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NATIONAL INSTITUTE OF RADIOLOGICAL SCIENCES

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Preface

National Institute of Radiological Sciences has conducted various activities aiming at advancement of radiological sciences as a unique institution conducting comprehensive scientific research for radiation and health since its foundation in 1957. The fiscal year 2005 was the last year of the 1st 5-year mid-term plan carried out as an independent administrative agency. During the past five years, our activities focused on the completion of projects and on planning towards the next 5-year mid-term.

The research activities generally advanced favorably along the fiscal year plan, and all projects proposed by the mid-term plan were successfully completed. Among them the clinical studies of cancer treatment with heavy charged-particle therapy made extensive progress, and the total number of the patients who received the treatment exceeded 2,600 in 2005. In order to enhance the capability of this exciting new treatment, we completed the technical development of basic design and technology for production of a compact carbon ion accelerator for clinical use. We also organized the international symposium on charged particle therapy in Austria, in February 2006, in order to obtain overseas publicity for this fruitful work. In the field of diagnosis and medical imaging for appropriate treatment planning,we provided special funding for development of four-dimensional X-ray CT and the next generation PET project, both of which were successfully completed. As we obtained special funding from MEXT (Ministry of Education, Culture, Sports, Science and Technology) as a core institution in the molecular imaging research program, we started a new research unit, “Molecular Imaging Center”, in November 2005 for promotion of molecular imaging research. Molecular imaging is the technology to visualize molecular processes in the living body by external measurements. It is expected to play a key role in post-genomic science, particularly when this technique is combined with the results of basic molecular biology, such as radiosensitive gene profiling or gene expression induced by radiation.

In addition to the joint projects for promoting these research activities efficiently, we carried out various exchange programs including the use of research facilities and equipment, education in radiation protection, and training of scientific staff and technologists. We have been actively involved in international cooperation programs related to radiation and health, such as UNSCEAR, WHO, ICRP, and IAEA, and in January 2006, NIRS was designated as an IAEA Collaborating Center on the biological effects of low-dose radiation. We continue our efforts to contribute as an international core center in radiation science.

I sincerely ask for your continuing support to NIRS and welcome any suggestions and critiques to advance our activities.

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

Annual Report 2004 - 2005

Contents

1. Outline of Research Activities

Five years have passed since the National Institute of Radiological Sciences (NIRS) was reformed as an Independent Administrative Institution (IAI) in April 2001, and this fiscal year (2005-2006) is the last year in the first Mid-term Plan of NIRS. I am delighted to be able to proudly report here the very smooth and efficient achievement of research activities, successful completion of all the research programs in the first Mid-term Plan, and smooth start of the second (new) Mid-term Plan from April 2006.

The seven projective research programs in the first Mid-term Plan were: the heavy ion clinical trials, the development of four-dimensional X-ray CT, the next generation PET project, the RadGenomic project, the low dose radiation effects research project, the project on biological and physical protection of man from space radiation, and the study for radiation emergency medical preparedness. Datails of these project studies and some fundamental studies to support them will be represented in the following pages. Some other research programs were also continued or newly started with supports of funding agencies including the Ministry of Education, Culture, Sports, Science and Technology (MEXT), the Ministry of Economy, Trade and Industry, the Ministry of Environment, and so on.

The clinical study of cancer treatment using with the Heavy Ion Medical Accelerator (HIMAC) was much progressed and was ranked as “S (very advanced program)” by the IAI Evaluation Committee of MEXT. In this program, approximately 400 patients were treated this year, and total number of patients reached more than 2600 by the end of March 2006. To promote and spread this extremely effective therapy world wide, many symposia, seminars, and workshops were held, including the NIRS-MedAustron Joint Symposium on Carbon Ion Therapy in Cancer that was held Innsbruck, Austria. The developmental study of medical imaging apparatus was also much progressed. The test machines for four-dimensional computer tomography (three-dimensional imaging with time lapse) and high sensitivity/resolution positron emission tomography (PET) were constructed and in evaluations they demonstrated excellent performance as expected. The research programs on the health effects of low dose radiation, space radiation protection, and radiation genomics also obtained many accomplishments this year. It was our great honor and privilege to be designated as the Collaborating Center of International Atomic Energy Agency (IAEA) in this field.

Among fundamental research programs, there are some that must be mentioned here. The brain research programs and the medial imaging study were newly funded by MEXT, reinforced, and scaled up to the Research Center for Molecular Imaging. This center will carry out activities as one of two national centers for molecular imaging. The developmental study of the compact accelerator was completed successfully. The basic design and concept of the major parts of the accelerator will be provided to Gunma University which is planning to built a new compact type heavy ion accelerator for cancer therapy.

The results of our research activities were disseminated in many ways. The most important was as research papers in scientific journals. The number of original papers published by NIRS members was over 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 reserchers were also very active: 84 collaborative studies were carried out, 1200 resarchers worked as visiting stuff, and 280 students were accepted as trainees.

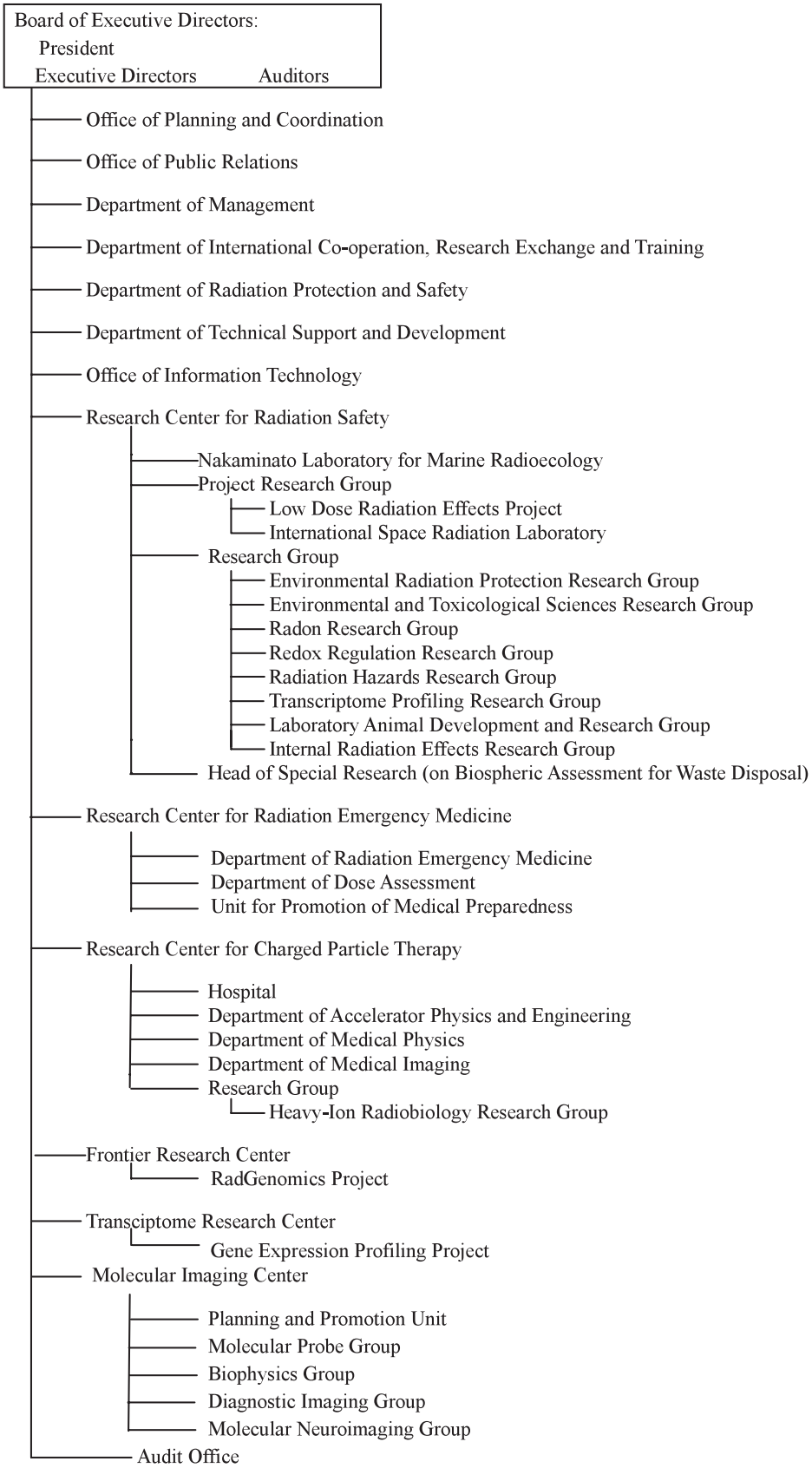
Much effort was made to construct the second Mid-term Plan, based on the successful accomplishments of the first Mid-trem Plan.The second Mid-trem Plan started in April 2006, and all the research activities are now progressing very smoothly.

We look forward to reporting the progress of the second Mid-term Plan in next year's Annual Report. I would like to finish with heartfelt thanks for cooperation and advice given to us during the year 2006.

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

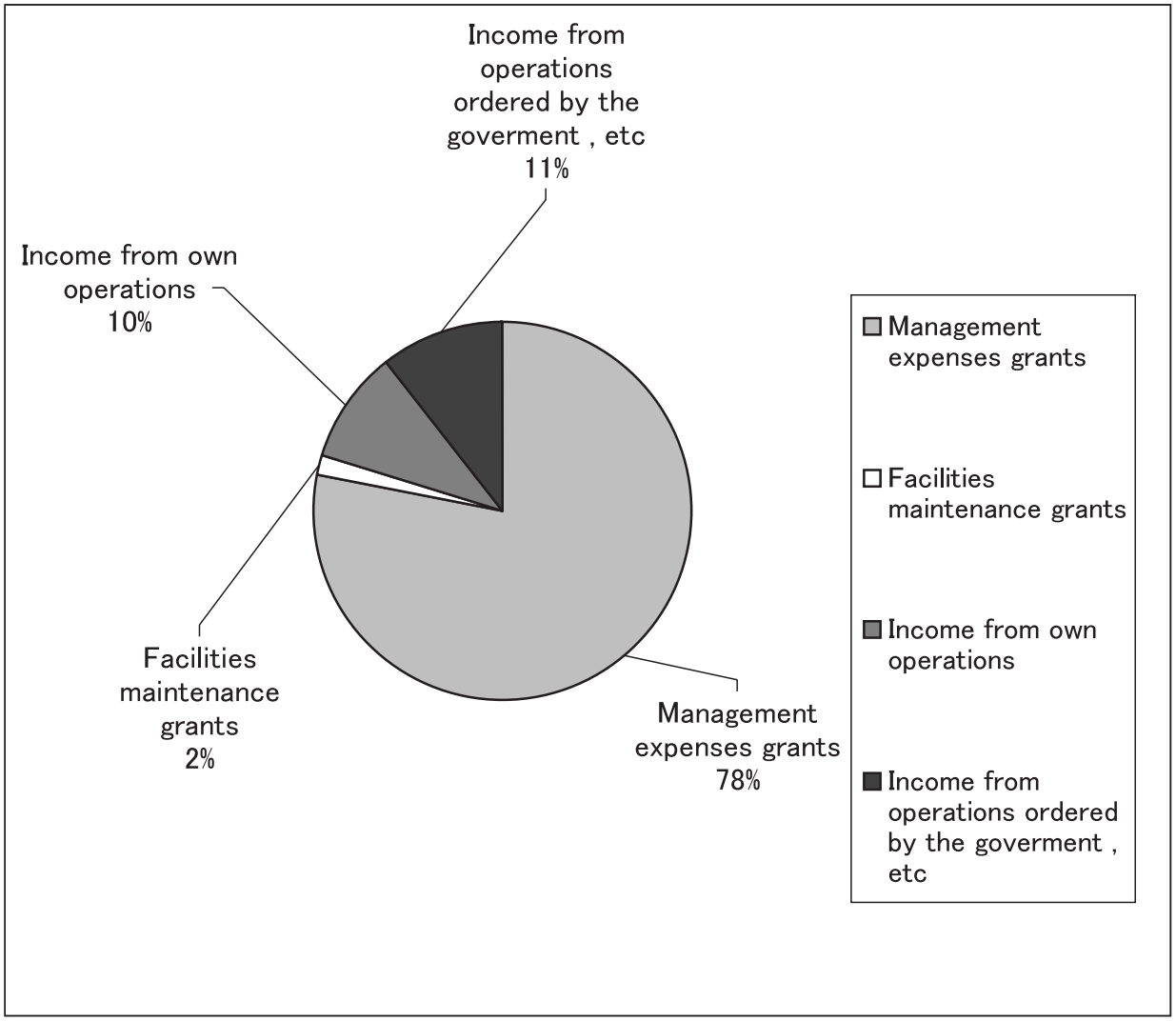
2. Organization Chart and Budget

(1) Organization



(2) Budget(2005.4～2006.3)

Total	17,025 million yen	%
Management expenses grants	13,301 million yen	78%
Facilities maintenance grants	290 million yen	2%
Income from own operations	1,640 million yen	10%
Income from operations ordered by the goverment , etc	1,794 million yen	11%



3. Research Center for Radiation Safety

Isamu Hayata, Ph.D.
Supervisory Director

Outline of Research Career:

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

Objectives:

The Research Center for Radiation Safety covers a wide range of research fields: environmental, biological, and medical aspects of radiation hazards and safety. The final goal of the Center is to provide a scientific basis for the secured utilization of ionizing radiation. Toward this goal, aims of the Center include (1) to understand mechanisms underlying the radiation effects on humans and other living organisms, and (2) to estimate risks from low dose radiation. Development of advanced technologies related to this field, such as development of genetically manipulated laboratory animals and implementation of advanced technology for radiation measurement, is also an important objective of the Center. The Center will also provide, based on its research activities, support for regulatory authorities, governmental committees, and international organizations related to radiation safety and radiological protection.

Overview:

In the fiscal year 2005 (FY2005), the last year of the 5-year mid-term plan, the Research Center for Radiation Safety performed all its research activities very smoothly; the research projects were completed by the end of this year. In addition to many oral and poster presentations in domestic and international meetings, 145 original papers, of which 105 were of principal contribution and 40 supportive, were published. Some of its activities were presented in newspapers and other media to inform the public of the research outcome. At the Presentation of Achievements during the First 5-year plan (FY2001-FY2005) of NIRS, a lecture open to the public was given to summarize the research findings of the Center.

The Center consists of 2 project research teams, 8 fundamental research groups, 2 research promotion sections, and the Nakaminato Laboratory for marine radioecology. The project teams are PR-1) Low dose radiation effects research and PR-2) Biological and physical protection of man from space radiation. The fundamental research groups are FR-1) Establishment of an environmental radiation protection system against radioactive materials released into the environment, FR-2) Research on environmental and toxicological science, FR-3) Research on environmental radon and its biological effects, FR-4) Research on redox regulation against radiation, FR-5) Basic study of radiation hazards, FR-6) Analysis of gene networks in response to ionizing radiation, FR-7) Development of experimental animals for research on the biological effects of radiation, and FR-8) Studies on

experimental carcinogenesis induced by plutonium compounds and Studies on changes and mechanisms of radioactive substances in the ocean and their environmental pollution assessment. In some research projects the Center collaborated with the Research Center for Radiation Emergency Medicine and Research Center for Charged Particle Therapy.

In FY 2005, we promoted feasibility studies following a research strategy for the next five-year plan. Studies on the following subjects have been initiated: (1) age dependency of radiation carcinogenesis, (2) biological effects of 2 MeV neutrons, (3) radiological protection of non-human biota, and (4) protection from naturally occurring radioactive materials (NORM). These research studies of the Center were supported by the Nuclear Safety Commission, the Ministry of Education, Culture, Sports, Science and Technology, Ministry of Environment, Agency for Natural Resources and Energy, and several foundations.

Regarding personnel, 80 permanent researchers, 10 post doctoral fellows, 39 temporary staff members, and 86 part time assistants contributed to the research of the Center this fiscal year. Supervisory Director, Dr. Hayata retired on March 31, 2006.

The Center promoted international research collaboration with some overseas institutions, and cooperation with international organizations, including UNSCEAR, IAEA, OECD/NEA and ISO. Especially, in FY 2005, NIRS was designated as Collaborating Center of the IAEA in the field of research on low-dose radiation effects which has a close relationship with radiation biology and radiation ecology. We celebrated this designation that recognizes the Center is an important research center from the global viewpoint of nuclear safety research regulations.

3.1. Low Dose Radiation Effects Research Project

Yoshiya Shimada, Ph.D.
Director, Low Dose Radiation Effect Research Project

Outline of Research Career:

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

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Objectives:

The overall objective of this research project is to provide basic information on the risk of cancer induction and genetic effects from low dose ionizing radiation for radiation protection. This project is classified into three studies: the biological effects of neutrons; cancer risks of low dose radiation; and the hereditary effects of low dose radiation. Data not available from epidemiological studies are obtained using animal models. For the neutron study, the final goal is to determine the energy dependence of the carcinogenic effects and to provide the RBE value. For the cancer risk assessment, the objective focuses on the dose-response modifying factor, which influences the effects of low dose radiation, i.e., the co-existence of environmental chemicals and genetic background. In studying the hereditary effect, a mega-sized DNA sequencing method is used to determine events and the frequency of mutations in offspring after paternal irradiation.

Progress of Research:

1) Biological Effects of Neutrons

After the criticality accident in Tokai-mura in 1999, the cancer risks and fetal effects of low doses of neutrons were matters of concern. The aim of this program is to investigate the biological effects of neutrons and determine the value of relative biological effectiveness (RBE) for leukemia and for fetal effects, and thereby to assess risks of neutrons. Cyclotron 10 MeV neutrons were first used in this program. About 2660 male C3H/HeNrs mice, a strain susceptible to radiation-induced myeloid leukemia, were divided into 13 groups; one control group, 6 dose-groups (0.05－2 Gy) for neutrons, and 6 dose-groups (0.2－4 Gy) for γ-rays. All animals were observed throughout their life, and dead or moribund mice were pathologically examined. The results indicated that a life-shortening effect was significant at more than 1 Gy of γ-rays, and at more than 0.2 Gy of neutrons. The RBE was calculated to be 3.3. The incidence of myeloid leukemia increased in a dose dependent manner. The RBE was calculated to be 0.94-1.56 depending upon the mathematical model used. The RBE of Harderian gland tumor was calculated to be about 5-7. Recently it has been reported that radiation-induced murine myeloid leukemias frequently harbor a partial allelic loss of chromosome 2 (del2). *PU.1*, which is located within this common deletion region, is proposed as a causative gene of myeloid leukemia. We, therefore, examined del2 and mutation analysis of *PU.1* in 13 γ-ray-induced and 9 neutron-induced leukemias. Del2, determined by FISH method, was observed in 11/13 γ-ray samples, and 9/9 neutron samples. Point mutations in DNA binding region of *PU.1* were observed in

more than 80 % of leukemia with del2 regardless of the radiation sources. These results suggested that *PU.1* is a common target for both γ-ray- and neutron-induced leukemogenesis, which is inactivated by point mutation and loss of wild type allele.

2) Cancer Risk-Combined Effect of Radiation with Chemicals

We are living in an environment filled with numerous natural and man-made chemicals. Radiation carcinogenesis in humans should be considered a result of interactions of these chemicals. The aim of this study is to determine the mode and mechanism of the combined effects of chemicals with radiation. TL was induced in B6C3F1 mice by weekly exposure to X-rays for 4 weeks or by being administered an ethyl-nitrosourea (ENU) for 4 weeks. The low dose radiation (less than 0.4Gy) showed an antagonistic effect when combined with ENU (X-rays→ENU), while that greater than 0.8Gy exhibited a synergistic effect. *Ikaros* is one important tumor suppressor gene in lymphomagenesis. Frequent *Ikaros* mutation was found in TL induced by combined treatment, and was predominantly point mutation. Aberrant splicing or transcriptional silencing was rarely observed. The spectrum was similar to that of ENU-induced TL. Point mutations in TL after combined treatment were G>T and T>A in addition to G>A, which was predominant for X-ray-induced TL and T>C, which was predominant for ENU-induced TL. The reverse sequence (ENU→X-rays) increased TL in an additive manner for a wide range of doses. Interestingly, aberrant splicing and transcriptional silencing were frequently observed. Taken together, the mechanism of lymphomagenesis by combined exposures is dependent upon the dose and the sequence of the treatment.

Female rats were treated either with γ-rays (0.2-2 Gy), methylnitrosourea (MNU; 20-40 mg/kg), PhIP (40mg/kg), or combinations thereof to induce mammary tumors. Generally, the combined effect of low dose radiation (<0.5 Gy) with chemicals elicited more than an additive (multiplicative) effect, while that of high dose radiation (>0.5 Gy) was an additive or sub-additive effect. Frequency of H-*ras* mutation increased to 78% in the tumors induced by combined exposure of MNU and radiation compared to 54% in MNU-induced tumors. Frequency of LOH, however, decreased in tumors by combined exposure of PhIP and radiation compared to that in PhIP-induced tumors. These results suggest that radiation plays a different role in the carcinogenesis in combined exposure depending on the combined counterpart.

