, N Yasuda, H Kitamura, et. al : Polyvinyltoluene scintillators for relative ion dosimetry : An investigation with Helium, Carbon and Neon beams, Nuclear Instruments & Methods in Physics Research Section B, 254, 3-9, 2007
5. T Kashiwagi, H Kitamura, Y Uchihori, et. al : Investigation of basic characteristics of synthetic diamond radiation detectors, IEEE Translations on Nuclear Science, 53 (2), 630-635, 2006

8. List of Original Papers

This list includes main publications by the staff members issued during the period from April 1, 2006 to March 31, 2007

* Outside Co-research

○ *Research Center for Charged Particle Therapy*

Developing advanced clinical therapy with charged particle

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4. Shingo Kato, Tatsuya Ohno, Hirohiko Tsujii, Takashi Nakano*, Junetsu Mizoe, Tadashi Kamada, Tadaaki Miyamoto, Hiroshi Tsuji, Hirotoshi Katou, Shigeru Yamada, Susumu Kandatsu, Kyosan Yoshikawa, Hidefumi Ezawa, Michiya Suzuki : Dose Escalation study of Carbon Ion Radiotherapy for Locally Advanced Carcinoma of the Uterine Cervix., International Journal of Radiation Oncology Biology Physics, 65 (2), 388-397, 2006
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6. Jun Shimazaki*, Kouichirou Akakura*, Hiroyosi Suzuki*, Tomohiko Ichikawa, Hiroshi Tsuji, Hitoshi Ishikawa*, Masaoki Harada, Hirohiko Tsujii : Monotherapy with Carbon Ion Radiation for Localized Prostate Cancer, Japanese Journal of Clinical Oncology, 36 (5), 290-294, 2006
7. Tatsuya Ohno, Wataru Noguchi*, Yuko Nakayama*, Shingo Kato, Hirohiko Tsujii, Yoshihiko Suzuki* : How Do We Interpret the Answer "Neither" When Physicians Ask Patients with Cancer "Are You Depressed or Not?", Journal of Palliative Medicine, 9 (4), 861-865, 2006
8. Hiroyuki Kitabayashi, Hideaki Shimada*, Shigeru Yamada, Shigeo Yasuda, Tadashi Kamada, Koichi Ando, Hirohiko Tsujii, Takenori Ochiai*: Synergistic growth suppression induced in esophageal squamous cell carcinoma cells by combined treatment with docetaxel and heavy carbon-ion beam irradiation, Oncology Reports, 15, 913-918, 2006
9. Yuuki Kase, Tatsuaki Kanai, Yoshitaka Matsumoto, Yoshiya Furusawa, Hiroyuki Okamoto, Tooru Asaba, Makoto Sakama, Hiroshi Shinoda : Microdosimetric Measurements and Estimation of Human Cell Survival for Heavy-Ion Beams, Radiation Research, 166 (4), 629-638, 2006
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11. Reiko Imai, Tadashi Kamada, Hiroshi Tsuji, Hirohiko Tsujii, Yoshiharu Tsuburai*, Shinichiroh Tatezaki* : Cervical spine osteosarcoma treated with carbon ion radiotherapy, The Lancet Oncology, 7, 1034-1035, 2006