3) Cancer Risks of Genetically Susceptible Mice

We have analyzed the pathway for the development of thymic lymphomas using scid, *Rag2*$^{-/-}$, and *Rag2*$^{-/-}$scid mice and have obtained results showing that thymic lymphomas were induced by γ-rays in these mice at a similar frequency. We have identified two pathways, the illegitimate V(D)J recombination and the microhomology-mediated end joining, for the deletion formation of *Notch1*, which is a major oncogene responsible for the development of thymic lymphomas. The illegitimate V(D)J recombination might occur via misrecognition and cleavage of cryptic recombination signal sequence-like sequence in the *Notch1* locus by the Rag complex and end ligation by the V(D)J recombination machinery. The microhomology-mediated nonhomologous end joining might be end joining of DNA double strand break via the pairing of short sequences of homology that emerged during end processing of broken DNA. Based on the pathways, the previous result indicates the preferential operation of the microhomology-mediated pathway for the Notch1 deletion under the deficient condition of V(D)J recombination in scid mice. In the present study, we examined the induction of thymic lymphomas in *Rag2*$^{-/-}$, *Atm*$^{-/-}$, and *Rag2*$^{-/-}$*Atm*$^{-/-}$ mice to elucidate the effect of *Atm* deficiency on thymic lymphoma induction. Atm protein is known to function in nonhomologous end joining repair of double strand break and to regulate V(D)J recombination. *Atm*$^{-/-}$ mice were remarkably susceptible to spontaneous and radiation-induced thymic lymphomas as reported by others. Unexpectedly, thymic lymphomas developed spontaneously at a relatively high frequency in *Rag2*$^{-/-}$ mice and were induced by radiation at a high frequency. The high susceptibility of *Rag2*$^{-/-}$ mice to the development of thymic lymphomas may be associated with differentiation arrest of thymocytes due to the absence of V(D)J recombination. In contrast to the case of scid mice, the *Rag2*$^{-/-}$*Atm*$^{-/-}$ mice exhibited reduced frequencies of spontaneous and radiation-induced thymic lymphomas as compared to those in *Atm*$^{-/-}$ mice. This indicates that V(D)J recombination-mediated event has a role in thymic lymphomagenesis in *Atm*$^{-/-}$ mice. Thus there are Rag-dependent and Rag-independent pathways for the development of thymic lymphomas. In scid mice, the Rag-independent pathway is the main route, while both pathways are involved in *Atm*$^{-/-}$ mice.

4) Hereditary Effects of Low-dose Radiation:

To investigate the hereditary effects of ionizing radiation, mutational events and their frequency in

mouse germ cells were analyzed by detecting changes in nucleotide sequences at a specific genomic locus and 150 STS in mouse offspring. Male mice irradiated with or without γ rays at 1-3 Gy were mated with intact females two weeks later. This procedure could determine the genetic effects of radiation at the spermatid stage. $5x10^6$bp of DNA from the offspring were analyzed. A mutation was detected in the offspring from the male mice exposed to 3 Gy γ rays, while spontaneous mutation was not detected ($<1x10^{-6}$). Mutation was not detected in offspring derived from male mice irradiated with 1 Gy of γ rays. Similar nucleotide sequence analysis of offspring derived from mouse spermatid exposed to 3 Gy of X-rays was performed at the *adenine phosphoribosyl transferase* gene locus (3088bp/locus, 537 mice), but no new mutation was detected. The dynamic mutation at the hyper-variable *Ms6-hm* tandem repeat was also analyzed in offspring derived from spermatid exposed to 1-3 Gy of X-rays. Dynamic mutation was observed in 5-10 percent of these, according to irradiation dose. However, dynamic mutation was not detected in the offspring in which the above mutation was detected. Thus, the occurrence of the dynamic mutation at the hyper-variable *Ms6-hm* did not correspond to the occurrence of classic mutations at the ordinary genomic loci.

5) Radiation Effects on Germ Cells

In this fiscal year, we have carried out mutation assays in germ cells from transgenic mice after irradiation of various doses of ionizing radiation at the post-meiotic spermatid stage, to learn the difference in sensitivity to ionizing radiation in mutation induction among somatic cells and male germ cells (pre-meiotic spermatogonial stem cell and post-meiotic spermatid stage). The transgenic mice used for the assay are the *gpt-delta* mouse strain, which carries about 80 copies of the bacterial *gpt* gene per cell as targets for mutagenesis. To measure the induced mutation frequencies in male germ cells (spermatid stage), sperms were extracted at the 14th day after irradiation of 2.5 or 5 Gy of X rays, corresponding to the spermatid stage at the time of treatment. The spontaneous *gpt* gene mutation frequency in male germ cells was 0.36×10^{-5}. The mutation frequencies in male germ cells irradiated with 2.5 or 5 Gy of X rays at the spermatid stage were 0.60 or 1.03×10^{-5}, respectively. The induced mutation frequencies in male germ cells irradiated at the spermatid stage were nearly the same as those irradiated at the spermatogonial stem cell stage (0.53 or 1.05×10^{-5} for 2.5 or 5 Gy of X-ray-treatment, respectively), and about three to four times lower than those in somatic cells (2.43 or 3.46×10^{-5} for 2.5 or 5 Gy of X-ray-treatment, respectively). This difference between somatic and male germ cells in the mutation frequency would be mainly due to the high base excision repair activity in male germ cells.

Major publications:

1) Yuka Ishida, Yasushi Ohmachi, Yukiko Nakata, Takeshi Hiraoka, Tsuyoshi Hamano, Shinji Fushiki, Toshiaki Ogiu: Dose-Response and Large Relative Biological Effectiveness of Fast Neutrons with Regard to Mouse Fetal Cerebral Neuron Apoptosis. Journal of Radiation Research, **47**(1), 41-47, 2006

2) Tatsuhiko Imaoka, Mieko Okamoto, Mayumi Nishimura, Yukiko Nishimura, Masami Ootawara, Shizuko Kakinuma, Yutaka Tokairin, Yoshiya Shimada: Mammary tumorigenesis in $Apc^{Min/+}$ mice is enhanced by X irradiation with a characteristic age dependence. Radiation Research, 165, 165-173, 2006

3) Yutaka Tokairin, Shizuko Kakinuma, Masami Arai, Mayumi Nishimura, Mieko Okamoto, Makoto Akashi, Yoshio Miki, Tatsuyuki Kawano, Yoshiya Shimada: Accelerated growth of intestinal tumours after radiation exposure in *Mlh1*-knockout mice: evaluation of the late effect of radiation on a mouse model of HNPCC. International Journal of Experimental Pathology, 87, 89-99, 2006

4) Jianyu Wu, Mitsuoki Morimyo, Etsuko Hongo, Tomoyasu Higashi, Masanori Okamoto, Akihiro Kawano, Yasushi Ohmachi: Radiation-induced germline mutations detected by a direct comparison of parents and first-generation offspring DNA sequences containing SNPs. Mutation Research, 596, 1-11, 2006

5) Naoko Shiomi, Masahiko Mori, Seiji Kito, Yoshinobu Harada, Kiyoji Tanaka, Tadahiro Shiomi: Severe growth retardation and short life span of double-mutant mice lacking Xpa and exon 15 of *Xpg*. DNA Repair, 4, 351-357, 2005

3.2. Project:"Biological and Physical Protection of Man from Space Radiation"

Ryuichi Okayasu, Ph.D.
Project Leader

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, PA and MD Anderson Cancer Center, Houston, TX. 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.

Contact point: rokayasu@nirs.go.jp

Objectives:

We have two teams focusing on physics (Team 1 and Team 2) and two teams focusing on biology (Team 3 and Team 4). The followings are the objectives from these four teams.

Team 1: In order to understand the radiation environment in space for spacecrafts and develop reliable and suitable radiation instruments, many passive detectors had been installed in space, and these detectors were investigated using artificial beams from accelerators. New neutron detectors and other detectors were developed for radiation measurements in spacecrafts and airplanes. Using commercial and developed radiation detectors, radiation measurements in airplanes have been performed.

Team 2: Dosimetry of cosmic radiation exposure of aircraft crew and passengers were performed. Effective doses on major routes of international flights from Japan were calculated with numerical models. Based on the calculation results, target criteria for controlling cosmic radiation exposure have been presented. Also, new small dosimeters suitable for individual monitoring in aircraft were developed; their responses to both ionizing and non-ionizing radiations have been investigated.

Team 3: The focus of this team is to investigate the cellular and molecular effects caused by low levels of cosmic radiation and use the data to protect humans from ill effects which could be caused by exposure to space radiation. We used mammalian cell cultures and animal models for this purpose. We fully utilized the HIMAC irradiation facility in order to examine the significant biological effects caused by heavy ions such as iron beams.

Team 4: Our aim is to develop good radio-protectors for space radiation using animal models. We also contribute to preventive medicine for space travelers by studying the combined effects induced by minimal gravity and radiation.

Progress of Research:

Team 1 (Physics): Measurement of radiation doses in space environment

Cosmic radiation levels in a Russian service module for the International Space Station were measured with several dosimeters, TLDs, OSLs, glass dosimeter and track-etch detectors and the data were analyzed. The measured dose levels were compared among several dosimeters installed by universities and institutes in Russia, USA and Austria and the results were published. Doses of heavy mass and energy ions were measured using several radiation instruments for radiation protection in the space station, and the measured values were compared at HIMAC in September 2005, as the 7th and 8th ICCHIBAN (project)s. We also organized the 10th Workshop for Radiation Monitoring in the International Space Station at NIRS. In this workshop, 40 researchers from foreign institutes and universities, and 40 scientists from Japan actively discussed the measurement of cosmic radiation; substantial amounts of data obtained in ICCHIBAN were discussed. The new detection technique of luminescence tracking was developed, and this will provide novel ways for radiation dosimeter development. In order to protect air crews, radiation doses encountered during long distance flights were measured at the Royal Military College of Canada. Based on the measurements, the calculation code of route doses, PCAIRE, was updated. The results from

these studies were presented in international conferences and published.

Team 2 (Physics): Protection from cosmic radiation

Effective doses received on 63 international flight routes from Japan were calculated using CARI-6 code and the results are now available to the general public on the NIRS web site (http://www.nirs.go.jp/jiscard/index.htm) as "Japanese Internet System for Calculation of Route Doses (JISCARD)". This system has recorded more than 30,000 accesses in a half year. For improving the reliability of model calculations, the cascade energy peak of cosmic neutrons was simulated with precise transport codes.

As candidates for the ESR dosimeter, radiation induced radicals of photochromic gel of titanium oxide and their stabilities at room temperature were examined with photons (ultraviolet radiation, gamma- and X-rays). The gel showed color changes for UV only, whereas ESR signals (electron or hole traps) were also observed for ionizing radiation.

The team leader, Hiroshi Yasuda, has contributed to the standardization of dosimetry by cosmic radiation exposure of aircraft crews as a core member of the working group of the International Standards Organization.

Team 3 (Biology): Cellular and molecular effects by cosmic radiation in vivo and in vitro

The function of rat brain irradiated with carbon and iron ions was examined using a water maze up to two years post-irradiation. The brain function did not significantly change after the 20 week post-irradiation point. An LET dependent carcinogenic effect was found with a rat strain susceptible to renal carcinoma. The molecular analysis of the responsible gene (TSC2) was performed, and the genetic changes by iron irradiation were found to be very different from those by X-irradiation.

Mutation induction at the HPRT locus in normal human cells after pre-treatment with very low doses of gamma-rays, neutrons, helium, and carbon ions was examined. After 1.5 Gy of X-rays, the mutation rate was significantly increased only in the cells pre-treated with carbon ions. We have summarized all the data for cell survival and mutation induction in normal human cells irradiated with various heavy ion particles and different LETs. A molecular analysis was also performed in the clones of mutated cells from the mutation experiments.

Using DNA double strand break (DSB) repair proficient and deficient human cells irradiated with X-rays and high LET heavy ions, we found that non homologous end joining (NHEJ) type DSB repair pathway was predominantly affected by heavy ion irradiation. Further molecular analysis showed that the phosphorylation status of DNA-PKcs, an NHEJ repair protein, was significantly affected by high LET heavy ion irradiation when compared to low LET X-irradiation.

Team 4 (Biology): Combined effects by microgravity and radiation and preventive medicine

The following studies were performed. 1) The protective effects of Deferiprone (L1) clinically used for Thalassaemia disease for a free radical scavenger were examined using x-irradiated rats. Deferiprone were administered orally with doses of 200 and 400mg/kg, 30 min before and just after whole body irradiation. The data indicated that Deferiprone was not effective upon lethal dose exposure. 2) We examined the effects of a natural product, milk basic protein (MBP) using the rat model for synergic factors of radiation and weightlessness in a space environment. Rats received x-ray exposures (3, 6 Gy) to the whole body, immobilization treatment of one-side hind leg, or combinations of these. The animals of each group were given 1% MBP diet for 3 months. The bone mineral density (BMD) in the trabecular bone area of the tibia was decreased by radiation alone or immobilization alone, and the combined treatment caused synergic actions. Although, in the MBP-groups, the clear increase in BMD was not observed, the increases in alkalinephosphatase activity and BGP in serum as biochemical makers of bone formation were observed. The decrease in urine pyridinoline as a marker of bone resorption was observed, suggesting that BMD may be expected by long-term intake or for less radiation exposure. Also, improvement effects of MBP on the steopenia in aged beagle dogs after ovariectomy were observed.

3) In the life span study on the effects of heavy ion (carbon) and x-ray whole body exposures, increases of incidences of ovary, lung, spleen and mammary tumors in female rats were observed when exposed to doses of 0.5-1.0 Gy carbon ions at 12 months old. The incidence of mammary tumors in the heavy-ion exposed rats was observed in a dose-dependent manner. Also, the life span in both the heavy ion and x-ray exposed groups was shorter than that of the no irradiation group. Finally, the results of this experiment will be compared with the data that is obtained from another group exposed at 8 weeks old in order to clarify the long-term effects of heavy ion and x-ray exposures.

Major publications:

1) Ryuichi Okayasu, Maki Okada, Atsushi Okabe, Miho Noguchi, Kaoru Takakura, Sentaro Takahashi: Repair of DNA damage induced by accelerated heavy ions in mammalian cells proficient and deficient in the Non-homologous End-joining pathway. Radiation Research, 165, 59-67, 2006
2) Masao Suzuki, Chizuru Tsuruoka, Tatsuaki Kanai, Takeshi Kato, Fumio Yatagai, Masami Watanabe: Cellular and molecular effects for mutation induction in normal human cells irradiated with accelerated neon ions. Mutation Research, 594, 86-92, 2006
3) N. Yasuda, T. Konishi, K.Matsumoto, T. Yamauchi, T. Asuka, Y. Furusawa, Y. Sato, K. Oda, H. Tawara, K.Hieda: Dose distribution of carbon ions in air asesed using imaging plates and ionizing chamber. Radiation Measurement, 40, 384-388, 2005
4) Masashi Takada, Erika Mihara, Takashi Nakamura, Kazunobu Fujitaka, et al. Neutron irradiation field produced by 25 MeV deuterons bombarding on thick beryllium target for radiobiological study. Nuclear Instruments & Methods in Physics Research Section A, 545, 765-775, 2006
5) Hiroshi Yamaguchi, Yukio Uchihori, Nakahiiro Yasuda, Masashi Takada, Hisashi Kitamura: Estimation of yields of OH radicals in water irradiated by ionizing radiation. Journal of Radiation Research, 46, 333-341, 2005

3.3. 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. In addition, the transfer model for predicting the radionuclide behavior in atmosphere-paddy soil-rice plant systems has been developed.

Progress of Research:

1) Transfer factors of stable elements and natural radioisotopes

In order to obtain local transfer factors (TFs) of long-lived radionuclides under natural/equilibrium conditions for assessment of radioactive waste disposal, global fallout isotopes such as ^{90}Sr and ^{137}Cs are good tracers. However, their radioactivity levels in plants are extremely low so that TF data observed under equilibrium conditions have been limited. To close the information gap, 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 and wheat, because the consumption of cereals is very high in Japan and other Asian countries. About 40-50 elements such as Cs, Sr, Th and U in plant and soil samples were measured by ICP-MS and ICP-OES.

The TF 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). Figure 1 shows the results of TFs (geometric mean) for 23 elements. Some elements showed TF values higher than 0.1: Mg, K, Mo and Cd for wheat; Mg, K, Zn and Mo for brown rice; and Zn and Mo for polished rice. The TFs of Th and U were also of interest: the values for brown rice were 0.0001 and 0.00005; those for polished rice were 0.00015 and 0.0002; and those for husked wheat were 0.0008 and 0.0002, respectively. Except for several trace elements, TFs were usually highest in wheat followed by brown rice and then polished rice.

Radium-226 and 228 are in the U and Th decay series, respectively, and these naturally occurring

radium isotopes are widely distributed in environmental materials, such as in rock, soil and plant materials. Ra-226, an alpha emitter with a half-life of about 1600 y, is of special interest because it is one of the important radionuclides for the assessment of radioactive waste disposal. Once Ra is taken into the human body by ingestion of food and water or inhalation, it can distribute on bone so it has a long biological half-life; exposure to Ra can cause cancers and other body disorders. Therefore its long-term management is required and understanding of Ra behavior in the environment is important. Measurement of Ra-226 concentration in compartments of the environment gives us useful information for this purpose. However, because Ra-226 concentrations in many environmental materials are extremely low, it is difficult to measure the radionuclide without chemical separations from sample matrices, especially for plant samples. Subsequently, soil-to-plant TF data are limited. Concentrations of Ra-226 under natural environmental conditions were determined in rice grains and associated paddy soils collected from 11 locations throughout Japan.

The radioactivity was measured with a Ge detector system for soil samples and a liquid scintillation counting system for brown rice after radiochemical separation. The recoveries of Ba, used as a chemical yield tracer for Ra, were more than 97% for all the samples. The concentrations of Ra-226 in paddy soil samples ranged from 20 to 65 Bq/kg−dry soil, and those in the brown rice samples ranged from 8 to 65 mBq/kg-dry except for two samples (<DL). Using the data, TFs were calculated and the average TF of Ra-226 from the paddy soil to the rice (brown rice) was 6.8E-4. This value was close to the TFs for maize reported in the IAEA Technical Reports Series No. 364.

2) Distribution coefficients (K_ds) of elements and their behavior in soils

From the viewpoint of nuclear waste management, ^{125}Sb (half life: 2.76 y) is of interest because it is a fission product of ^{235}U and is found in nuclear wastes. Mobility of antimony (Sb) in Japanese agricultural soils was observed using the soil-soil solution distribution coefficients (K_ds). The K_ds of Sb were measured for 110 soil samples (59 upland and 51 paddy samples) which were collected throughout Japan. These samples were taken from the surface layer (0-20 cm depth). K_d was measured for the soil samples by the batch technique using ^{124}Sb (chemical form: $SbCl_3$, half life: 60.2 d) as a tracer. The K_d measurements for all samples were triplicated.

The K_d-Sb values are listed in Table 1, and the values ranged from 1 to 2065 L kg^{-1}. The geometric mean value (excluding the one extremely high value of 2065 L kg^{-1}) was 62 L kg^{-1}, that is, 86% of the added Sb was sorbed onto the soils. From the soil pH and Eh, Sb form in the soil solution was regarded as an anion (SbO_3^-), and the Sb mobility was the same level as that for selenite (SeO_3^{2-}). Among soil groups, the Regosol group had the lowest average K_ds. For other soil groups, the K_d-Sb ranges were similar, and no significant K_d-Sb difference between upland and paddy soils was found.

Experimental measurement of K_ds showed a decrease with both increasing pH and increasing phosphate concentration. The latter suggested that one aspect of the Sb sorption phenomena in Japanese soil was influenced by specific adsorption of anions such as phosphate. However, other aspects could not be explained by this specific adsorption mechanism, because only 20-40% of soil-sorbed Sb could be extracted by phosphate solution.

3) Determination of As and Se concentrations in major rivers in Japan

Among selenium (Se) radioisotopes, Se-79 (half life: 65000 y) is of interest because it is a fission product of uranium and present in spent nuclear fuel and the wastes resulting from reprocessing this fuel, thus, Se should be controlled in the natural environment. Moreover, in the national and international guidelines for drinking water quality, it is recommended that arsenic (As) and Se concentrations in drinking water do not exceed 0.01 mg L^{-1}. Since As and Se concentrations are thought to be lower than 1/10 of the recommended values in >90% of surface river waters, it is difficult to describe nationwide As and Se concentration levels in Japan. The recently developed octapole reaction system for inductively coupled plasma mass spectrometry (ORS-ICP-MS) could achieve low detection limits for As and Se compared to atomic absorption spectrometry and ICP optical emission spectrometry. Thus, direct measurement of trace levels of As and Se in river water for 25 major rivers, 10 samplings per river, were carried out using ORS-ICP-MS.

The concentrations of As and Se were determined in more than 95% of the samples, and the cumulative probability distributions of these elements were on log-normal lines. Their respective geometric mean concentrations were calculated as 0.68 μg L^{-1} (range: 0.08-12.8 μg L^{-1}) for As and 0.062 μg L^{-1} (range: <0.01-1.17 μg L^{-1}) for Se, respectively, and these values were lower than the recommended

ones. The concentration ranges of these elements in ten samples collected from the upper stream to the river mouth were usually narrow. Possibly, the observed concentrations originated from weathering of bedrock.

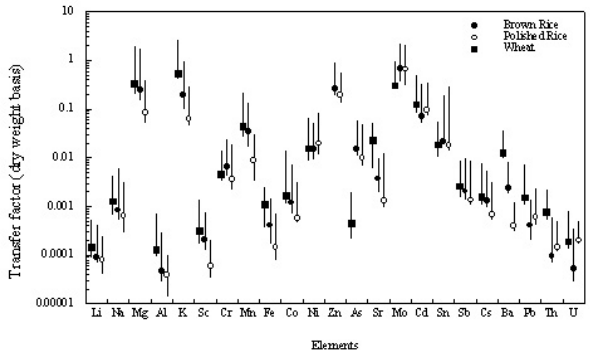

Fig 1. Geometric means of TFs (dry weight basis) for wheat, brown rice and polished rice. Both ends of bar show maximum and minimum TF values.

Major publications:

1) Uchida, S., Tagami, K., Tabei, K.: Comparison of alkaline fusion and acid digestion methods for the determination of rhenium in rock and soil samples by ICP-MS, *Analytica Chimica Acta* **535**, 317-323, 2005.
2) Ishii, N., Uchida, S.: Gram-negative bacteria responsible for insoluble technetium formation and the fate of insoluble Tc in the water column above flooded paddy soil, *Chemosphere* **60**, 157-163, 2005.
3) Tagami, K., Uchida, S.: A comparison of concentration ratios for technetium and nutrient uptake by three plant species, *Chemosphere* **60**, 714-717, 2005.
4) Nakamaru, Y., Tagami, K., Uchida, S.: Depletion of selenium in soil solution due to its enhanced sorption in the rhizosphere of soybean, *Plant and Soil* **278**, 293-301, 2005.
5) Tagami, K., Uchida, S.: Sample storage conditions and holding times for the determination of total iodine in natural water samples by ICP-MS, *Atomic Scpectroscopy* **26**, 209-214, 2005.

Table 1. Chemical characteristics and the K_d-Sb values of each soil group and land use.

Soil groups		pH (H_2O)	Cation exchange capacity ($cmol_c$ kg^{-1})	Active-Al (g kg^{-1})	Active-Fe (g kg^{-1})	Total C (%)	Total Sb (mg kg^{-1})	K_d-Sb (L kg^{-1})
Andosol (n=33)	Mean[a]	6.1	17	29.1	17.3	5.2	0.6	102
Fluvisol (n=53)	Mean[a]	6.0	13	2.4	7.1	1.8	0.8	53
Cambisol (n=21)	Mean[a]	6.2	12	3.1	6.2	1.2	0.9	65
Regosol (n=3)	Mean[a]	6.7	1	0.4	0.8	0.1	0.2	2.6
All upland soils	Mean[a]	6.2	13	7.0	8.7	2.0	0.7	57
(n=59)	Max.	8.3	38	96.2	76.3	10.9	1.9	505
	Min.	4.7	1	0.3	0.4	0.0	0.2	1
All paddy soils	Mean[a]	6.0	14	3.5	8.4	2.2	0.7	67
(n=51)	Max.	7.7	43	65.1	36.0	8.5	2.1	2065
	Min.	4.8	7	0.9	2.3	0.3	0.4	8
All samples	Mean[a]	6.1	14	5.1	8.5	2.1	0.7	62
(n=110)	Max.	8.3	43	96.2	76.3	10.9	2.1	2065
	Min.	4.7	1	0.3	0.4	0.0	0.2	1

[a] Mean indicates geometric mean of samples. The arithmetic mean was used only for pH values. For K_d-Sb, the geometric mean values were calculated without the value 2065 (L kg^{-1}).

3.4. Evaluation of Radiation Protection System against Radioactive Materials Released into the Environment

Yoshikazu Nishimura, D.V.M., Ph.D., Director, Environmental Radiation Protection Research Group

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 studies how to reduce radionuclide concentrations in animals and humans using natural chelating agents such as chitin and chitosan. Since April 2005 he has been a group leader of the Environmental Radiation Protection Research Group.

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Objective:

The more than 50 nuclear power plants operating in Japan provide about 34% of the country's total electricity supply. To establish a nuclear fuel cycle, which is a fundamental energy policy of the government, a commercial-based uranium enrichment plant is operating at Rokkasho-mura and a huge reprocessing plant is under construction. Nowadays, radionuclides are used extensively in the fields of science, engineering, agriculture and medicine. There is a potential risk for radiation exposure with these applications. Therefore, exposures should be controlled so that the doses and risks to individuals do not exceed levels acceptable for the human population. The objective of this research is to obtain scientific information needed to protect the human body from radiation and radioactive materials released into the environment from nuclear and radiation facilities by clarifying the amount and behavior of radioactive materials in the environment, the intake of the materials by the human body, their behavior within the human body, the doses to the human body and low-dose risk assessment by epidemiologic studies. Our research group conducts marine studies at the Nakaminato Laboratory for Marine Radioecology and half of the research group members serve at the Research Center for Radiation Emergency Medicine, where they are responsible for studies on dose assessment of exposed patients as well as ongoing practical activities in an emergency.

Progress of Research:

1) Behavior of radionuclides in the environment

Uranium isotopic compositions determined in soil samples in the Chernobyl exclusion zone showed significant deviation from natural uranium. The $^{236}U/^{238}U$ ratio could be determined in the samples and used as a finger-print to differentiate between contamination or a natural source. Enrichment of ^{235}U was noticeable for soil as well as ground water samples. Iodine concentrations in the topsoil layer of the exclusion zone varied from 1.1 to 3.6 ppm depending on the soil types. Also, ca. 400 diet samples were collected by the duplicate portion method from all 25 regions in Ukraine. About 20 elements in the diet were analyzed. The Ukrainian element intakes were compared with those of worldwide reported values. Especially dietary iodine intake (40μg) in Ukrainians was lower than the level of the RDI (150 μg). Intakes of essential microelements (Mn, Cu, and Zn) were also lower than worldwide mean values. The results should be a useful database in future work, e.g., determining countermeasures after accidents, doing nutrition and health studies and so on in Ukraine.

2) Behavior of radionuclides within the body

To investigate the precise tissue distribution of elements, such as Sn, U, Cs, and Mo, whose minor signals are interfered with by endogenous major elements, such as Ca and K, we tried to use high-energy incident X-rays for detecting major signals of these elements by synchrotron radiation X-ray fluorescence (SR-XRF) analysis. XRF spot analysis with a microprobe was employed for testicular

sections of rats exposed to tributyltin chloride, an environmental pollutant. Sn was detected in the spermatozoa of the testis. Embryo development of natural plants is susceptible to radioactive contamination of the environment. In pre-embryogenic cells of Japanese cedar, the proliferation was inhibited by dose rates for chronic irradiation as low as 5 mGy / h. The radio-sensitiveness in early stages of embryo development was also analyzed with *in vitro* cultures of tobacco embryos.

3) Internal dosimetry for radiological protection

We measured the BOMAB phantoms by using a whole body counter and compared results with the data measured in the former Japan Atomic Energy Institute Tokai Laboratory and Japan Nuclear Cycle Development Institute Tokai Branch (now united into the Japan Atomic Energy Agency). The results were consistent with each other. Furthermore, similar measurements were done in three local radiation emergency medical organs. And we studied standardization of whole body counting.

We verified the program and database of MONDAL3(monitoring to dose calculation Ver.3) which was last year. We can easily calculate the equivalent dose of each organ or tissue from monitoring data by using this software. CD-ROMs were made and distributed to the public by NIRS free of charge. We are making an effort to diffuse this version now.

We analyzed and processed MRI images which were taken of a volunteer to make a mathematical phantom. And we partially outlined the lung and rib bones.

4) Radiation epidemiology and risk assessment

Further analysis of 1969-98 mortality data for the radiological technologist cohort suggested an increase for lymphoid/ haematopoietic tissues and prostate cancers among early sub-cohort. Computational simulations to estimate occupational exposure showed that the dose was from several to several tens of μSv per one procedure of X-ray photograph and that the important factors for the variation were tube voltage and target material. Research on potential radiation risks in areas with a nuclear power plant (NPP) based on ecological 1972-97 mortality data from two cancer combined groups (lymphoid/ haematopoietic tissues and non-digestive solid cancers) showed a relatively constant standardized mortality ratio by six blocks through Japan over the long period. Analysis of 100 selected municipalities noted a superficial increase or decrease for these cancers in 20 municipalities with an NPP in adulthood, especially in females and indicated that the confounding was likely to be caused by temporal changes of age specific mortality and of the number of cancer deaths in the elderly. Furthermore, epidemiologic reviews were conducted with respect to lifetime risk of radiation (including fallout), indoor radon and cosmic radiation exposure among aircrews. As well, cooperation with other research institutes in Japan and abroad has continued for occupational exposures such as experienced by nuclear industry workers.

5) Distribution of radionuclides in the ocean

Plutonium activities and $^{240}Pu/^{239}Pu$ ratios in the East China Sea and Okinawa Trough sediment cores were determined by isotopic dilution inductively coupled plasma mass spectrometry (ID-ICP-MS). The results showed that $^{240}Pu/^{239}Pu$ ratios in the East China Sea and Okinawa sediments were much higher than the reported value of global fallout. The highest $^{240}Pu/^{239}Pu$ ratios (0.32-0.33) were observed in the deepest Okinawa sediment samples. These ratios suggested the US nuclear weapons tests in the early 1950s at the Pacific Proving Grounds in the Marshall Islands were a major source of Pu in the East China Sea and Okinawa Trough sediments, in addition to the global fallout source. It was proposed that close-in fallout Pu was delivered from the Pacific Proving Grounds test sites via early direct tropospheric fallout and continued releases by the North Pacific Equatorial Circulation system and Kuroshio Current into the Okinawa Trough and East China Sea. The total $^{239+240}Pu$ inventories in the sediment cores were about 150-200 % of that expected from direct global fallout, among them, about 46-67 % of the total inventories were delivered from the Pacific Proving Grounds. Much higher $^{239+240}Pu$ inventories were observed in the East China Sea sediments than in sediments of the Okinawa Trough, because in the open oceans, part of the $^{239+240}Pu$ was still retained in the water column, and continued Pu scavenging was higher over the margin than the trough. The vertical distributions of $^{239+240}Pu$ activities and $^{240}Pu/^{239}Pu$ ratios in these cores showed that sediment mixing was the dominant process in controlling profiles of Pu in this area. Faster mixing in the coastal samples has homogenized the entire $^{240}Pu/^{239}Pu$ ratio record today; slightly slower mixing and less scavenging in the Okinawa Trough has left the surface sediment ratios closer to the modern North Pacific water end member and with higher ratios at the bottom of the cores.

6) Mechanism of accumulation of radioisotopes by marine organisms

The bioaccumulation mechanisms of radioisotopes in aquatic organisms (algae, planktons, invertebrates and fishes) were examined by RI tracer experiments and elemental analyses. Although freshwater fishes had several times higher concentration factors than seawater fishes, it was found by constructing an imitating ecosystem in the laboratory that the major reason for this resulted from the difference in contribution of sediments between freshwater fishes and seawater fishes. As a result of application of ^{99}Tc analytical procedures developed by our team to marine environmental samples, the concentrations of ^{99}Tc in marine organisms in Japan were found to be very low, compared with marine organisms in the Atlantic Ocean. For example, the concentration of ^{99}Tc in a green alga *Bryopsis maxima* showing the highest concentration among Japanese marine algae was 1/136,000 of that of a brown algae *Fucus vesiculosus* collected at the Sellafield area in UK. The biological behavior of Tc was similar to Re belonging to the same group in the periodic table. But chemical behaviors of ^{99}Tc were not completely like to those of Re.

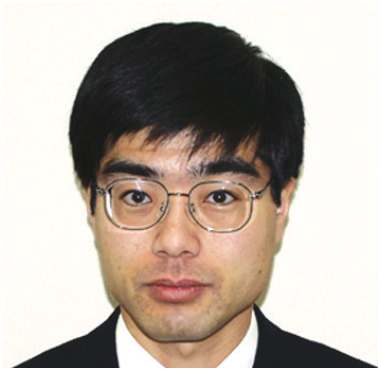
7) Assessing the impact of radioactive substances released into the marine environment

Radioactivity and mineral composition were determined for several species of marine algae and mollusks with special regard to exploring candidate organisms for a biological monitor to use in environmental monitoring. In general, algae were characterized by the presence of ^{214}Bi and ^{228}Ac on a gamma spectrum measured using a Ge semiconductor detector, which revealed that algae accumulated their ancestor radionuclides, ^{226}Ra and ^{228}Ra, respectively. A genus of green algae, *Bryopsis*, most effectively accumulates Ra isotopes and could be applied to monitoring for evaluating load of naturally occurring radionuclides in the marine environment. On the other hand, mollusks were characterized by the presence of ^{108m}Ag in their viscera and its radioactivity concentration was higher in the viscera of snails than in those of cephalopods, whereas ^{137}Cs concentration was higher in cephalopods than in snails. Marine snails are likely to have properties appropriate for the biological monitor. The concentration of elements in each group of organisms would not differ very much from one species to another and the values were expected to be distributed around the arithmetic mean values with some variation. Marine organisms sometimes showed an extremely high concentration, however, the concentration was specific both to species of organisms and to species of elements. An extremely high concentration of element could be identified as an 'outlier' statistically by Smirnov's examination. Manganese concentration in a species of bivalves, *Cyclosunetta menstrualis*, could be identified as a typical example of outlier, which was possibly used as a biological monitor for surveying the release of ^{54}Mn from nuclear facilities. An extremely high concentration of alkaline earth metals including Sr and Ba was also observed in the above mentioned green algae, which would be most useful in the case of ^{90}Sr and ^{140}Ba-^{140}La contamination, although relatively high concentrations of alkaline earth metals were generally observed in common algae, especially in species of brown algae.

Major Publications:

1) Shiraishi, K., Ko, S., Sahoo, S.K., Muramatsu, Y., Los, Y.P., Korzun, V.N., Tsignakov, N. Y., Zamostyan, P. V. : Dietary iodine intake in residents of Northwestern regions of Ukraine contaminated by the Chernobyl accident. *Health Physics*, **90**, 11-15, 2006.
2) Homma-Takeda,S, Nishimura, Y., Watanabe, Y., Imaseki, H., Yukawa, M.: Tin accumulation in spermatozoa of the rats exposed to tributyltin chloride by synchrotoron radiation X-ray fluorescence (SR-XRF) analysis with microprobe. *Nuclear Instruments & Methods in Physics Research Section B*, **231**, 333-337, 2005.
3) Aono, T., Yamada, M., Kudo, I., Imai, K., Nojiri, Y. and Tsuda, A.: Export fluxes of particulate organic carbon estimated from ^{234}Th/^{238}U disequilibrium during the Subarctic Pacific Iron Experiment for Ecosystem Dynamics Study (SEEDS 2001). *Prog. Oceanogr.*, **64**, 263-282 , 2005.
4) Zheng, J., and Yamada, M.: Determination of U isotope ratios in sediments using ICP-QMS after sample cleanup with anion-exchange and extraction chromatography. *Talanta*, **68**, 932-939, 2006.

3.5. Environmental and Toxicological Sciences Research Group



Satoshi Yoshida, Ph.D.
Director, Environmental and Toxicological Sciences 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 (PhD in environmental chemistry)

Professional Activities: 1989-present, National Institute of Radiological Sciences

Research Interests: Environmental chemistry, geochemistry, and radioecology.

- *Behavior of radionuclides and related stable elements in ecosystems, with special emphasis on the role of biological activities.*

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Objectives:

The recent rapid progress in technology and industry has led to the release of a variety of toxic substances which harm the environment and have adverse effects on human health. This research group aims to develop scientific methods for assessing and comparing the impacts of radioactive substances and other environmental toxicants, and to create a safe environment, under the "Comparative Study of the Effect of Radiation and Other Environmental Risk Sources on People and Ecosystems". These activities also provide basic information on environmental radiation protection, which is increasingly becoming a worldwide concern. The group consists of four research teams: Environmental Behavior Research Team, Experimental Model Ecosystem Research Team, Environmental Toxicology Research Team, and Numerical Analysis and Computer Simulation Research Team. The following describes the progress of each of these teams during fiscal year 2005.

Progress of Research:

1) Environmental Behavior Research Team

This team investigates the levels and behavior of environmental toxicants in natural and semi-natural ecosystems, such as forests and farmland. To obtain the parameters which will enable the behavior of radionuclides and other environmental toxicants such as heavy metals to be compared, environmental samples (e.g., soils, plants, mushrooms, and earthworms) are being analyzed for more than 40 elements, as well as for radionuclides. The role of biological activities on the behavior of radionuclides and related stable elements in ecosystems is one of the primary concerns. This team is also developing simple, accurate methods for analyzing long-lived radionuclides, such as Tc, Pu and U, in environmental samples.

Determination of isotopic composition gives useful information on the source term and the behavior of radionuclides including Pu in the environment. However, there is only a limited volume of quality data available on the levels and distributions of ^{239}Pu and ^{240}Pu isotopes in the environment. The team successfully determined Pu isotopes in environmental samples by double focusing sector field inductively coupled plasma mass spectrometry. Several sample introducing systems were used to improve detection limit and precision of the isotope ratio. A method for sample preparation was also improved by using a microwave decomposition system with an acid mixture followed by coprecipitation and ion-exchange separation. The ^{240}Pu/^{239}Pu atom ratios observed in Japanese soils were usually in the range of global fallout (0.17 - 0.19), except for very low ratios found in Nishiyama area, Nagasaki Prefecture. The low ratios (minimum 0.032) observed in the

Nishiyama area indicated the remaining Pu contamination from the atomic bombing in 1945. Since the area is contaminated also by global fallout, the $^{240}Pu/^{239}Pu$ atom ratio can be more sensitive indicator of bomb-derived Pu than Pu activity concentration.

In order to make an environmental safety assessment for ^{129}I, it is necessary to obtain information about the pathways of iodine transfer in the environment. The team has demonstrated that some filamentous fungi have a significant ability to volatilize iodine from the medium into the atmosphere and also to accumulate iodine in mycelia. Five strains of basidiomycetes, one strain of ascomycete and six strains of imperfect fungi were cultured in a liquid medium containing a radioactive iodine tracer (^{125}I), and were tested for their abilities to volatilize or accumulate iodine. Most of the fungal strains tested volatilized a considerable amount of iodine, with *Lentinula edodes* showing the highest volatilization rate of 3.4%. The volatile organic iodine species emitted from fungi cultures was identified as methyl iodide (CH_3I). Six fungal strains accumulated a considerable amount of iodine from the medium. Especially, *Alternaria alternata* and *Cladosporium cladosporioides* showed high concentration factors of 22 and 18, respectively. Considering their great biomass in soils, filamentous fungi may contribute to the global circulation of stable iodine and also the long-lived radioiodine, ^{129}I (half-life: 1.6×10^7 y), released from nuclear facilities into the environment.

2) Experimental Model Ecosystem Research Team

This team has already proposed an index for the holistic evaluation of effects on various ecological parameters, such as sizes of population or community. This ecological effect index (EEI) represents differences in values of applicable parameters between exposed and control ecosystems by the Euclidean distance function weighted by the ecological importance of each parameter. The usefulness of the index was demonstrated in previous studies by using the data on the effects of various toxicants on a microcosm, i.e., an experimental model ecosystem consisting of *Euglena*, *Tetrahymena* and *Escherichia coli*. The EEI was positively correlated with doses of each toxic agent, and the relationship between them could be fitted by a sigmoid curve. From this curve, a 50-percent effective dose (ED_{50}), at which the EEI became 50 percent, could be obtained for each toxic agent. The ED_{50} was used to evaluate quantitatively the ecological toxicity of each toxicant. This result indicates that the ED_{50} might be also a useful index for quantitative evaluation of effects on model ecosystems and on natural ecosystems.

As a study on ecological effects of radiation, we had previously investigated effects of acute γ-irradiation on the microcosm. In this year, we studied effects of chronic γ-irradiation on this microcosm, which are more important in ecological risk assessment. Significant differences were not observed in cell densities of any species between control microcosm and irradiated microcosm at 1.2 Gy/d for 247 days. At 5 Gy/d, *E. coli* was decreased compared with control after day 127, though the other two species were not affected. Irradiation at 10 Gy/d did not have significant effects on any species. At 23 Gy/d, *Euglena* died out first, then *Tetrahymena* died out, and finally *E. coli* died out after day 127. Some of these effects were not dependent on dose rates, and *E. coli* was more radio-resistant than the other species at 23 Gy/d. These responses of the microcosm to chronic γ-irradiation were different from those to acute γ-irradiation, suggesting that it is not easy to predict ecological effects of chronic irradiation from those of acute irradiation.