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Cavity for Beam Transport Line of HiECR Ion Source, Japanese Journal of Applied Physics, 45 (5A), 4227-4231, 2006
4. Mutsumi Tashiro, Shinichi Minohara*, Tatsuaki Kanai, Ken Yusa*, Hideyuki Sakurai*, Takashi Nakano* : Three-dimensional velocity mapping of lung motion using vessel bifurcation pattern matching, Medical Physics, 33 (6), 1747-1757, 2006
5. Tatsuaki Kanai, Nobuyuki Kanematsu, Shinichi Minohara, Masataka Komori, Masami Torikoshi, Hiroshi Asakura*, Noritosi Ikeda*, Takayuki Uno*, Yuka Takei : Commissioning of a conformal irradiation system for heavy-ion radiotherapy using a layer-stacking method, Medical Physics, 33 (8), 2989-2997, 2006
6. Takuji Furukawa, Kouji Noda, Tetsuya Fujimoto*, Takehiro Uesugi, Shinji Shibuya*, Masami Torikoshi: Optical matching of a slowly extracted beam with transport line, Nuclear Instruments & Methods in Physics Research Section A, 560 (2), 191-196, 2006
7. Taku Inaniwa, Toshiyuki Kohno*, Takehiro Tomitani, Mitsutaka Kanazawa, Shinji Satou, Eriko Urakabe*, Tatsuaki Kanai : Application of MLE method to range determination with induced beta+ activity in hadron therapy, Nuclear Instruments & Methods in Physics Research Section A, 562 (2), 1017-1019, 2006
8. Kouji Noda, Takuji Furukawa, Yoshiyuki Iwata, Tatsuaki Kanai, Mitsutaka Kanazawa, Nobuyuki Kanematsu, Atsushi Kitagawa, Masataka Komori, Shinichi Minohara, Masayuki Muramatsu, Takeshi Murakami, Shinji Satou, Yukio Satou, Shinji Shibuya*, Masami Torikoshi, Satoru Yamada: Design of carbon therapy facility based on 10 years experience at HIMAC, Nuclear Instruments & Methods in Physics Research Section A, 562 (2), 1038-1041, 2006
9. Takuji Furukawa, Kouji Noda, Katsuhisa Yoshida*, Takehiro Uesugi, Masashi Katsumata*, Tadahiro Shiraishi*, Takuya Shimojyuu*, Shinji Shibuya*, Tomohiro Miyoshi*, Mitsutaka Kanazawa, Masami Torikoshi, Eiichi Takada, Satoru Yamada : Design of synchrotron and transport line for carbon therapy facility and related machine study at HIMAC, Nuclear Instruments & Methods in Physics Research Section A, 562 (2), 1050-1053, 2006
10. Takuji Furukawa, Kouji Noda : Compensation of the asymmetric phase-space distribution for a slowly extracted beam from a synchrotron, Nuclear Instruments & Methods in Physics Research Section A, 565 (2), 430-438, 2006
11. Mitsutaka Kanazawa, Toshiyuki Misu, Akinori Sugiura, et. al : RF cavity with co-based amorphous core, Nuclear Instruments & Methods in Physics Research Section A, 566 (2), 195-204, 2006
12. Yoshiyuki Iwata, Tetsuya Fujimoto*, Nobuyuki Miyahara, Takashi Fujisawa, Hiroyuki Ogawa*, Satoru Yamada, Takeshi Murakami, et. al : Model cavity of an alternating-phase-focused IH-DTL, Nuclear Instruments & Methods in Physics Research Section A, 566 (2), 256-263, 2006
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○ *Research Center for Rradiation Protection*

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○ *Research Center for Radiation Emergency Medicine*

The Study for Medical Treatment for High Dose Exposure

1. Keiko Suzuki, Izumi Tanaka, Ikuo Nakanishi, Ayako Kurematsu, Haruko Yakumaru, Nobuo Ikota, Hiroshi Ishihara : Drastic effect of several caffeic acid derivatives on the induction of heme oxygenase-1 expression revealed by quantitative real-time RT-PCR., BioFactors, 28 (3-4), 151-158, 2006
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○ *Fundamental Technology Center*

Research of Fundamental Technology / Research on instrumentation technology of radiation

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Research of Fundamental Technology / Research on irradiation technology of radiation

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9. Roster of Researchers

Status of March 31, 2007
Yoshiharu Yonekura, M. D., Ph. D., President
Sentaro Takahashi, Ph. D., Executive Director
Takayuki Shirao, Executive Director

Research Center for Charged Particle Therapy
Hirohiko Tsujii, M. D., Ph. D., Director
Ohtsura Niwa, Ph. D., Deputy Director
Head of Special Research
Tadahiro Shiomi, Ph. D.
Planning and Promotion Office
Hirohiko Tsujii, M. D., Head [1] and 4 staffs

Hospital
Junetsu Mizoe, M. D. Director
Administration Section
Yoichi Kawamura, Head and 7 staffs
Medical Informatics Section
Yutaka Ando, M. D., Ph. D., Head
Masami Mukai, M. S.
Clinical Oncology Section
Tadashi Kamada, M. D., Head
Tadaaki Miyamoto, M. D.
Hirotoshi Kato, M. D.
Shigeru Yamada, M. D.
Shigeo Yasuda, M. D.
Reiko Imai, M. D.
Masayuki Baba, M. D.
Hiroshi Tsuji, M. D.
Tatsuya Ohno , M. D.
Takeshi Yanagi, M. D.
Kenji Kagei, M. D.
Ryusuke Hara, M. D.
Hiroyuki Kato, M. D.
Clinical Diagnosis Section
Susumu Kandatsu, M. D., Head
Kyosan Yoshikawa, M. D.
Riwa Kishimoto, M. D.
Clinical Laboratory Section
Shingo Kato, M. D., Head
Hidehumi Ezawa, M. D.
Junko Noguchi
Katsunori Shimizu
Taijyu Yamada
Mari Motomura
Nursing Section
Misako Nakamura, Head
Chiemi Murakami, Chief Nurse
Sadayo Saito, Chief Nurse
Kiyoko Tahara, Chief Nurse
Yoko Yamasita, Chief Nurse
31 staffs Members and 10 assistants
Pharmacy Section
Shin Watanabe, Head and 1 staff
Radiological Technology Section
Kazuhiro Watanabe , Head and 11 staffs