Effects of chronic γ-irradiation at very low dose rate were also investigated in the pure-culture systems of *Euglena* constituting the microcosm. When *Euglena* was exposed at a dose rate of 0.5 mGy/day, the growth rate was higher than that of control at a dose rate of 0.02 mGy/day. The result suggests that *Euglena* may be stimulated by chronic irradiation at low dose rate. Stimulating effects of ionizing radiations on cell growth have been reported episodically in the literature; however, few efforts have been devoted to this problem because results were often conflicting and sometimes un-reproducible. For the evaluation of ecological toxicity of radionuclides released to aquatic environments, the stimulating effects by very low dose rate irradiation should be elucidated and the implication of low dose rate irradiation to the ecosystem should be assessed.

3) Environmental Toxicology Research Team

This team is comparing the relative risks of radiation and other environmental toxicants, using their ability to induce DNA damage as a toxicological index, because DNA damage is considered the most important cause in serious biological events such as mutation, cell death and cancer induction. DNA damage, particularly DNA double strand breaks, and colony-forming abilities in animal and human cells exposed to radiation and several environmental toxicants have been quantified.

Furthermore, gene expression analysis in cells has been performed to seek genes expressed in response to DNA damage.

Gene expression analysis is one of the most useful means to detect biological responses. We applied a quantitative reverse transcription-PCR (RT-PCR) to measure the effect of ionizing radiation in human cells. The cells (HFLIII and MCF-7) were allowed to grow confluently before irradiation with X-rays (0 - 4 Gy). Total RNA was extracted 0, 2 and 4 hrs after the irradiation and subjected to expression profiling by RT-PCR. Comparison analyses were performed among the data from various challenges of dose and time courses. The expressions of the radio-responsive genes were found to be altered in a dose and time dependent manner. Those involved *CDKN1A* ($p21^{Waf1/Cip1}$), *Gadd45alpha*, *Mdm2*, *CyclinG*, and *XPC* genes, for which expression increased at 2 hrs after the X-irradiation (2 - 4 Gy). The HFLIII cells were also exposed to arsenite (0.02 mM) and the total RNA was subjected to RT-PCR. The expression level of C*DKN1A* ($p21^{Waf1/Cip1}$) was elevated up to 4-fold in a dose-dependent manner at 6 hrs after the treatment; this does not alter the cell survival in conventional colony formation assays. Thus, it was demonstrated that the RT-PCR is a sensitive strategy to measure environmental toxic reagents.

In the most current study, the team compared cytotoxicity of irradiation, arsenite and paraquat, all of which are known to induce DNA damage, using their ability to induce the interphase apoptotic cell death in mouse peritoneal resident macrophages as a cytotoxic index. Typical apoptosis was induced by irradiation, the most representative DNA damaging agent; however arsenite induced apoptosis with a peculiar morphological feature possibly not mediated by DNA damage, and paraquat did not induce apoptosis, rather it suppressed apoptosis induced by irradiation. Therefore, it is concluded that DNA damaging ability predominates the toxicological consequence of some environmental toxicants but not others.

4) Numerical Analysis and Computer Simulation Research Team

The behavior of environmental toxicants and their harmful influences on the sustainability of ecosystems are the latest topic for radiological protection of the environment. Since they are complicated and diverse issues, they cannot be fully understood by experimental studies or field surveys of natural ecosystems independently. This team is developing a computer simulation model based on accumulated experimental data of the behavior of toxicants in the environment, and their effects on the individual living organisms observed in experimental ecosystem studies and field surveys. The goal of the model is to estimate the potential impacts of radiation on the ecosystem by extrapolating from the umbrella effects at the individual level of environmental species. Another goal of the team is to contribute to the international trend to protect the environment from the effects of ionizing radiation, by developing a theoretical methodology for evaluating the radiation exposure of non-human species. It is also developing a mathematical model and computer simulation code to estimate impacts on the populations and communities of non-human biota to define the protocols to determine radiological harms that would threaten the whole species or create irreversible imbalances between species, and thereby affecting the sustainability of the ecosystem.

The population dynamics, and mass and energy budgets, of an aquatic microbial ecosystem have been collected by other research teams, and they are being simulated as a computer simulation code. A particle-based model has been used to duplicate this microcosm's self-organized, sustainable system of complexity, by simulating interactions among species, such as the predator-prey relationship, competition for common resources, autolysis of detritus and the detritus-grazing food chain, and interactions among organisms and habitats. Chronic, acute exposures to radiation and chemical toxicants by the microcosm are being observed experimentally, and the results will be reflected in modifications to the simulation model. Validity of the model is checked by using data from the microcosm experiments. In the analysis, the intrinsic parameters of umbrella endpoints (especially, acute lethality, impacts on morbidity, reproductive growth and mutation at the individual level). The simulation results are implemented to determine the population-level, community-level, and ecosystem-level disorders of ecologically crucial parameters (e.g., intrinsic growth rate, carrying capacity, variation, etc.), that relate to the probability of extinctions of the microorganisms. Numerical analysis and computer simulations will help us to compare the effects of various environmental toxicants, and to develop and implement measures to protect the environment.

Major Publications:

1) K. Yamamoto, T. Sakashita, K. Miyamoto: Development and validation of an atmospheric dispersion model for tritium using the IAEA BIOMASS scenario, *Fusion Science and Technology*, 48, 500-503, 2005.
2) D. Galeriu, H. Takeda, A. Melintescu: Energy metabolism and human dosimetry of tritium, *Fusion Science and Technology*, 48, 795-798, 2005.
3) Y. Kubota, S. Takahashi, H. Sato, K. Suetomi: Radiation-induced apoptosis in peritoneal resident macrophages of C3H mice: selective involvement of superoxide anion, but not other reactive oxygen species, *International Journal of Radiation Biology*, 81, 459-472, 2005.
4) T. Ban-nai, S. Yoshida, Y. Muramatsu, A. Suzuki: Uptake of radiocesium by hypha of basidiomycetes -radiotracer experiments-, *Journal of Nuclear and Radiochemical Sciences*, 6, 111-113, 2005.
5) S. Yoshida, Y. Muramatsu, W. Peijnenburg: Multi-element analyses of earthworms for radioecology and ecotoxicology, *Radioprotection*, 40, 491-495, 2005.
6) M. Doi, I. Kawaguchi, N. Tanaka, S. Fuma, N. Ishii, K. Miyamoto, H. Takeda, Z. Kawabata: Model ecosystem approach to estimate community level effects of radiation, *Radioprotection*, 40, 913-919, 2005.

3.6. Studies on Environmental Radon and Its Biological Effects

Yuji Yamada, Ph.D.
Director, Radon Research Group

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 filter. He has had 26 years of experience in research on radioactive aerosol and its 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 using a cast model. He was honored for studies on air filter by Japan Health Physics Society in 1986 and Japan Association of Aerosol Science and Technology in 1997.

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Objectives:

Radon is a radioactive gas emanated from soil, water and building materials. Radon and its decay products in the air are inhaled into the human respiratory system where their further decay results in exposure. The alpha radiation, emitted from the decay products, has the potential to damage DNA of respiratory tissues, which would be the first step to cancer. It is well known that exposure to high radon concentration causes lung cancer from the results of many epidemiological and experimental studies. However, it has not been clear whether long-term exposure to environmental radon causes similar health effects. The radon levels in most homes are much lower than those in most uranium mines.

Among sources of natural radiations, radon and its decay products contribute the largest percentage to the total average annual effective dose to the public. There are two different ways to estimate dose from radon exposure; the epidemiological approach and the dosimetric approach. Currently, there is a large difference by a factor of 3 in exposure dose. The data on behavior in the environments and dose estimation for thoron, one of the radon isotopes, are very limited.

The aims of this research are to investigate the behavior of radon and thoron in the environments discriminatively, and to re-characterize their decay products for dose evaluation. This information would lead to a solution of the problems in risk estimation from exposure to radon and help to re-evaluate the dose conversion factor (DCF) from exposure concentration to exposure dose.

Progress of Research:

Main subjects of studies carried out this year are summarized below.

1) Thoron in the living environment of Japanese

Additional study concerning the behavior of the thoron in the living environment was carried out. While thoron concentrations have been found to show a large spatial distribution, information for spatial distribution of thoron decay products in the living environment has not been reported. The study for thoron focused on the investigation of spatial distribution of thoron decay products using a deposition monitor (Fig.2). The uniform distribution that was logically expected was not found. This result might be caused by the low concentration of the decay products and measurement error due to the large variation of deposition velocity with small movement of the ambient air. Very high thoron concentrations were found in various indoor locations in Japan and dose estimates due to inhalation of the decay products become more important. It is necessary to accumulate evidence and to find the cause of the variation to obtain accurate dose estimation from inhalation of thoron decay products.

2) A comparison of dose conversion factor for radon/thoron decay products

The dose due to short-lived thoron decay products was calculated using a dosimetric approach. The calculations were based on a computer program LUDEP, which implements the ICRP 66 respiratory tract model. The dose per equilibrium equivalent concentration for thoron (EETC) was calculated with respect to: (1) equivalent dose to each region of the lung tissues (bronchial, bronchiolar and alveolar); (2) weighted equivalent dose to organs other than lung;

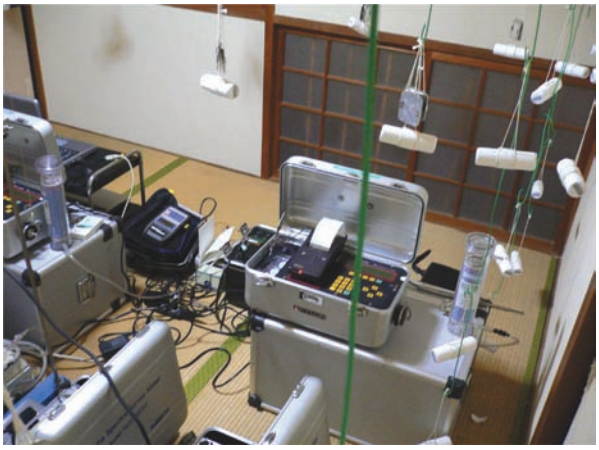

Fig 2. Thoron survey conducted in a traditional Japanese room.

and (3) effective dose.

The calculations indicated that: (1) the most exposed region of the lung tissues was the bronchial for unattached fraction and the bronchiolar for attached fraction; (2) the contribution to effective dose mostly resulted from the lung dose; and (3) the effective dose per EETC was about four times larger than the effective dose per equilibrium equivalent concentration for radon (EERC).

The calculated dose conversion factors were applied to comparative dosimetry for some thoron-enhanced areas where EERC and EETC were measured. In the case of a spa in Japan, the dose from thoron decay products was larger than the dose from radon decay products.

3) Particle size distribution of radon/thoron decay products

Sizing method of radon/thoron decay products using GSA technique was optimized. The sampling period ranged from 5 min to 30 min, and it depended on the concentrations of radon/thoron decay products. Even in the mixed area of radon and thoron, 5-min sampling was enough time to measure size distribution of radon decay products. For thoron decay products, 30-min sampling was necessary when EETC was about 5 Bq m-3. The longer sampling was not always good for size measurements. For the same carrier aerosol, no differences were observed in size distribution between radon and thoron decay products.

4) Biological effects due to radon/thoron exposure

The micronuclei for rat tracheal epithelial cells (RTE cells) were examined by *in vitro* exposure to radon and thoron. The rat tracheal epithelial cells were exposed in air-liquid interface culture, which was developed for the purpose of simulating *in vivo* conditions. As a result, the micronucleus induction gradually increased when the dose rate was over 1 mGy h^{-1}. This dose rate was equal to the dose rate for the indoor condition which radon concentration was 10^5 Bq m^{-3}. This result indicated that micronucleus induction was not affected by short-period exposure when radon concentration was quite high.

To examine the molecular basis of the biological effect caused by radon and its short-lived decay products, an attempt was made to establish a new experimental system using mouse FM3A cells to simulate the condition of epithelial cells being exposed to environmental stress. The 6-TG resistant phenotype was used for detecting the genetic effect of radon. As a result, the frequency of 6-TG resistant colonies increased 100 times higher than that of control at more than 300 mGy exposure. On the other hand, no increasing was observed at less than 10 mGy exposure. As a result of PCR analysis, significant increasing was observed at less than 1mGy exposure. More consideration is needed to determine the low-dose radiation effects.

Major publications:

1) J. Chen, S. Yoshinaga, S. Tokonami, H. Yonehara, Y. Yamada: Japanese individual risks of radon induced lung cancer for different exposure profiles. *J. Health Phys.*, **40** (3), 285-294, 2005
2) Y. Yamada, Q. Sun, S. Tokonami, S. Akiba, W. Zhuo, S. Zhang, T. Ishikawa, M. Furukawa, K. Fukutsu, H. Yonehara: Radon-thoron discriminative measurements in Gansu province, China, and its implication for dose estimates. *Journal of Toxicology and Environmental Health. Part A,* **69** (7-8), 723-734, 2005.
3) Y. Yamada, A. Koizumi, K. Ishikawa, Y. Hishinuma, K. Tatenuma: Development of a radon trap device using a corona discharge. *Radiation Protection Dosimetry,* **117** (4), 414-418, 2005.
4) S. Tokonami, H. Takahashi, Y. Kobayashi, W. Zhuo: Up-to-date radon-thoron discriminative detector for a large scale survey. *Review of Scientific Instruments,* **76** (1), - , 2005 (in press).
5) T. Ishikawa, S. Tokonami, S. Yoshinaga, Y. Narazaki: Airborne and waterborne radon concentrations in areas with use of groundwater supplies. *Journal of Radioanalytical and Nuclear Chemistry,* **267** (1), 85-88, 2006.

3.7. Research on Redox Regulation against Radiation

Nobuo Ikota, Ph.D.
Director, Redox Regulation Research Group

Outline of Research Career:

Dr. Ikota was born in Saitama in 1947 and received B.S.(1971) and Ph.D.(1976) from University of Tokyo. After working as a postdoctoral fellow (1976-1978) at Cornell University, he joined the Faculty of Pharmaceutical Sciences, University of Tokyo as Assistant Professor in 1978. In 1982, he moved to NIRS. His research interest is the development of antioxidants and radioprotectors, and the elucidation of their defense mechanism.

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Objectives:

The redox (reduction and oxidation or oxidoreduction) processes have an important role in the physiological regulation of living organisms. Reactive oxygen species (ROS), reactive nitrogen species (RNS), and free radicals are produced in living organisms exposed to stresses from external factors such as radiation, ultraviolet light, metals, and toxic substances, and internal factors such as inflammation and ischemia-reperfusion. Living organisms usually maintain homeostasis through their own control systems to remove ROS, RNS, and free radicals. However, oxidative stresses arise from insufficient removal of these species and cause various diseases such as arteriosclerosis, cancers, and aging. Redox regulation protects the living organisms from various oxidative stresses and maintains homeostasis by controlling the redox states *in vivo*. The redox regulation research group consists of four teams which conduct studies on redox regulation research for biochemical effects of living body from molecular, cellular, and tissue levels to the whole-body level through the participation of ROS, RNS, and free radicals generated by radiation. The research includes studies on bioradicals (development of the method to detect radicals such as hydroxyl radical ($\cdot$OH), peroxyl radicals (LOO $\cdot$), and nitric oxide (NO) generated *in vivo* by radiation), studies on biological effects (detection of oxidative damages of DNA, protein, and lipid, and elucidation of regulatory mechanisms on self-mutagenic and inducible genes and dysfunction of proteins, and radiation effects on endocrine systems) caused by irradiation, and studies on redox regulation substances (development of antioxidants, radical scavengers, and radioprotectors from synthetic compounds, natural products, and medicines, and elucidation of their scavenging mechanisms for ROS, RNS, and free radicals).

Progress of Research:

1) Studies on bioradicals generated by radiation

This year further evaluation to improve the sensitivity of the *ex vivo* spin trapping method using *N-tert*-butyl- α-(4-pyridyl-1-oxide) nitrone (POBN) as a spin trapping reagent for detecting hydroxyl radical generation by X-ray irradiation of rat and evaluation of relationship between the generation of ROS by irradiation and damages of mouse skin, and evaluation of *in vivo* ESR images observed in X-ray irradiated living mice using acyl-protected hydroxyl amine probe (ACP) were performed.

A spin trapping agent, POBN was tried instead of *N-tert*-butyl- α-phenylnitrone (PBN) to improve the sensitivity of the *ex vivo* spin trapping method for detecting *in vivo* hydroxyl radical generation by X-ray irradiation of rat. Although the ESR signal intensity increased, it was not analogous to X-ray irradiation, indicating that POBN was not useful. Formation of ascorbyl radical in the X-ray irradiated skin was observed and the time-dependent increase of the ascorbyl radical correlated with the increase of lipid peroxidation in the skin. Generation of nitric oxide and hydroxyl radical by photo-irradiation was also evaluated.

Acyl-protected hydroxyl amine probe (ACP) was incubated in liver homogenates prepared from X-ray irradiated and non-irradiated mice and the oxidation rate of CPH, the deacylated form of ACP, and reduction rate of CP, the oxidized form of CPH, were measured. The irradiation decreased the reduction rate of CP whereas the oxidation rate of

CPH was not affected. This finding suggested that the different intensity of *in vivo* ESR images observed in X-ray irradiated and non-irradiated living mice was due to the difference in reduction activity of liver for the nitroxyl probe. Therefore, the ACP method might be applicable for *in vivo* evaluation of reduction activity of living animals.

2) Studies on regulatory mechanisms of self-mutagenic and inducible genes activated by radiation and fluctuation of cellular redox conditions

This year molecular mechanisms of radiation-induced genetic instability mediated by endogeneous retrovirus and of activation of gene for enzyme to contribute to remove ROS were investigated.

Endogenous retrovirus, intracisternal A-particle (IAP), is a construct of viral RNA and coat protein and ubiquitously present in normal mouse cells. IAP is a potential mutagen since the complementary DNA molecule reverse-transcribed from IAP RNA can be integrated to the genomic DNA. To investigate the radiation effect on the reverse transcription mechanism, we constructed a series of reporter plasmids that were designed to express IAP RNA by stable- transfection in mouse cells. To distinguish the nucleic acids of the transgene from endogenous nucleic acids derived from thousands of the IAP cDNA in normal mouse genome, oligonucleotide blocks with unique sequence were inserted in the plasmid. Stable transformed lines with the cDNA-reporter plasmid in RAW264.7 mouse macrophage cells were established. We succeeded in constructing methodologies for the exact measurement of both RNA and cDNA of the transgene using real-time PCR. In the transformants, the cDNA levels were increased following X-ray irradiation at the dose of 3Gy, suggesting that radiation enhanced reverse transcription of endogeneous retrovirus in the cells. We also established a transgenic mouse with the cDNA-reporter gene to study behavior of IAP in various tissues following radiation (Fig.3).

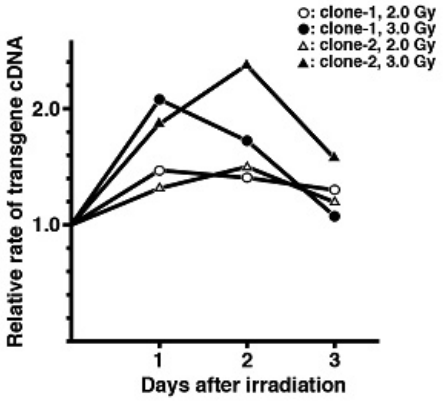

Fig 3. Activation of IAP cDNA synthesis by radiation.
Two clones of RAW264.7 cells that possess transgene of the entire IAP element as cDNA-reporter gene were X-ray irradiated at 0, 2 or 3 Gy. After incubation for 1 to 3 days, total DNA was prepared from the irradiated and non-irradiated cells and applied for semi- quantitative PCR amplification. Aliquots isolated from each PCR cycle were electrophoresed and the ethidium bromide-stained DNA levels were measured by lasor scanning. Levels of cDNA from transgene RNA were determined by the measurement of amplification of the unique structure generated specifically by retroviral reverse transcription. As an internal standard, single copy gene for interleukin(IL)-1 beta was used for the simultaneous amplification. Relative rates of transgene cDNA in irradiated cells per cDNA in the non-irradiated cells are shown in the graph.

Mammalian cells have a mechanism to activate genes encoding proteins that reduce damages by ROS. Since hemeoxygenase-1 (HO-1) is a member of ROS-related metabolism, various derivatives of caffeic acid (CA) esters were compared on the effect to activate HO-1 gene in RAW264.7 cells. Quantitative studies of mRNA level by real-time RT-PCR revealed that the drastic induction of HO-1 mRNA of more than 30-fold was observed by the treatment with ethyl and phenthyl esters of CA. In contrast, other CA esters did not give any effect on the expression of HO-1 gene. Since all the CA esters have similar level of reducing activity, it was suggested that the drastic induction of HO-1 gene was driven by the chemical structure of the CAs rather than the effect of redox status in the cells. We constructed reporter genes that possess different regions of HO-1 gene locus in mouse genome to use for future studies that reveal the regulation mechanism of the drastic level of induction.

3) Radiation effects on endocrine systems

This year an induction profile of iNOS by radiation was investigated to explore the relationship between the doses of X-ray-exposure, the time for the induction of iNOS and the expression of iNOS protein. The effect of prolactin (PRL), a peptide hormone produced by the anterior pituitary gland and important in the breast development, on the expression of iNOS in the mammary gland was also investigated.

Mammary gland well developed in pregnant or lactating rats exhibits a high susceptibility of tumorigenesis to ionizing radiation. Our previous reports have shown that inducible nitric oxide synthase (iNOS) is induced locally in rat mammary glands X-ray irradiated and in turn an excess amount of nitric oxide (NO) is produced in the glands, and that NO generated excessively in the mammary glands may correlate with mammary tumorigenesis induced by X-rays. The mammary glands were excised from Wistar-MS rats (11-week-old) primed by implantation with a pellet of estradiol, and cultured with 10% FCS-MEM including insulin, EGF and PRL. The cultured glands were then irradiated with different doses (~20 Gy, 1.1 Gy/min) of X-rays, and tissue homogenates were prepared for the immunoblot analysis of iNOS protein at various times after the X-ray exposure. The concentration of nitrite (NO_2^-) converted from NO produced and secreted by the glands into the conditioned culture medium was determined by Griess reagent to estimate the concentration of NO generated by them.

Western blot analysis showed that an immunoreactive band of iNOS protein in the cultured mammary glands was slightly increased at 6 h after the X-ray irradiation (20 Gy) in comparison with non-irradiated control culture, and the iNOS expression further increased in a time-dependent manner up to 24 h after the X-ray exposure. This indicated that iNOS protein was still retained at a higher level in the mammary gland at 24 h after X-ray irradiation. An apparent increase of iNOS in the cultured mammary gland with X-ray irradiation (5 Gy) was detected at 24 h after the irradiation and the enhancement of iNOS induction was a dose-dependent manner up to 20 Gy at 24 h after the irradiation. In addition, nitrite concentration in the culture exposed to X-rays was enhanced with increasing iNOS expression. On the other hand, an addition of exogenous PRL to the culture enhanced iNOS expression in the rat mammary glands in a dose-dependent manner up to 2 μg/ml. This was consistent with our report indicating that a higher concentration of PRL during pregnancy or the lactating period may contribute to the induction of mammary tumors by irradiation. In any event, not only the high rate of DNA synthesis and mammary cell mitosis caused by PRL, but also NO generated by iNOS induced excessively in the mammary gland stimulated with PRL and ionizing radiation may be associated with the initiation and the high incidence of mammary tumors due to irradiation.

4) Studies on redox regulation substances

This year evaluation of the radical scavenging mechanism for nitroxides was done and the development of new catechin derivatives as an antioxidant was studied based on the information for radical scavenging mechanism for natural phenol compounds previously explored by this team.

The one-electron oxidation potentials of various nitroxyl radicals were compared in order to estimate their radical-scavenging ability as an antioxidant. The reaction between 3-carbamoyl-2,2,5,5-tetramethylpyrrolidine-*N*-*oxyl* (3-carbamoyl-PROXYL; CP), a cyclic nitroxyl radical, and cumylperoxyl radical generated under irradiation of a propionitrile solution of cumene, di-*tert*-butyl peroxide, and molecular oxygen at -80 ℃ was examined by the electron spin resonance (ESR) technique. The scavenging reaction of cumylperoxyl radical by CP was significantly accelerated by the presence of scandium ion, indicating that the reaction proceeded *via* an electron transfer from CP to cumylperoxyl radical rather than *via* a radical coupling reaction.

Novel catechin derivatives, in which the catechol and chroman structure in (+)-catechin were constrained to be planar, was also synthesized based on previous mechanistic information about the radical-scavenging reactions by phenolic antioxidants, such as a vitamin E model and (+)-catechin. The radical-scavenging activity of the planar catechin derivatives thus obtained was found to be 5-10 times higher than that of (+)-catechin.

Major Publications:

1) Nishizawa C., Takeshita K., Ueda J., Nakanishi I., Suzuki K., and Ozawa T.: Reaction of para-hydroxybenzoic acid esters with singlet oxygen in the presence of glutathione produces glutathione conjugates of hydroquinone, potent inducers of oxidative stress, *Free Radical Res*., **40**, 369-371, 2005.
2) Chi C., Tanaka R., Okuda Y., Ikota N., Yamamoto H., Urano S., Ozawa T., Anzai K.: Quantitative measurements of oxidative stress in mouse skin induced by X-ray irradiation, *Chem. Pharm. Bull*., **53**, 1411-1415, (2005).
3) Nakanishi I., Nishizawa C., Ohkubo K., Takeshita K., Suzuki K. T., Ozawa T., Hech S. M., Tanno M., Sueyoshi S., Miyata N., Okuda H., Fukuzumi S., Ikota N., Fukuhara K.: Hydroxyl Radical Generation via Photoreduction of a Simple Pyridine *N*-Oxide by an NADH Analogue, *Org. Biomol. Chem*., **3**, 3263-3265, 2005.
4) Fukuhara K., Nagakawa, M. Nakanishi I., Ohkubo K., Imai K., Urano S., Fukuzumi S., Ozawa T., Ikota N., Mochizuki M., Miyata N., Okuda H.: Structural Basis for DNA Cleaving-Activity of Resveratrol in the Presence of Cu(II), *Bioorg. Med. Chem*., **14**, 1437-1443 , 2006.
5) Takeshita K., Chi C., Hirata H., Ono M., Ozawa T.: In vivo generation of free radicals in the skin of live mice under ultraviolet light, measured by L-band EPR spectroscopy, *Free Radic. Biol. Med*., **40**, 876-885, 2006.

3.8. Basic Study of Radiation Hazards

Shiro Aizawa, Ph.D.
Director, Radiation Hazards Research Group

Outline of Research Career:

Dr. Aizawa received his Ph.D. in 1976 for his study on *in vitro* spermatogenesis. He has had 28 years of experience in research on radiation immunology, hematology and carcinogenesis at NIRS. He served as a Director in the Office of Planning and Coordination between 2004 and 2005. Since July 2005, he has been a group leader of the Radiation Hazards Research Group.

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Objectives:

The aim of this research group is to investigate radiation hazards overall at the levels of a molecule, cell, tissue, organ, and an individual. The group consists of four teams. Each team's major subjects are: cytogenetics and cytometry (first team), hematology and teratology (second team), molecular biology (third team), and proliferation and differentiation (fourth team). Objectives are as follows.

1) First team

The analysis of radiation-induced DNA damage, including chromosome aberrations, provides useful information about the effects of radiation on the human body as well as dose estimation. The first team has worked to establish accurate and speedy systems for chromosome analysis using up-to-date techniques of electronics and biotechnology.

2) Second team

The second team has been analyzing effects of radiation in irradiated mouse fetuses and hematological change in irradiated mice. Radiation-induced teratogenetic effect on embryogenesis and its modification by priming low-dose irradiation or applications of chemicals are of great interest in radiation protection and novel bioresponse mechanisms. The most remarkable effects of radiation can be detected in the hematological tissues. As viruses are one of the common environmental factors for humans, study on the combined exposure with radiation and virus is with a critical impact on risk assessments.

3) Third team

Molecular mechanisms underlying radiation hazards are analyzed, aiming at establishing the scientifically justified risk assessment of radiation as well as further advancement of radiation medicine.

4) Fourth team

The purpose of this team's study is to elucidate the mechanism of the effects of radiations on the proliferation and differentiation of mammalian cells at cellular and molecular levels.

Progress of Research:

1) First team

There is an incentive to develop a culture system of mouse peripheral blood lymphocytes (PBLs) to serve as models for studying genotoxic effects in humans exposed to mutagens, including ionizing radiation. However, many past approaches have been laborious, complex and only partly reproducible. Therefore, we established an improved culture system of mouse PBLs by removing blood and/or plasma, which was found to inhibit *in vitro* mitotic stimulation or proceeding cell cycles of lymphocytes. We compared the reactions of isolated PBLs to mitogens between the classical method and the present improved one.

As a result, the 42-h culture and the long-term treatment of colcemid at low concentration gave a maximal number of first *in vitro* metaphase cells and good morphology of chromosomes, which is suitable for conventional cytogenetic analysis. Then, we applied this method to the cytogenetic analysis using chemically-induced premature chromosome condensation (PCC) as well as the conventional analysis, and demonstrated that the frequency of excess fragments observed in PCC cells might be useful to quantify the radiation-induced damages on chromosomes.

2) Second team

After exposure to a high dose of radiations in late organogenesis, radiation-induced Trp53-dependent apoptosis in cells in the predigital regions is responsible for final digital defects in fetal mice. Although single administration of pififthrin, a Trp53 inhibitor, or Z-VAD, pan-caspase inhibitor, suppressed the occurrence of apoptosis, no significant effect was observed on reduction of digital malformation. However, application of Na_3VO_4, an inhibitor that could block the upstream of Trp53 signal transduction, successfully led to reduction of radiation-induced apoptosis and digital malformation. Priming low-dose irradiation also showed a suppressive effect on induction of apoptosis and malformations by the high dose of irradiation. Life-long study on the mice that were survivors of the fetuses receiving a high dose of prenatal irradiation (5 Gy) due to an induced adaptive response by priming low-dose irradiation, showed high postnatal mortality (Figs. 4, 5), delayed neurophysiological development, increased malformations in main organs such as the brain, behavioral alterations, and shortening of life span. The results indicated that adaptive response could rescue some fetuses from the killing effects of high dose radiation, while the surviving animals were not healthy and did not develop normally.

Exposure of C3H mice infected by Friend leukaemia virus to whole-body irradiation at a sublethal dose of 3 Gy caused a significant increase in mortality within 1 month post-irradiation. This acute radiation effect was attributed to haematopoietic death as most animals manifested a severe loss of cellularity in the spleen, bone marrow and peripheral blood 2 weeks after irradiation. Decreases of CFU-S and peripheral blood cells were almost to the same extent as those in the animals that received a lethal dose of radiation. This deleterious effect of virus infection was both Trp53- and mouse strain-dependent and was observed only when they were irradiated at around 1 week after virus inoculation. The results indicated that Friend leukaemia virus infection could enhance radiation sensitivity of haematopoietic cells in mice under certain restricted conditions.

3) Third team

Genome instability is involved in crucial biological effects caused by ionizing radiation. To identify genes responsible for the maintenance of chromosome integrity, we previously isolated 25 temperature-sensitive CHO-K1 cell mutants exhibiting chromosome instability. One of these mutants, tsTM18, exhibits chromosomal instability and cell cycle arrest at S and G_2 phases with decreased DNA synthesis at the nonpermissive temperature, 39ºC. To identify the causative mutation, we fused tsTM18 cells with normal human cells to generate hybrids carrying fragments of human chromosomes. Analysis of chromosome content of temperature-resistant transformants and introduction of a bacterial artificial chromosome containing part of human chromosome 9 led to isolation of the human *SMU1* gene. Comparison of sequences of the *Smu1* gene from wild-type and mutant cells revealed that the mutant phenotype was caused by a G-to-A transition that yielded a gly-to-arg substitution at position 489 in hamster Smu1. The substituted glycine was located in the WD-repeat domain of Smu1. Single-stranded DNA accumulated in the nuclei of mutant cells at 39ºC. Furthermore, cdc2 kinase was not activated during G_2 phase, and there was no chromosome segregation due to incomplete assembly of the spindle during M phase. Thus, Smu1 appeared to be involved directly or indirectly in DNA replication, activation of cdc2 kinase, spindle assembly, and maintenance of chromosome integrity, reflecting the important roles of Smu1 in cellular function.

4) Fourth team

Repeated exposure to ultraviolet radiation (UVB) on the dorsal skin of hairless mice induced the development of pigmented spots long after its cessation. The proliferation and differentiation of epidermal melanocytes in UVB-induced pigmented spots were greatly increased, and those effects were regulated by keratinocytes rather than by melanocytes. Primary melanoblasts (ca. 80%) and melanocytes (ca. 20%) derived from epidermal cell suspensions of mouse skin were cultured in a medium supplemented with granulocyte-macrophage colony-stimulating factor (GMCSF). GMCSF induced the proliferation and differentiation of melanocytes in keratinocyte-depleted cultures. Moreover, an antibody to GMCSF inhibited the proliferation of melanoblasts and melanocytes from epidermal cell suspensions derived from the pigmented spots of UV-irradiated mice, but not from control mice. Further, the GMCSF antibody inhibited the proliferation and differentiation of melanocytes co-cultured with keratinocytes derived from UV-irradiated mice, but not from control mice. The quantity of GMCSF secreted from keratinocytes derived from the pigmented spots of UV-irradiated mice was much greater than that secreted from keratinocytes derived from control mice. Moreover, immunohistochemistry revealed the expression of GMCSF in keratinocytes derived from the pigmented spots of skin in UV-

irradiated mice, but not from normal skin in control mice. Expression of mRNA of GMCSF gene in UVB-irradiated keratinocytes was greater than in control keratinocytes. These results suggested that GMCSF was one of the keratinocyte-derived factors involved in regulating the proliferation and differentiation of mouse epidermal melanocytes from UVB-induced pigmented spots.

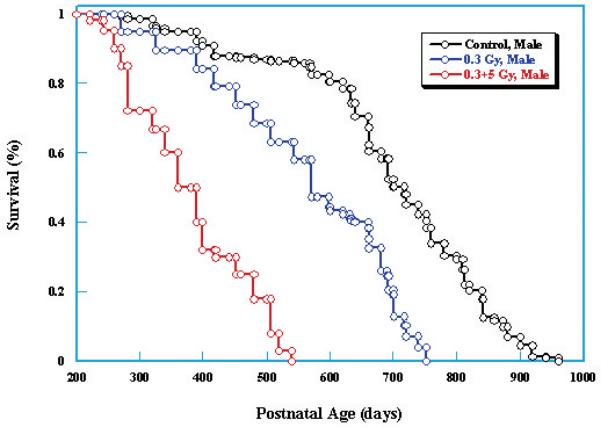

Fig 4. Survival curve of the controls that received no prenatal irradiation (black circles), of those that received prenatally 0.3 Gy on E11 (blue circles), and of those survivors of 5 Gy on E12 with a priming dose of 0.3 Gy on E11 (red circles) in the male offspring mice.

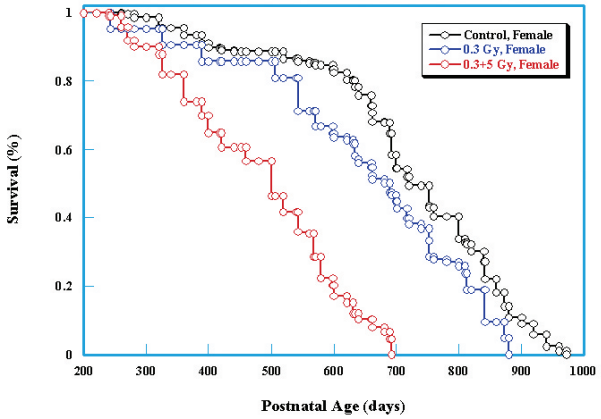

Fig 5. Survival curve of the controls that received no prenatal irradiation (black circles), of those that received prenatally 0.3 Gy on E11 (blue circles), and of those survivors of 5 Gy on E12 with a priming dose of 0.3 Gy on E11 (red circles) in the female offspring mice.

Major Publications:

1) Reiko Kanda, Yi Shang, Satsuki Tsuji, Kiyomi Eguchi-Kasai, Isamu Hayata: An improved culture system of mouse peripheral blood lymphocytes for analysis of radiation-induced chromosome aberrations. *Bioscience Reports*, 24, 641-650, 2004
2) Masahiro Murakami, Issay Narumi, Katsuya Satoh, Akira Furukawa, Isamu Hayata: Analysis of interaction between DNA and Deinococcus radiodurans PprA protein by Atomic force microscopy. *Biochimica et Biophysica Acta. Proteins and Proteomics*, 1764, 20-23, 2006
3) Bing Wang, Masahiro Murakami, Kiyomi Eguchi-Kasai, Kumie Nojima, Yi Shang, Kaoru Tanaka, Kazuko Fujita, Herv Coffigny and Isamu Hayata. Effects of Prenatal Irradiation with an Accelerated Heavy-Ion Beam on Postnatal Development in Rats: I. Neurophysiologic Alterations. *Radiation Research*, 164, 561-566, 2005.
4) Manabu Koike and Aki Koike: Ku70-binding site of Ku80 is required for the stabilization of Ku70 in the cytoplasm, for the nuclear translocation of Ku80, and for Ku80-dependent DNA repair. *Experimental Cell Research*, 305, 266-276, 2005.
5) Kimihiko Sugaya, Etsuko Hongo and Hideo Tsuji: A temperature-sensitive mutation in the WD repeat-containing protein Smu1 is related to maintenance of chromosome integrity. *Experimental Cell Research* 306, 242-251, 2005.

3.9. Study for Genes-expression Network in Response to Ionizing Radiation

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

Objectives:

Long-range objectives (5-year project)

To understand the mechanisms underlying the biological effect in response to ionizing radiation, we will develop a next-generation gene expression profiling technology. Next, with the new procedure we will seek the radio-responsive genes comprehensively and will obtain quantitative information in their expression. Lastly, we will prepare the cells, in which the gene of interest is disrupted, and try to elucidate the genes-expression network including the radio-responsive genes.

Short-range objectives for 2005:

1) Cloning of IR-responsive transcripts, which was detected by HiCEP analysis, in ES cells.
2) Identifying IR-responsive transcripts in somatic cells.
3) Studying the RecQL4 using gene-expression profiling.

Progress and results of research:

For 1): It has been demonstrated that HiCEP technology is useful for analyzing the gene expression change in response to most types of stress, because some of the changes in their gene expression are very small.

We conducted an experiment to seek transcripts within embryonic stem (ES) cells in response to ionizing radiation, especially for very low dose. At 5cGy IR we identified transcripts: induced 20 and reduced 17. Further, at 2 cGy we detected two induced transcripts and 5 reduced transcripts. The transcript, which exhibited the biggest induction, was also induced by even 0.5 cGy. Currently we are performing an *in vivo* study. This is the first case that transcript, which responded to low doses of less than 10 mGy, was identified. Furthermore we demonstrated that the induction was ES specific and extremely low-dose IR specific.

For 2): With HiCEP analysis, Fujimori, Okayasu and Takahashi identified genes which responded to 1 cGy IR in human fibroblast cells.

For 3): RecqL4 is the responsible gene for RTS (Rothmund-Thomson syndrome) and known to play a critical role in genome integrity. In order to reveal the genes that are governed by the RECQL4 we prepared two RecqL4 knockout ES cells and compared their transcriptomes and those of parent ES cell line, R1. As a result, we identified 44 and 4 of respectively induced and suppressed peaks by the disruption of RecqL4 gene.

3.10. Development of Experimental Animals for Research on the Biological Effects of Radiation

Satoru Matsushita, D.V.M., Ph.D.
Director, Laboratory Animal Development and Research Group

Outline of Research Career:

Dr. Matsushita's studies are in the field of laboratory animal sciences. Major topics are research for infectious diseases of mice and rats, pathological and physiological research for already established and newly developed mouse and rat strains, and research for biological effects of radiation using laboratory animals. He also manages the laboratory animals and laboratory animal facilities; these tasks involve him in issues of animal welfare and protection as well as ethics for animal experimentation.

D.V.M., Ph.D., Diplomate of the Japanese College of Laboratory Animal Medicine, Member of the Japanese College of Veterinary Pathologists

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Objectives:

The purposes of this project are to develop new biotechnology to establish genetically modified animals for research on the biological effects of radiation, to produce animals highly sensitive to radiation, and to establish genetically and microbiologically controlled laboratory animal systems. The following are the specific objectives of this project.

1) To establish techniques for intracytoplasmic sperm injection (ICSI) which are applicable to production of transgenic mice and cryopreservation of sperm and to develop modified reproductive biotechnology such as *in vitro* fertilization and oocyte maturation using inbred mice.
2) To establish a method of mutagenesis in medaka and to produce at least one strain of radiation-sensitive medaka.
3) To improve the diagnostic technology for infectious diseases of laboratory animals including molecular biological methods, and to simultaneously collect and disseminate physiological and pathological data on newly and already established strains of laboratory animals.

In order to accomplish these objectives, the following tasks were undertaken in 2005.

1) Establishment of methods to identify the estrus cycle for the study of rat embryo manipulation and application of the superovulation regimen by hormone injection.
2) Studying the effects of oxygen tension and bovine serum albumin (BSA) on *in vitro* development of rat 2-cell embryos.
3) Screening mutant medaka at the third generation and performing genetic studies on candidate mutant medaka strains for radiation sensitivity.
4) To examine subpopulation of lymphocytes in the affected lungs of BALB/c-nu/+ and A/J mice in order to clarify the pathology of CAR bacillus-infected mice.
5) To develop practical usage of materials and/or equipment in order to improve the quarantine system for small laboratory animals (rodents).

Progress of Research:

Fiscal year 2005 was the last year in the Middle Range Research Plan; in its five years we have published 32 original papers and accomplished all project objectives in the Plan. The following are our research accomplishments in this year.