Department of Accelerator and Medical Physics
Tatsuaki Kanai, Ph. D., Director
Accelerator Development Section
Koji Noda, Ph. D., Head
Masayuki Kumada, Ph. D.
Mitsutaka Kanazawa, Ph. D.
Yoshiyuki Iwata, Ph. D.
Atsushi Kitagawa, Ph. D. [1]
HIMAC Operation Section
Eiichi Takada, Ph. D., Head
Koji Kono
Shinji Sato
Masayuki Muramatsu
Yukio Sakamoto
Technical Management Section
Takeshi Murakami, Ph. D., Head
Akinori Sugiura
Cyclotron Operation Section
Toshihiro Honma, Ph. D., Head
Satoru Hojo
Beam Delivery Systems Section
Masami Torikoshi, Ph. D., Head
Masataka Komori, Ph. D.
Therapy Systems Section
Shinichi Minohara, Ph. D., Head
Nobuyuki Kanematsu, Ph. D.
Naruhiro Matsufuji, Ph. D.

Quality Control Section
Tatsuaki Kanai, Ph. D., Head [1]
Hideyuki Mizuno, Ph. D.

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

Promotion of Carbon Therapy Section
Atsushi Kitagawa, Ph. D., Head [1]
Toru Kurihara
Takashi Fujita
Tomoko Miyagishi

1) Dual Capacity
2) Visiting Research
3) Postdoctoral Fellow

Particle Therapy Research Group

Tadashi Kamada, M. D., Director [1)]

Clinical Trial Research Team

Tadashi Kamada, M. D., Team Leader [1)]

Clinical Database Research Team

Yutaka Ando, M. D., Ph. D., Team Leader [1)]

Radiation Effect Research Team

Naruhiro Matsufuji, Ph. D., Team Leader [1)]

Medical Physics Research Group

Koji Noda, Ph. D., Director [1)]

Accelerator Development Research Team

Mitsutaka Kanazawa, Ph. D., Team Leader [1)]
Takashi Fujisawa, Ph. D.
Toshihiro Honma, Ph. D. [1)]
Masayuki Kumada, Ph. D. [1)]
Eiichi Takada, Ph. D. [1)]
Takeshi Murakami, Ph. D. [1)]
Yoshiyuki Iwata, Ph. D. [1)]
Masayuki Muramatsu [1)]
Kota Torikai, Ph. D. [1)]
Akinori Sugiura [1)]
Tetsumi Tanabe, Ph. D. [2)]
Daisuke Osawa, Ph. D. [2)]

Irradiation Systems Research Team

Masataka Komori, Ph. D., Team Leader [1)]
Yumiko Ohno, Ph. D.
Takuji Furukawa, Ph. D.
Masami Torikoshi, Ph. D. [1)]
Shinji Sato [1)]
Yuka Takei [1)]
Satoru Hojo [1)]
Hirotsugu Ogawa [2)]

Therapy Systems Research Team

Nobuyuki Kanematsu, Ph. D. Team Leader [1)]
Toshihiro Yonai, Ph. D.
Hiroko Koyama-Ito, Ph. D.
Shinichi Minohara, Ph. D. [1)]
Naruhiro Matsufuji, Ph. D. [1)]
Taku Inaniwa, Ph. D. [1)]

Compact Heavy-Ion Therapy Systems Research

Atsushi Kitagawa, Ph. D. [1)]
Tatsuaki Kanai, Ph. D. [1)]
Takashi Fujita [1)]
Yukio Sakamoto [1)]
Yasuo Hirao, Ph. D. [2)]
Kiyomitsu Kawachi, Ph. D. [2)]

Diagnosis and Treatment Advancement Research Group

Tadashi Kamada, M. D., Director [1)]

Image Diagnosis Research Team

Kyosan Yoshikawa, Ph. D., Team Leader [1)]

Image Processing Research Team

Susumu Kandatsu, M. D., Team Leader [1)]

Quality Control Research Team

Akifumi Fukumura, Ph. D., Team Leader [1)]

Radiological Protection Team

Kanae Nishizawa, Ph. D., Team Leader [1)]
Tooru Matsumoto
Shin-ichiro Mori, Ph. D. [2)]

RadGenomics Research Group

Takashi Imai, Ph. D., Director

Genetic Information Team

Takashi Imai, Ph. D., Team Leader [1)]
Yuichi Michikawa, Ph. D.
Ken-ichi Ishikawa, Ph. D.
Yoshimi Ohtsuka
Tomo Suga, M. S.
Naoko Shiomi

Molecular Radiooncoloy Team

Mayumi Iwakawa, M. D., Ph. D., Team Leader
Takashi Moritake, M. D., Ph. D.
Kaori Imadome, M. S.
Miyako Nakawatari, M. S.
Minako Sakai, B. S.

Molecular Biostatistics Team

Gen Kobayashi , M. D., Ph. D., Team Leader
Atsuko Ishikawa, B. S.
Kaori Ohta, Ph. D.

Heavy-Ion Radiobiology Research Group

Ryuichi Okayasu, Ph. D., Director

Biophysics Team

Yoshiya Furusawa, Ph. D., Team Leader
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