1. At first, we tried to establish a method to identify the estrus cycle in naturally cycling rats. Two methods, measurement of vaginal impedance and checking a vaginal smear, were compared. Vaginal smear was more precise than measurement of impedance to identify proestrus stage for natural mating. To determine breeding of rats for embryo research, the number of ovulated eggs were compared after natural mating between Slc:WI and Crlj:WI. Crlj:WI rats ovulate more eggs (13.8 eggs/animal) than Slc:WI (9.7 eggs/animal). Superovulation regimen was also examined in these two strains. None of the Slc:WI females responded to

hormonal treatment, while 5 out of 12 Crlj:WI females responded to hormonal treatment and ovulated 42.8 eggs per animal.

2. To improve rat development *in vitro*, effects of oxygen tension and BSA were studied using Slc:WI and Crlj:WI rats. Developmental responses to blastocyst stage were different between the two strains; Slc:WI embryos were significantly sensitive to oxygen tension and Crlj:WI embryos were sensitive to BSA. When nuclear numbers were compared, the highest numbers of nuclei were observed in the presence of 3mg/ml BSA under low oxygen tension (5%) in both strains. However, these numbers were still significantly lower than *in vivo* produced blastocysts, indicating *in vitro* culture conditions were still suboptimal.

3. For the mutagenesis in medaka, male fish (F_1) were treated with chlorambucil (0.2 mM) and the resultant mutations were recovered in the F_3 progeny by the method of three-generation crosses. The mutations for radiation sensitivity were screened in the F_3 progeny by exposing them to X-ray irradiation at the dose of 2Gy (no effect is found in normal medaka embryos at this exposure dose). By screening of 160 pairs from 20 F_1 families in total, we found two candidate mutant strains (802 and 1108) which had high sensitivities to radiation. In order to examine inheritance of the trait in each strain, several single-pair crosses between siblings were performed, and the radiation sensitivity was examined again in the F_4 progeny. We confirmed that the trait, a high sensitivity for radiation, was genetically inherited in each strain.

4. In experimental infection of CAR bacillus, the qualitative analysis of the lymphocyte subpopulation of affected lungs was carried out using the immunohistochemical method. As a result, the same histopathological findings (peribronchial lymphoid hyperplasia) were observed in affected BALB/c-*nu*/+ and A/J mice after 21 days of infection. No differences in lymphocyte subpopulation (CD4, CD8) of BALB/c-*nu*/+ and A/J mice were observed. The numbers of CD4 positive cells were higher than those of CD8 in BALB/c-*nu*/+ and A/J mice. These results suggested that the resistance mechanism of the mucosa in the host cells was important for CAR bacillus infection.

5. We improved the extraction material used for nasal swabs, which are applied for genetic testing of such things as respiratory tract infections. It was possible to collect nasal swab samples in live animals. Moreover, we have developed a new type of cage lid which divides cages into two rearing spaces. We demonstrated that this type of cage lid was useful in quarantine of animals for infectious studies such as CAR bacillus infection.

6. The identification of bacteria was performed by bacterial culture and PCR methods in the bacterial lines isolated from NIRS, ATCC12555, ATCC35149 and *Pasteurella haemolytica*. ATCC1255 and ATCC35149 are standardized bacterial lines of *Pasteurella pneumotropica*. As a result, bacterial lines isolated from NIRS had equivalent character to standardized P. *pneumotropica*.

7. Collaborative studies with the Transcriptome Research Center and the Transcriptome Profiling Group were promoted this year. Experiments for the production of gene-manipulated mice, in which new genes related to radiosensitivity and related traits were identified by studying their transcriptome profiles, were carried out. We generated chimeric mice derived from embryonic stem (ES) cells, by manipulating three genes (Ra, Sn and Te) using the aggregation method with ES (R1) cell- BDF2 embryo. Aggregated embryos were transferred to the pseudopregnant recipients, and the percentage of chimeric mice among weanlings was 33.6% (113 chimeras/260 weanlings) in untreated controls. The percentages of male chimeras among weanlings in the experiments of each gene were as follows: Ra, 43.5% (20/46); Sn, 75.0% (27/36); Te, 25.5% (13/51). Successful chimera production of 60 totals was achieved for the three genes. Among these, three chimeras derived from Sn and Te genes were found to have germline transmission as a result of test cross. The production of aggregation chimeras using the frozen-thawed host embryo was tested from last year. The percentages of chimera production from non-frozen embryos in untreated controls and Ra, Te genes using frozen embryos were 55.8 and 8.3, 18.9%, respectively. We found that the frozen-thawed host embryo was suitable for producing chimeras by this method. Resulting collaborative studies this year successfully produced gene-manipulated mice (+/-) of one strain originating in the Sn gene.

8. Regarding the collection of basic anatomical data on our inbred mice, six strains of mice were examined in collaboration with the Laboratory Animal Development and Management Office. The data on A/JNrs, BALB/c-*nu/nu* and BALB/c-*nu/+* mice were released to the public.

Major Publications:

1) Y. Ishikawa, N. Yamamoto, M. Yoshimoto, T. Yasuda, K. Maruyama, T. Kage, H. Takeda, H. Itou: Developmental origin of diencephalic sensory relay nuclei in teleost. *Brain, Behavior and Evolution*, **69**, 87-95, 2007.
2) S. Kito, Ohta, H. Medium effects on capacitation and sperm penetration through the zona pellucida in inbred BALB/c spermatozoa, *Zygote*, **13**, 145-153, 2005.
3) J.Wu, M. Morimyo, E. Hongo, T. Higashi, M. Okamoto, A. Kawano, Y. Ohmachi: Radiation-induced germline mutations detected by a direct comparison of parents and first-generation offspring DNA sequences containing SNPs. *Mutation Research*, **596**, 1-11, 2006.

3.11. Studies on Experimental Carcinogenesis Induced by Plutonium Compounds

Yutaka Yamada, D.V.M., Ph.D.
Team Leader, Internal Radiation Effects Research Group

Outline of Research Career:

Dr. Yamada received a Ph.D. in Veterinary Medicine from Hokkaido University in 1988. He has conducted studies on biological effects of alpha emitters at NIRS. He was at the Life Sciences Division, Los Alamos National Laboratory, USA as a visiting scientist where he studied alpha particle-induced mutation in hprt locus from 1993 through 1995. He was at the Institute for Environmental Sciences as a senior scientist from 1999 through 2001.

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Objectives:

The purpose of this research is to investigate the biological effects and cancer risks of internally deposited radionuclides, especially alpha-emitting plutonium compounds, by using experimental animals and *in vitro* alpha particle exposure systems. To clarify the cellular and molecular mechanism of high LET radiation-induced carcinogenesis, current studies include: 1) identifying target cells for the lung and bone tumors induced by inhalation and injection of plutonium, 2) establishing primary cell cultures of the target cells and cell lines from the tumor tissues, 3) analyzing radio sensitivity and biological effectiveness of alpha particle in the target cells, identifying gene mutations and chromosome abnormalities in bronchial and lung epithelial cells, 4) defining the role of genetic and epigenetic changes of oncogenes and tumor suppressor genes in the development of lung tumors and the influence of irradiation on targeted genes, and 5) determining variation in target cells for lung tumors as related to lung cancer susceptibility.

Progress of Research:

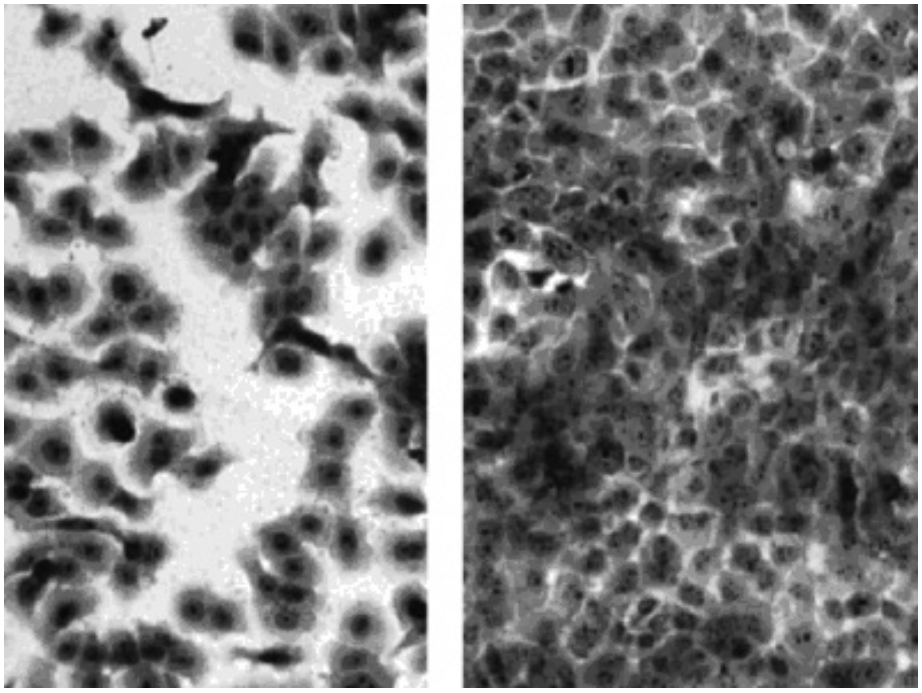
Comparison of radiation sensitivity of rat respiratory tract epithelial cells

Lung model of ICRP publication 66 describes that the cells at risk in respiratory tract tissues are secretory and basal cells in bronchial airways, and Clara and Type II cells in the alveolar interstitial region. Previous animal studies show that radiation-induced pulmonary adenomas and adenocarcinomas mostly originate from either alveolar Type II pneumocytes or bronchiolar Clara cells, while adenosquamous and squamous cell carcinomas may be derived from the other epithelial cell components. Histological examination reveals that most primary lung tumors are adenoma and adenocarcinoma in our experiments utilizing female Wistar rats. This phenomenon indicates that the susceptibility of radiation-induced carcinogenesis in lung is different in the respiratory tract region. It is, however, unclear whether there is a difference in radiation sensitivities between the target cells. The purpose of this study is to compare the dose-response relationships of radiation-induced cell death and transformation in primarily cultured rat tracheal epithelial (RTE) and rat lung epithelial (RLE) cells.

The RLE cells were isolated from female Wistar rats (4-6-week-old) by enzyme digestion and gradient centrifugation. The RLE cells were recovered from Type II cell-rich fraction of density about 1.06 g/ml. Trachea were filled with enzyme solution, and then RTE cells were rinsed from inside the trachea. RLE (Fig. 6a) and RTE cells were cultured in serum free medium including epidermal growth factor and other necessary factors. The cells were replated in dishes with 4μm thick Mylar films serving as bottoms. The cells were

irradiated using an alpha source of ^{238}Pu (3.6MeV, approximately 0.8Gy/min) or a gamma source of ^{137}Cs (8.2Gy/min). The cytotoxic responses of the cells to irradiations were determined in colony formation assay. Transformants formed dense colonies in serum-containing and growth factor-free selective medium. Frequencies of transformation were calculated from the number of enhanced growth variant colonies (Fig. 6b).

The irradiation caused a similar exponential decrease in survival in RLE and RTE cells, and the D_{37} of alpha particles and gamma rays were 0.65 Gy and 3.6 Gy, respectively. The RBE for cell killing was 5.5 in both types of cells. The transformation frequencies (TF) of RLE and RTE cells were $3.7x10^{-3}$ and $2.4x10^{-3}$ at 2 Gy of alpha particles, respectively. At 7.5 Gy of gamma rays, the TF for RLE and RTE increased to $8.0x10^{-3}$ and $7.1x10^{-3}$, respectively. The RBE for transformation of RLE was 1.7, and that of RTE was 1.3 (Table 2). These results indicate that there is no significant difference in radiation susceptibility between RLE and RTE cells. The dominance of adenoma and adenocarcinoma in the radiation-induced carcinogenesis of the Wistar rat lung may be due to the difference of target cell numbers and/or modification effects of the carcinogenesis, such as immune response. This primary epithelial cell culture system will be useful for analysis of radiation sensitivity among different target cells and mechanistic studies of early changes in the rat lung carcinogenesis induced by alpha-particles.



a) Primary cultured cells b) Transformants after alpha irradiation

Fig 6. Rat lung epithelial cells on culture dish

Table 2. Transformation frequencies and RBE of rat respiratory tract epithelial cells

	RTE	**RLE**
0 Gy	$0.3\text{-}1.0x10^{-4}$	$0.3\text{-}1.0x10^{-4}$
2Gy Alpha	$2.4x10^{-3}$	$3.7x10^{-3}$
7.5Gy Gamma	$7.1x10^{-3}$	$8.0x10^{-3}$
RBE	1.3	1.7

4. Research Center for Radiation Emergency Medicine

Kenzo Fujimoto, Ph.D.
Supervisory Director

Outline of Research Career:

Dr. Fujimoto graduated in Science from Kyoto University and obtained a Doctoral Degree in Engineering at the University of Tokyo. He has spent most of his career in studies on natural environmental radiation, especially 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 Research Center for Radiation Emergency Medicine (since 2003), an International Editorial Adviser of the *Journal of Radiological Protection* and an Advisory Editorial Board Member of *Nuclear Technology & Radiation Protection*.

Contact Point: kenzofuj@nirs.go.jp

Objectives:

This Research Center had the unique experience of receiving three highly exposed victims at the time of the JCO criticality accident in Tokai in September 1999, because the Center has been assigned as the final stage radiation emergency medicine hospital within 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.

Our required aims are as follows.

To accept radiation exposed victims who require specialized diagnosis and treatment

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

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

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

To promote technical development and research on radiation emergency medicine

To develop skilled manpower for a radiation emergency

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

1. Studying pathologic physiology of high-dose exposure
2. Developing chelating agents for removing radionuclides
3. Developing systems for precise measurement and evaluation in emergencies
4. Mitigating radiation injuries
5. Developing emergency responses to environmental contamination

Overview:

After the nuclear accident at Three Mile Island in 1979, the Central Disaster Prevention Council (CDPC) in the Prime Minister's office reinforced 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 heavily exposed or contaminated victims due to nuclear or radiological accidents. From January 2004 the Research Center has served as a liaison institution of WHO/REMPAN.

The Research Center carries out the following activities to maintain and enhance or strengthen the emergency preparedness system required 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 disaster or a radiological accident. The cooperation involves dispatch of an expert in the specific field in an emergency, arrangement of acceptance of patients at medical facilities affiliated with the expert's organization, and provision of advice. Such collaboration is expected to reinforce the functions of NIRS. NIRS will call the Radiation Emergency Medicine Network Council to solicit cooperation when it is requested by authorities (or when NIRS thinks the necessity arises) to respond to radiation emergencies. This council was working 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.

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
The course is held three times a year with 20 participants in each course. More than 260 participants have been trained so far. Many of them are working actively in primary or secondary medical emergency hospitals and playing an important role in local radiation emergency exercises.

(B) Emergency rescue training course
The course is held three times a year with 30 participants in each course. The duration of the course was one week.

(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 were trained to be able to measure and estimate internal dose by themselves.

3) Emergency Exercises

Japanese national and local governments regularly organize emergency exercises to which we send our staff to take roles in emergency medicine and radiation protection. On 10 November 2005 the Japanese government conducted a nuclear disaster prevention exercise in Niigata prefecture. Our staff participated in this. Moreover we conducted an additional exercise to simulate emergency handling of a patient transferred to NIRS by helicopter (Fig.7).

4) Follow-up Studies

The Research Center for Radiation Emergency Medicine conducts research work in a wide range of areas: medical care, radiation measurement and investigation, health physics, cytogenetics, and psychology. In addition, we study dose evaluation which facilitates decision-making in treatment methods, identification of radionuclides, treatment for high-dose exposure or reduction of high-dose exposure hazards, and rapid evaluation of population exposure.

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

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

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

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

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

Thorotrast is a radioactive contrast medium for angiography. The main constituent is thorium dioxide. A German company started sales 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 malignant carcinogenesis, and elucidates the effects of long-term internal radiation exposure on human bodies.

5) Database

A database including the cases of radiation exposure on Bikini Atoll and cases of thorotrastosis is being constructed. Since radiation accidents are rare, the maximum amount of information must be collected from each accident and accumulated to help medical 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 (Radiation Emergency Medical Preparedness And Response) exchanges information on radiation accidents, including those in the database owned by the US REAC/TS (Radiation Emergency Assistance Center/Training Site). REMPAN has a collaborating center at Ulm University in Germany and manages a SEARCH database of patient information. It aims to construct an international database by registering cases that are attributable to the Chernobyl accident and other radiation accidents. The NIRS registered the Dai-go Fukuryu-maru accident in the SEARCH database. In addition, our center is constructing a database by collecting the medical data of the victims of radiation accidents and exchanging information with countries that have developed radiation accident medicine.

6) International Cooperation (Fig.8)

(A) Our center participated in CONVEX (3) Exercise organized by WHO on 11 and 12 May 2005.

(B) Three professionals from Beijing Institute of Radiation Medicine and five from Taiwan visited our facility and discussed radiation emergency medicine with NIRS staff.

(C) Our staff was invited to deliver lectures in the following meetings and training courses.

(1) A training course held in Thailand from 5 to 11 June 2005.

(2) 2005 Radiation Emergency Medical Care Workshop held in Taipei on 29 and 30 July.

(3) European Bone Marrow Transplantation Radiation Accident Consensus Meeting held in Vaux de Cernay in France on 25 and 26 October 2005.

(4) Workshop on Research and Training Advancement in Radiation Emergency Medicine held in Seoul on 3 and 4 November 2005.

(5) Third National Convention on Health Emergency Management held in Manila from 4 to 7 December 2005.

(D) A training course on Medical Treatment of Patients Contaminated with Alpha Emitters was held for 15 medical doctors from Tri-service General Hospital in Taiwan on 1 and 2 September 2005.

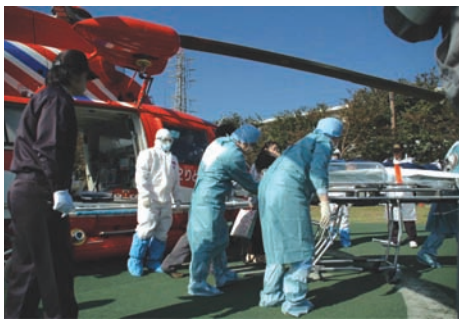
(E) Our staff attended International Conference on Monitoring, Assessments and Uncertainties for Nuclear and Radiological emergency Response held in Rio de Janeiro from 21 to 25 November 2005.

(F) Our staff was invited to attend DOE/IAEA Assistance Work Group (AWG) and Expert Groups (EG) meetings held in Alexander, Ireland on 19-23 September 2005 and in Buenos Aires on 21-23 February 2006.

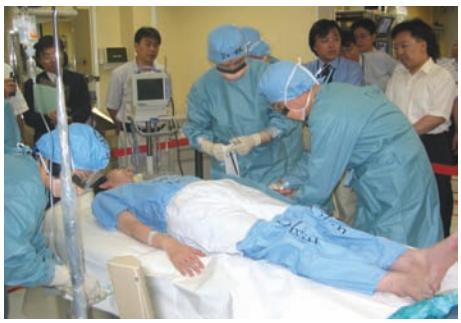
(G) WHO-REMPAN Regional Workshop on Radiation Emergency Medical Preparedness and Response in the Western Pacific Asia was organized on 23 and 24 March 2006 in collaboration with WHO and a regional assistance scheme was discussed with 13 participants from Korea, China and the Philippines.

(H) Our staff attended The 11th Coordination and Planning Meeting of the WHO REMPAN Collaborating Centers and Liaison Institutions

held in Kiev on 25-28 April 2006.



Receiving a patient at the heliport in NIRS



Treatment of a patient in NIRS

Fig 7. Nuclear disaster prevention exercise (10 November 2005)

Discussion with
Beijing Institute of Radiation Medicine
(26-27 April 2005)

Seminar for Tri-service General Hospital in Taiwan
(1-2 September 2005)

Fig 8. International cooperation

4.1. The Study for Radiation Emergency Medical Preparedness

Makoto Akashi, M.D., Ph.D.
Director, Department of
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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 works are:
1) establishment of radiation emergency medical preparedness; 2) research on radiation injuries, including molecular and cellular mechanisms; 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:

1) Study on patho-physiology in exposure to high-dose radiation

This study aims to understand the effects of high-dose radiation on intracellular signal transduction and the mechanisms of transmitting the signals among cells; these need to be known for treatment of acute radiation injury. The study also aims to identify genes that are related to skin injury caused by high-dose radiation, and to establish an in vitro model system of gene therapy for radiation injuries to skin.

2) Study on agents for removing radionuclides that have been incorporated

The study does experiments using experimental animals to investigate the removal of radionuclides (RNs) that have been incorporated by new agents and also to examine their adverse effects. This study aims to prepare manuals describing safe and effective treatments with these agents (DTPA, Prussian blue, etc.) for accidents of internal contamination on the basis of the data from these experiments.

3) Establishment of systems for radiation measurement and dose-assessment in emergencies

This research aims to develop devices for measuring low-level radiation in easy-to-prepare specimens by fast and precise methods for evaluating the dose received. This study also includes development of methods for biological dose estimation.

4) Rsearch on the mitigation of radiation injuries

This research investigates factors or agents to mitigate the damage to patients exposed to radiation by conducting animal experiments. The study also aims to quantify the effects of protectors on late radiation effects using mice that have gene mutation markers.

5) Study on emergency response to environmental pollution with RNs

Aims of this study are to prepare for environmental pollution due to accidents at nuclear facilities, mishandling of RNs at research institutions, missing radiation sources, or accidents during transport of RIs. It focuses on the development of new technology for identification of contaminated areas and estimation of doses received by rescue teams and residents at an accident site. Development of various accident scenarios and handling manuals is also envisaged.

Progress of Research:

1) Study on patho-physiology in exposure to high-dose radiation

Roles of reactive oxygen species (ROS) in damage to mitochondrial DNA (mtDNA) following ultraviolet (UV)-irradiation were investigated in the human hepatoma cell line SK-HEP-1. We altered the intracellular status of ROS by the overexpression of manganese superoxide dismutase (MnSOD) and/or catalase. Using HPLC, we analyzed 8-oxo-7, 8-dihydro-2'-deoxyguanosine (8-oxodGuo), known as a marker of damage to DNA molecules. UV-irradiation resulted in the accumulation of 8-oxodGuo in these cells. The overexpression of MnSOD enhanced the accumulation of 8-oxodGuo by UV. The co-overexpression of catalase inhibited the accumulation of 8-oxodGuo by UV in MnSOD-transfectants. The overexpression of MnSOD reduced the colony forming capacity in SK-HEP-1 cells and the co-overexpression of catalase with MnSOD stimulated the capacity compared to control. UV-irradiation inhibited the colony forming capacity in these cells; no difference was observed among the capacities of control, MnSOD- and catalase-transfectants. However, the overexpression of MnSOD/catalase significantly rescued the reduction of colony forming capacity by UV-irradiation. Our results suggest that the accumulation of hydrogen peroxide plays a key role in the oxidative damage to mtDNA of UV-irradiated cells, and also that the overexpression of both MnSOD and catalase reduces the mtDNA damage and blocks the growth inhibition by UV. Our results also indicate that the increased activity of MnSOD may lead to a toxic effect on mtDNA by UV-irradiation.

2) Study on agents for removing radionuclides that have been incorporated

Recently, many reports have demonstrated that chemical structure of uranium varies according to pH of the dissolved solution, suggesting that the toxicity may be altered *in vivo* and the effects of chelating agents may also be affected. In order to clarify effects of pH on the toxicity of depleted uranium (DU), five groups of male rats (each group consisted of five rats), were injected intramuscularly with 8 mg/kg DU dissolved in solution adjusted to pH 1, 3, 5, 7 and 10. Rats were observed for 21 days. Within 6-10 days after DU injection, three rats died in the pH 3, 7 and 10 groups, indicating the survival rates were related to pH; the survival rate was the lowest (40%) in the pH 10 group. The ratio of NAG/creatinine, which is a biochemical marker of renal function and the total DU concentrations in the kidney, liver, spleen, femur increased in a pH-dependent manner; DU was the highest in the pH 7 and 10 groups. The levels of DU in the muscle injected site also increased in a pH-dependent manner, and were the highest in the pH 5 and 7 groups, indicating that the formed uranium was not removed easily or excreted from the body. The results demonstrate that DU toxicity depends on pH.

We also examined the effects of pH on DU removal by chelating agents. Five groups of male rats (each group had 15 rats) were injected intraperitonelly with 8 mg/kg DU dissolved in the solution with either pH 1, 3, 7 or 10. In each pH group, then, five rats were injected intraperitoneally with a chelating agent, either 240 mg/kg CBMIDA [catechol-3,6-bis(methyleiminodiacetic acid)] or 10 mg/kg EHBP (ethane-1-hydroxy-1,1-bisphoshonate) continuous by for 3 days; the remaining five rats were used as control with no chelating agent. At pH 7 when various DU-complexes were formed, the DU toxicity, including renal dysfunction, increased, and preventing DU-induced toxicity. The efficacy of CBMIDA was superior to EHBP, particularly in the prevention of renal dysfunction. The results demonstrated that the removal effects of chelating agents varies according to pH differences, and lost completely at pH 7, indicating that the treatment with chelating agent should begin in the DU-contaminated person as soon as possible after an accident.

Effects of Deperiprone, a medicine for Thalassaemia and five newly synthesized compounds for removal of incorporated DU were tested in rats. Among them, Deperiprone and 4,6-demethyl-1-hydroxypyrimidin-2 (1H)-one were effective for decreasing DU deposition in the injected muscle, excreting DU in urine on the first day, and preventing renal damage. However, no significant increase in the amount of DU in the excreta or decrease in DU concentration in organs other than the muscle was found. The results are inconclusive, and therefore further studies are required. .

3) Establishment of systems for radiation measurement and dose-assessment in emergencies

For treatment of internal contamination, detection of radionuclides at an early stage plays an important role in radiation emergency medicine. Especially for making treatment decisions, identification of internally incorporated RNs is essential. A quick detection system which can identify RNs taken in the body was developed. The system was designed for the measurement of α-, β-, and γ-rays by four π-coincidence method, which consisted of two detectors and a signal processing unit. These detectors were NaI(Tl) and liquid scintillators. The

NaI(Tl) scintillator (well type of 40mm diameter) was used as a γ-ray detector and also as a guard counter for the liquid scintillator. The liquid scintillator, with which the subject specimen was intermingled homogeneously was put in a polypropylene vial and placed in the well of the NaI(Tl) scintillator. Scintillation light generated by β or α-rays in the liquid scintillator was distributed optically onto two photomultipliers through a half mirror. Only the signals from these photomultipliers which had simultaneity were summed again in order to reduce random thermal noise generated in each photomultiplier. Detector signals from the NaI(Tl) and liquid scintillator were digitized directly at the front-end of the signal processing unit with 14-bit ADC. The data were also processed in FPGA (Field Programmable Gate Array) and FIFO (First In First Out) memory for waveform capture. These energy and signal pulse shape data with time stamps of each event were employed in the DSP (Digital Signal Processor) of a subsequent stage. β-rays were then distinguished from α-ray in the DSP by the difference of signal decay pattern. Consequently, the time correlation with γ-rays and these identified α or β-rays were examined in a computer to determine the RN. Evaluation of spiked sample with ^{241}Am demonstrated sensitivity down to 0.1 Bq/cm^3 with 30 minute measurement.

4) Research on the mitigation of radiation injuries

Radioprotective effect of TMG (2-(α-D-glucopyranosyl)methyl-2,5,7,8-tetramethy- chroman-6-ol, a water-soluble vitamin E derivative) and selenomethionine containing torolox derivative (TroSeM) was studied in mice following whole-body X-ray irradiation. These compounds show excellent antioxidant activity with strong superoxide and hydroxyl radical scavenging ability in examination using a spin-trapping method employing ESR *in vitro*. A solution of TMG (dissolved in saline) or TroSeM (suspended in 0.5% methylcellurose) was administered intraperitoneally to C3H mice (male, 10 weeks old) before or after whole-body X-ray irradiation, and the protection for TMG and TroSeM against lethal irradiation was evaluated from 30-day mouse survival rate, TMG (650 mg/Kg) was injected ip just before or after the X-ray irradiation(7 Gy), the survival rate was about 80% showing a significantly high survival rate compared to the control experiment (25%). The survival rate was 50% even when administrated 60 min after irradiation. The $LD_{30/50}$ was about 7.8 Gy for TMG-injected mice (administrated immediately after irradiation) and 6.6 Gy for control mice, yielding a DRF for TMG (650 mg/kg bw) of 1.18. On the other hand, TroSeM (30mg/Kg) was injected ip 30 min before X-ray irradiation (7.5 Gy), the survival rate was about 60%, whereas it was about 40% immediately after irradiation in contrast to control (10%). TroSeM was effective both pre- and post irradiation against lethal irradiation. Since most of the radioprotectors were effective when administered prior to irradiation, the effectiveness of these compounds when administered postirradiation suggests possibility for protection against accidental radiation exposures.

5) Study on emergency response to environmental pollution with RNs

In the case of radiological emergency due to missing sources or contamination, it is necessary to find out the location of the sources. For that purpose one of the simplest γ-spectrometry systems that can provide directional information of incident γ-rays has been developed. The system consists of a 3" x3" ϕ NaI (Tl) scintillator, a specially shaped lead shield, and software. The measurement was carried out four times by rotating the shield position along the axis of the detector to obtain four energy spectra at one location. Four count rates at a special region of interest in the spectra were fed into the software for determining incident directions of γ-rays. Experiments using ^{137}Cs and ^{54}Mn at the same time demonstrated that the direction of γ-rays from several dominant sources from any direction could be identified with good precision in a total measurement time of 10 to 20 minutes. The system could be used to identify the locations of missing radioactive sources or the cause of elevation in ambient radiation dose rates. The disadvantages of the present system are follows. (1) It requires four time measurements at one location. (2) It can provide only one pseudo incident angle when several contamination sources exist around the detector system and emit the same energy γ- rays. (3) It can scan only one plane geometry which is usually chosen as the horizontal plane.

Major publications:

1) Yutaka Tokairin, Shizuko Kakinuma, Masami Arai, Mayumi Nishimura, Mieko Okamoto, Makoto Akashi, Yoshio Miki, Tatsuyuki Kawano, Yoshiya Shimada: Accelerated growth of intestinal tumours after radiation exposure in Mlh1-knockout mice: evaluation of the late effect of radiation on a mouse model of HNPCC, *International Journal of Experimental Pathology*, **87**, 89-99, 2005.
2) Saori Kawamura, Daisaku Takai, Keiko Watanabe, Makoto Akashi, et al. Role of Mitochondrial DNA in Cells Exposed to Irradiation : Generation of Reactive Oxygen Species (ROS) is Required for G2 Checkpoint upon Irradiation, *Journal of Health Science*, **51**(3), 385-393, 2005.
3) Takuya Iyoda, Kisaburo Nagata, Makoto Akashi, Yoshiro Kobayashi: Neutrophils accelerate macrophage-mediated digestion of apoptotic cells in vivo as well as in vitro., *Journal of Immunology*, **175**(6), 3475-3483, 2005.
4) Mamoru Haratake, Masahiro Ono, Makoto Akashi, Morio Nakayama, et.al: Synthesis of hydrophilic macroporous chelating polymers and their versatility in the preconcentration of metals in seawater samples, *Analytica Chimica Acta*, **561**, 183-190, 2006.
5) Satoshi Fukuda, Haruzo Iida, Mizuyo Ikeda, Xueming Yan, Yuyuan Xie : Toxicity of uranium and the removal effects of CBMIDA and EHBP in simulated wounds of rats. *Health Phys*, **89**,81-88, 2005.
6) Satoshi Fukuda : (Review) Chelating agents used for plutonium and uranium removal in radiation emergency medicine. *Current Medical Chemistry*, **12**, 2765-2770, 2005.
7) Satoshi Fukuda, Mizuyo Ikeda, Momoko Chiba, Kazunari Kaneko : Clinical diagnostic of renal and bone damage in rats intramuscularly injected with depleted uranium. *Radiation Protection Dosimetry*, 2006, On line.
8) Kenzo Fujimoto: A simple gamma ray direction finder. *Health Physics*, **91**(1),29-35, 2006.

5. Research Center for Charged Particle Therapy

Hirohiko Tsujii, M.D.
Supervisory Director

Overview:

The Research Center for Charged Particle Therapy was established in 1993 when the NIRS completed construction of the HIMAC (Heavy Ion Medical Accelerator in Chiba), and in 1994 started carbon ion therapy. Since then it has been carrying out medical practice and related research using heavy ion beams generated from the HIMAC, as well as medical research on advanced diagnostic imaging techniques such as PET, MRI and CT. After clinical trials of carbon ion therapy had been carried out for various types of malignant tumors, the Center was successful in obtaining approval from the Ministry of Health, Welfare and Labor for "Highly Advanced Medical Technology" in October 2003. Thereafter, we have been offering the state-of-the-art therapy called "Charged Particle Therapy for Solid Tumors" for specific tumors in which carbon ion therapy had shown satisfactory results in terms of its safety and clinical effectiveness. Thus carbon ion therapy has achieved for itself a solid place in general practice by accumulating clinical experiences over a decade.

In fiscal year 2005, a number of committee meetings were held to evaluate the eligibility of each patient to be treated with carbon ion therapy and to scientifically and ethically review the treatment results. Multi-user utilization of the HIMAC has been successfully implemented for medical, biological and physics research. The big events of this year were the 2nd International Advisory Committee held in April 2005 and NIRS-MedAustron Joint Symposium held at Innsbruck University in February 2006.

Progress of Research:

1) Medical Practice and Research on Carbon Ion Therapy

The Center includes a hospital which has specialized in radiation therapy and imaging diagnosis. Radiation therapy includes carbon ion radiotherapy with HIMAC, conventional photon therapy with a linear accelerator and brachytherapy with the remote after-loading system (RALS). The hospital is equipped with state-of-the-art diagnostic imaging equipments including CT, MRI, PET-CT, US and endoscopies on a scale and level well above those of a general hospital. The center hospital has also been designated as Japan's Third Medical Facility functioning as a core medical place to provide emergency services for accidental radiation exposures primarily in the eastern part of Japan. Have been actively engaged in establishing and maintaining a service outfit in readiness for radiation exposure accidents, jointly with the Research Center for Radiation Emergency Medicine.

To fulfill the above role, the hospital has both outpatient and inpatient wards as well as a full complement of pharmacies and clinical laboratories to well above normal standards. An extensive amount of medical information has been obtained from the clinical trials on carbon ion radiotherapy and also from long-range photon therapy including diagnostic images and medical records.

In an effort to achieve higher levels of sophistication, the clinical data have been systematically classified and standardized to establish data access methods based on a unified system of data management. This year, extensive medical records and diagnostic images were stored in the data-servers, and we put into practice a PACS

including a filmless Radiology System, which enabled images and data to be delivered to medical users anywhere they have access to a high speed broadband internet connection. This system benefited the hospital in several ways. ①It improved patient care by allowing participating physicians and nurses access to the patient's current and prior imaging studies and associated clinical information as soon as the patient's exam is completed. ②The process for exam report turnaround was improved, helping physicians to treat their patients expeditiously. ③ Since the system allowed the use of computer imaging, the cost of the use of film, chemicals, and processor equipments was minimized. ④The system improved workflow for the radiology staff and enhanced productivity.

2) Clinical Results of Carbon Ion Therapy

As of February 2006, the number of patients registered was in excess of 2,600. Experiences to date indicate that carbon beam therapy is advantageous, ①by histology, to adenocarcinoma, adenoid cystic carcinoma and sarcoma (malignant melanoma and bone/soft-tissue sarcoma); ②by tumor origin, to skull base, head and neck, lung, liver, prostate, bone/soft tissue, uterine cervix, and rectum (pelvic recurrence); ③by location, to tumors located in the vicinity of critical organs such as the eye, spinal chord and bowels. Tumors that infiltrate or originate in the digestive tract, however, appeared difficult to control with carbon ions alone.

The patient load continues to rise year after year, due not only to the way in which the irradiation techniques have been established but also as a result of the significant reduction in the number of fractions per patient. There is a rationale to justify the use of short-course RT due to the superior dose localization and the unique biological property of carbon ions. This has been proved in treatment of early stage lung cancer and hepatoma, where the fraction number has been successfully reduced to 1 or 2 fractions in 1 or 2 days. Even in prostate cancer and bone/soft tissue tumor, treatment has been performed using 16 to 20 fractions in 4 to 5 weeks with acceptable morbidity, roughly half the number of fractions required in the case of other conventional radiotherapy. This offers the potential of the facility to be operated more efficiently, allowing treatment for a larger number of patients than is possible with other modalities over the same period of time. Currently, the number of irradiation sessions per patient averages 13 fractions over three weeks in carbon ion therapy.

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

3) Development of a Compact Accelerator

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

The injector system of the compact accelerator consists of a 10GHz permanent magnet ECR source, RFQ linac, and IH type drift tube linac. Operation frequencies of both linacs were chosen at the same value of 200 MHz. The APF (Alternating Phase Focusing) structure was adopted for both transverse and longitudinal focusing in the IH linac. The APF-IH linac structure has long been studied theoretically and experimentally because of its high energy efficiency and easiness in operation. This type of linac, however, has never been put to practical use since time-consuming model studies are required to fix the cavity geometry. The beam tests of the RFQ and APF-IH linacs were carried out using the 10 GHz permanent magnet ECR source, and they successfully accelerated C^{4+} with the intensity of more than 350 μA up to 4.0 MeV/u. A cobalt based amorphous core was found to have high permeability approximately twice that of a typical magnetic alloy, FINEMET, core. We have developed this type of amorphous core to be used in *the RF cavity for a synchrotron*. Due to its excellent RF characteristics of high shunt impedance and low quality factor, a cobalt-based amorphous-core loaded RF cavity covers a wide frequency range without any tuning elements to keep its high-energy efficiency. The RF cavity was installed in the HIMAC synchrotron, and the beam test was successfully carried out. *The beam delivery system* of this compact machine should be designed to permit a residual range of 250 mm with a carbon energy of 400 MeV/u and an irradiation-field diameter of 220 mm at maximum with a port length of 5.5 m. For this purpose, a spiral-wobbler method has been proposed. It was experimentally verified that this method could deliver the desired uniform irradiation field in the lateral direction.

4) Physical and Biological Aspects of Heavy Charged Particles

The Department of Medical Physics is researching physical aspects of carbon ion therapy and developing PET next generation scanners. In addition, the department has a responsibility to support clinical trials on heavy ion therapy including quality assurance and control (QA/QC) services, treatment planning, and fabrication of treatment devices such as patient collimators and compensators.

Dose profile in depth and calibration of the dose monitor in the beam port for different energies are measured and checked every day by medical physicists. The control system for irradiation devices and patient positioning is maintained to keep stable treatment operation after being improved to achieve irradiation with the highest possible precision. The final parameter set for treatment planning of each patient is approved by medical physicists. This work has been done in collaboration with the Hospital and the Department of Accelerator Physics and Engineering.

One of the topics this year was the application of two port treatment for eye melanoma. We started using orthogonal two-field irradiation to decrease damages of normal tissue in and around the eye-ball. The target of eye melanoma is very small and close to a critical organ, therefore it is necessary to keep high precision within less than 0.5mm in all processes during the treatment procedures. Procedures have used detachable dedicated nozzles for eye irradiation, patient positioning with a high-resolution x-ray image using the flat-panel detector, and an improved treatment planning system based on commercially available planning software. These techniques and experiences can be extended to other are as of treatment with HIMAC.

A novel PET scanner which has high spatial resolution and high sensitivity by discriminating multi-layer depth-of-interaction (DOI) information was developed, and improved to allow application to clinical examinations. This research project includes not only detectors but also the software to acquire a large data set at highspeed and to reconstruct three-dimensional images.

The Heavy-ion Radiobiology Research Group has done studies to evaluate the optimum fractionation regimen for carbon ion therapy and to develop methods for identifying the types of tumors suited to carbon ion radiotherapy. In the study on cultured human malignant melanomas, carbon ions suppressed a wider range of genes than x-rays. Effectiveness of carbon ions in gene expression was homogenous between different cell lines. It was found that rejoining of DNA double strand breaks played an important role in the oxygen effect of x-rays and carbon ions. In an animal study on the brain, correlation was found between the memory disturbance and the degree of blood vessel density in hippocampus after carbon ion irradiation. A good correlation was found between the early incorporation of radio-labeled thymidine and the late response in animal tumors after carbon ion irradiation. Repair kinetics of mouse skin damage during fractionated irradiation with high-LET carbon ions was found to be different from that with photons.

The group has also engaged in an inter-facility comparative study between NIRS and GSI by investigating biological effects of carbon ions.

5) Medical Exposure Assessment

To evaluate collective doses and risks on diagnostic exposures in Japan, dose estimations using methods of measurements, calculations and nationwide surveys have been performed for the data of frequencies and effective doses. In this fiscal year, doses of patients on MDCT (Multi-Detector CT) examinations were measured by dosimeters and phantoms, and CTDIs (CT Dose Index) were estimated by both measurements and Monte-Carlo calculations. Doses of patients and operators during IVR (Interventional Radiology) were also measured as one example of high dose exposure examinations.

6) Medical Imaging Research

Medical imaging research has been directed to the promotion of cancer radiotherapy and biological function imaging with respect to oncology and neurosciences. This year, a preparatory study was mades aiming at next year's competitive MEXT grant-in-aid in the field of molecular imaging for visualizing biological functions *in vivo*.

As in previous years, a wide variety of PET radiopharmaceuticals were developed and routinely produced for clinical application. A new method was developed for remote-control production of ^{62}Zn by irradiating ^{62}Cu with protons from the NIRS isochronous cyclotron. The production of ^{62}Cu/^{62}Zn generator was established. ^{62}Cu-ATSM, known as a hypoxic PET imaging agent, was synthesized with ^{62}Cu eluted from the generator, approved for clinical application by IRB in NIRS and its use for volunteer studies with PET was started. Multi-center collaboration will start next year, using ^{62}Cu-ATSM from the ^{62}Cu/^{62}Zn generator supplied by NIRS. The old facilities in the Cyclotron Building, especially the 2nd hot laboratory were renovated to produce safe radiopharmaceuticals under clean circumstances.

The Medical Imaging Building was also renovated. An original new type of clean bench was designed and installed in the 2nd hot laboratory to perform various types of procedures, such as dispensing, pH measurement, radioactivity measurement, radiochemical purity measurement with HPLC and so on, more effectively. Various kinds of molecular probes have also been developed for the purpose of imaging malignant tumor, A_{β} related to Alzheimer's diseases and so on. In research activities related to diagnostic machines, the major parts of a 4-D X-ray CT machine and a next-generation PET system were successfully developed.

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

7) Brain Imaging Project

The research has been focused on mental disorders and functional brain imaging using PET and MRI. In pharmacotherapeutic research on schizophrenia, we measured extrastriatal dopamine D2 receptor occupancy of two conventional benzamide antipsychotics, Sulpiride and Sultopride, using PET to investigate the rationale of their clinical dose. Although the clinical potency of both benzamides was considered to be equivalent, Sultopride required about 50 times lower dose than Sulpiride to obtain similar receptor occupancy. The registered clinical doses of Sultopride were found to be about 10 times higher than the calculated optimal doses. The present results suggest that a much lower dose of Sultopride would be sufficient to treat psychotic symptoms. Appropriate dosage setting of conventional antipsychotics based on dopamine D2 receptor occupancy would be helpful for rational antipsychotic therapy. In the study of the neurophysiology of schizophrenia, the abnormal inter-regional connectivity has been reported. We focused on the connectivity of regional dopamine D2 receptor binding and applied a structural equation method to evaluate the connectivity in schizophrenic patients. The results indicated that a systems-level change that could be reflected in the connectivity of D2 receptor binding was present in schizophrenia.

In the trials to develop new ligands for PET research, we have evaluated a new agonistic radioligand for dopamine D2 receptors and [^{18}F]SPA-RQ, an antagonisitic radioligand for central substance P receptors.

5.1. Heavy Ion Clinical Trials

Tadashi Kamada, M.D, Ph.D.
Head, Hospital

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 25 years of experience in clinical reseach on radiation oncology, including 10 years experience in carbon ion radiotherapy at NIRS. Since 2003, he has been project leader of the Heavy Ion Clinical Trial.

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Objectives:

The Heavy Ion Medical Accelerator in Chiba (HIMAC) is the world's first heavy ion accelerator complex dedicated to medical use in a hospital environment.

Among the high linear energy transfer (LET) particle beams used in cancer treatment, the carbon ion beam possesses unique physical and biological properties. It has a well-defined range and insignificant scatter in tissues, and the energy release is enormous at the end of its range. This well-localized energy deposition (high-dose peak) at the end of the beam path, called the "Bragg peak", is a unique physical characteristic of charged particle beams, as is the induction of more cell cycle- and oxygenation-independent, irreversible cell damage than that observed with low LET radiation.

In order to investigate these useful properties, we conducted carbon ion radiotherapy clinical trials in patients with various types of malignant tumors.

Progress of Research:

From June 1994 to February 2006, a total of 2,629 patients were enrolled into clinical trials using carbon ion beams generated by HIMAC. Carbon ion radiotherapy of these patients was carried out by 40 different phase I/II or phase II protocols and highly advanced medical technology. Tumor sites and annual patient accrual are listed in Table 3. We treated 437 new patients in 2005. Lung, head and neck, prostate, liver and bone and soft tissue tumors are the leading 5 tumor types in the trials. A total of 2,371 patients who had a follow-up period of 6 months or more were included in this report. Local tumor control rate and survival in five major tumor sites, head and neck, lung, liver, prostate, and bone and soft tissue tumors are summarized.

1) Head and Neck Tumors

The tumor type primarily treated in the clinical trials consisted of tumors in the nasal cavity and paranasal sinus with invasion to the skull base. Many of these patients had locally advanced lesions considered difficult to cure with other procedures. In the initial phase I/II clinical trials, a fractionation regimen of 18 fractions/6 weeks was applied, with 17 patients having been treated on this schedule until February 1996. Beginning in April 1996, a new phase I/II clinical trial was initiated on a shorter irradiation course of 16 fractions/4 weeks. The number of patients enrolled in this second trial was 19. Comparison of the toxic reactions and efficacy recorded in these two trials led to the conclusion that there was no significant difference between the two treatment schedules. Beginning in April 1997, the prescribed dose for the second protocol was fixed at 57.6GyE/16 fractions/4 weeks.

Until the present, this treatment schedule has not given rise to any particularly serious toxicities, and a clear relationship has been found to exist between vision and irradiation dose.

The treatment results obtained so far can be summed up by stating that a very favorable local control rate of as high as 80 - 90% has been achieved mainly for adenocarcinoma, adenoid cystic carcinoma and malignant melanoma. With regard to malignant melanoma, however, a combined regimen of carbon ion radiotherapy and chemotherapy was initiated in order to control or prevent distant metastasis. The decision to embark on radio-chemotherapy was based on the assessment that while radiotherapy on its own provided favorable local control further improvements in the patients' long-term survival were needed. For primary bone and soft-tissue sarcoma in the head and neck region, the local control is still not satisfactory and dose escalation trials are still ongoing.

2) Lung cancer

Stage I Lung Cancer (T1-2/NO/MO)

The stage I lung cancer patients were divided into two groups according to tumor location: peripheral-type and central-type. This classification was made on the assumption that as both may have different tolerance doses different fractionation regimens need to be investigated for each. The patients eligible for either treatment schedule were subjects for whom surgery was not indicated or subjects refusing surgery. For the peripheral-type of stage I lung cancer patients, clinical trials are currently in progress using a single-dose regimen that should produce a result identical to surgery and may be described as the ultimate point of treatment. To arrive at this, the fraction number and treatment time have been reduced in gradual steps from 18 fractions/6 weeks through 9 fractions/3 weeks to 4 fractions/1 week. The initial two clinical trials have already been reported. The 129 patients treated subsequently with the 9 fraction and 4 fraction regimens have shown results comparable to those achieved with surgery: There were no serious toxic reactions and the local control rate was 91.5%, with a five-year overall survival rate of 45.3% (survival rate from the primary lesion 67.0%). Dose escalation trials on the single-dose schedule were initiated with 28GyE and have meanwhile progressed to the 42GyE level. These clinical trials are due to be concluded in a few months' time.

For the treatment of the central-type of stage I lung cancer a larger fraction number is used. This type of cancer is characterized by the presence of a large number of relatively superficial lesions and may therefore be safely controlled with a lower dose (57.6GyE/9 fractions/3 weeks) than is necessary for the peripheral-type lung cancer.

Locally Advanced Lung Cancer (Chest wall infiltration type)

For locally advanced cancer, preoperative irradiation was initially performed in order to make a pathological assessment of the effect of irradiation first. Of the total of five patients, surgery was performed as planned on three. In two of these patients, malignant cells were not found pathologically. Based on this outcome, the second clinical trial was performed for locally advanced lung cancer and 37 patients were eligible for analysis. The results were comparable to surgery in terms of local control rate and survival rate.

3) Liver Cancer

Clinical trials have so far been carried out on four protocols. In the first phase I/II trial, 24 patients were treated on a 15 fractions/5 weeks irradiation schedule. The overall five-year local control rate in this trial was 81%. In the second phase I/II trial, successive dose escalation was implemented from 12 fractions/3 weeks through 8 fractions/2 weeks to 4 fractions/1 week in an attempt to develop a short-course irradiation regimen. It was possible to conduct all of these fractionation regimens with an acceptable level of toxicities. Based on these results, a third phase II trial using a fractionation schedule of 52.8GyE/4 fractions/1 week was conducted. This dose was the recommended dose already decided prior to the trial. The total number of patients treated with four fractions in both the second and third clinical trials was 75, and the results indicated that this was a satisfactory fractionation schedule in terms of both safety and local efficacy. Post-treatment change in hepatic function was minimal in these patients and the local control and survival rates after four years were recorded as 94% and 40%, respectively. More recently, the fourth clinical trial using an even shorter irradiation schedule of 2 fractions/2 days has just been closed with encouraging results in terms of a favorable local control rate and the absence of any particular serious toxic reactions.

4) Prostate Cancer

A total of three clinical trials have so far been carried out. The first carbon ion radiotherapy trial with concomitant endocrine therapy was conducted for B2-C stage patients. The second trial was available for a wider scope of eligibility, and consisted of carbon ion therapy on its own for stage

A2-B1 prostate cancer, and carbon ion radiotherapy combined with endocrine therapy for stage B2-C. In the first clinical trial, the most serious toxicities in the rectum were recorded among the patients exposed to the highest dose level in connection with dose escalation. As a result, the safe dose for the digestive tract was established and no serious toxic reactions were subsequently encountered in the later clinical trials. DVH analysis was also performed to identify the tolerance dose of the gastrointestinal organs, and the results have yielded a DVH curve permitting the risks of gastrointestinal ulceration to be predicted. This curve is of immense usefulness and has made it possible to prevent severe reactions in new patients by comparing the DVH curves at the time of treatment planning.

Based on these trials, it was thus possible to establish an irradiation schedule for prostate cancer and to commence the third (phase II) clinical trial in April 2000. For the purposes of this trial, the patients were divided into a high-risk and a low-risk group on the basis of their various pre-treatment factors (PSA, Gleason Score, TNM classification). The high-risk group received combined carbon radiotherapy with endocrine therapy while the low-risk group was treated with carbon ion therapy alone. Therapy was administered at a fixed irradiation dose of 66GyE/20 fractions/5 weeks. (The dose was reduced by 5% for patients with severe concomitant diabetes mellitus). There have been no serious toxic reactions to-date and the survival rate is also satisfactory. This dose corresponds to the tolerance dose for both the rectum and the urethra and is at the same time also virtually sufficient to achieve local control. External radiation for prostate cancer is generally performed using 40 fractions (over 7 - 8 weeks). In contrast, carbon ion radiotherapy can be accomplished on a much shorter fractionation schedule of only 20 fractions/4 weeks. Clear evidence of local recurrence was discovered in only one patient who had been treated with the lowest dose in the initial period.

5) Bone and Soft Tissue Tumors

As the bone and soft tissue tumors are generally considered to be photon beam resistant and because of the presence of critical organs in their vicinity ordinary radiotherapy presents problems. Advanced tumors originating from the spine, the pelvis and the retroperitoneum in the trunk part of the body, in particular, are in many cases not resectable and have a poor prognosis. Such patients have been almost totally excluded from treatment with conventional radiotherapy. The use of carbon ion beams does offer a favorable prospect of improved local control in view of their superior biological dose distribution.

The patients enrolled in our initial phase I/II dose escalation trial were primarily subjects not responding to surgery or totally inoperable. This trial has produced a favorable local control rate of 73% and it has been realized, in particular, that chordoma and osteosarcoma are prime candidates for carbon ion radiotherapy. Some 10% of those patients whose lesions are close to the body surface so that it is not possible to avoid exposure of the skin to high radiation doses were found to develop severe reactions such as skin erosion or ulceration. As more experience has been gained and significant improvements in irradiation techniques have been achieved such severe reactions no longer occur. It has also been established that there is a definite proportional relationship between dose and local tumor control. In view of these findings, the recommended dose has been fixed at 70.4GyE/16 fractions/4 weeks.

Bone and soft tissue tumors in the trunk are the most typical lesions qualifying for carbon ion radiotherapy and they have been treated in the Advanced Therapy scheme. Clinical trials are in progress in order to extend conservative treatment also to tumors of the extremities.

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 2005.

Major Publications:

1) Hiroshi Tsuji, Takeshi Yanagi, Hitoshi Ishikawa, Tadashi Kamada, Junetsu Mizoe, Tatsuaki Kanai, Shinroku Morita, Hirohiko Tsujii: Hypofractionated radiotherapy with carbon ion beams for prostate cancer. International Journal of Radiation Oncology Biology Physics, 63(4), 1153-1160, 2005
2) Azusa Hasegawa, Junetsu Mizoe, Atsushi Mizota, Hirohiko Tsujii: Outcomes of visual acuity in carbon ion radiotherapy:analysis of dose-volume histograms and prognostic factors. International Journal of Radiation Oncology Biology Physics, 2005
3) 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 Radiation for Locality Advanced Carcinoma of the Cervix. International Journal of Radiation Oncology Biology Physics, 2005
4) Tadaaki Miyamoto, Sachiko Ishii, Kiyomi Eguchi-Kasai, Kumiko Saegusa: Radiosensitivity of hypoxic and proliferating clonogen in a human lung cancer grown in nude mice. Oncology Reports, 14, 1421-1428, 2005

TABLE 3. Patient distribution of carbon ion radiotherapy at NIRS (Treatment: June 1994 to February 2006)

Sites	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	Total	%
Head & neck	9	10	19	31	22	38	29	39	40	33	47	35	352	13.4
Brain	6	8	10	6	9	7	15	10	6	5	3	5	89	3.4
Base of Skull	-	-	-	6	4	2	2	4	8	3	8	5	42	1.6
Lung	6	11	27	17	28	33	45	51	55	50	55	45	420	16.0
Liver	-	12	13	19	25	17	22	28	18	22	14	10	200	7.6
Prostate	-	9	18	10	30	30	31	44	47	77	62	73	431	16.4
Uterus	-	9	13	11	10	11	13	5	10	4	8	10	107	4.1
Bone & soft tissue	-	-	9	13	19	18	25	23	32	43	57	54	291	11.1
Esophagus	-	-	1	16	4	-	2	-	-	-	9	9	41	1.6
Pancreas(pre/op)	-	-	-	-	-	-	3	7	12	18	11	13	64	2.4
Rectum(p/o pelvic rec)	-	-	-	-	-	-	-	10	13	15	18	11	67	2.5
Eye melanoma (advanced)	-	-	-	-	-	-	-	8	16	18	13	4	59	2.2
Lacrimal gland	-	-	-	-	-	-	-	-	5	2	1	4	12	0.5
Miscellaneous	-	24	16	30	17	32	14	12	14	41	93	162	454	17.3
Total	**21**	**83**	**126**	**159**	**168**	**188**	**201**	**241**	**276**	**333**	**396**	**437**	**2629**	**100**

5.2.1. Development of Four-dimensional X-ray CT (4D CT)

Masahiro Endo, Ph.D.
Director, Department of Research Promotion

Outline of Research Career:

Dr. Endo received his B.S. degree from the Department of Pure and Applied Science, University of Tokyo in 1971 and completed the M.S. program there in 1973, when he joined the National Institute of Radiological Sciences. He was engaged in development and application of new medical imaging systems, such as X-ray CT, MRI, and PET. He was also engaged in development of the patient treatment system at HIMAC. He is now the leader of this project and the director of the Department of Research Promotion. He holds a Ph.D. degree, and is the president of Japan Society of Medical Physics and a councilor of several radiological societies.

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Objectives:

Since the advent of CT in 1973, dynamic imaging of moving organs in living humans has been the ultimate dream in this field. This concept is simply called 4D CT because it takes a 3D image with the additional dimension of time. With 4D CT, we may take stop-motion volume images of moving organs such as lung or heart, make 3D dynamic studies, and navigate operators in minimum invasive surgery such as for interventional therapy. The objectives of this project are developing a 4D CT and exploring its clinical potentials. The project goals were 1) developing a prototype of 4D CT-scanner that can continuously take volume images (10 cm long, 50 cm diameter) with 1 mm spatial resolution and 0.5 s temporal resolution by the end of the fiscal year 2004, and 2) making clinical studies in fiscal year 2005. The detailed specifications are listed in Table 4. Because volume data (3D data) can be acquired by cone-beam CT using rotation of the cone-beam, continuous rotation of the cone-beam allows dynamic volume data (4D data) to be acquired. Our approach was to develop a novel large-size 2D detector based on the present CT technology, and to develop an ultra-high-speed reconstructor. We developed a prototype detector (256 × 912), and mounted it on the gantry frame of a state-of-the-art CT-scanner to make the first model of 4D CT in fiscal year 2001 and have been evaluating its performances since that time. We also developed the ultra-high-speed reconstructor in fiscal year 2002, and completed detailed design of the second model of 4D CT in fiscal year 2003 and completed its construction in fiscal year 2004.

Progress of Research:

In fiscal year 2005 (the last year of a 5-year project), we achieved the following.

1) Performance evaluation of the second model

Image characteristics such as image noise, point spread function (PSF), slice sensitivity profile (SSP) and low-contrast detectability were evaluated with stationary phantoms in a single rotation, in addition to dose profile and its integral. Results were compared with those obtained similarly for the first model. Results show that all characteristics have been improved from those of the first model, with a remarkable improvement in low-contrast detectability and slice sensitivity profile. Although the slice sensitivity profile (SSP) and low-contrast detectability of the first model were inferior to those of commercial CTs due to its prototype nature, these two image quality variables are remarkably improved in the second model and approach the level obtained with commercial CT equipment. The spatial resolution was 0.7 mm × 0.8 mm × 0.8 mm.

2) Clinical study

We carried out pilot clinical studies with healthy volunteers and patients using the second model. All studies were approved by the Institutional Review Board of NIRS, and written informed consent was obtained from all subjects before beginning the study. Fig. 9 shows 3D images of a lung cancer patient under free breathing obtained under different respiratory phases. Fig. 10 shows a 3D image of the heart enhanced by intravenous injection of contrast agent without electrocardiographic gating. The left anterior descending (LAD) artery and diagonal branches were visualized on the left ventricle. Fig.

11 shows long-axis sections of the same heart in end-diastolic and end-systolic phases. The LAD artery was clearly visualized again in the figure. For both studies a 0.5 s/rotation dynamic scan was employed.

As described above, the 4D CT with a greater than 10 cm field-of-view in the cranio-caudal (CC) direction, is able to capture the whole heart or tumor lesions in the moving lung while the subject breaths continuously. This may therefore provide new diagnostic information. Such wide CC coverage will also allow cerebral perfusion studies of the whole brain. We are now conducting clinical studies in patients with heart disease and lung cancer to examine the potential of this equipment in cardiology and 4D radiation therapy planning.

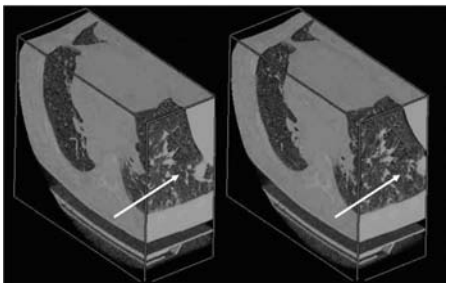


Fig 9. 3D images of a lung cancer patient under free breathing in the different respiratory phases. Arrows show movement of the tumor.

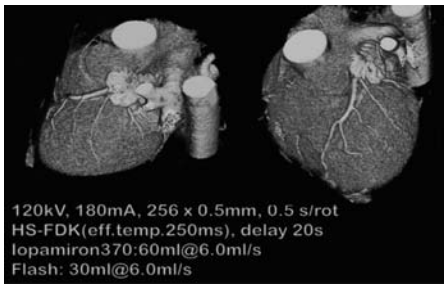


Fig 10. 3D images of normal heart. The left anterior descending (LAD) artery and diagonal branches were visualized on the left ventricle.

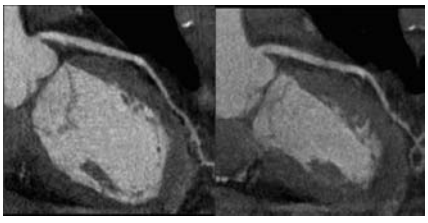


Fig 11. Long-axis sections of the same heart as in Fig 10 in end-diastolic and end-systolic phases.

Major Publications:

1) S. Mori, M. Endo, K. Nishizawa, T. Tsunoo, T. Aoyama, H. Fujiwara, K. Murase: Enlarged longitudinal dose profiles in cone-beam CT and the need for modified dosimetry. *Medical Physics*, **32**, 1061-1069, 2005
2) S. Mori, T. Obata, R. Kishimoto, H. Kato, H. Fujiwara, K. Murase, S. Kandatsu, S. Tanada, H. Tsujii, M. Endo: Clinical potentials for dynamic contrast-enhanced hepatic volumetric cine imaging with the prototype 256-MDCT scanner, *American Journal of Roentgenology*. **185**, 253-256, 2005
3) N. Funabashi, K. Yoshida, H. Tadokoro, K. Nakagawa, K. Odaka, S. Mori, M. Endo, S. Tanada, I. Komuro: Cardiovascular circulation and hepatic perfusion of pigs in 4-dimensional films evaluated by 256-slice cone-beam computed tomography. *Circulation Journal*, **69**, 585-589, 2005
4) N. Funabashi, K. Yoshida, H. Tadokoro, K. Odaka, T. Tsunoo, S. Mori, M. Endo, S. Tanada, I. Komuro: Three-dimensional segmented myocardial perfusion images by selective intracoronary injection of contrast using 256-slice cone-beam computed tomography. *Heart*, **91**, 1349-1351, 2005
5) C. Kondo, S. Mori, M. Endo, K. Kusakabe, N. Suzuki, A. Hattori, M. Kusakabe: Real-time volumetric imaging of human heart without electrocardiographic gating by 256-detector row computed tomography: Initial experience. *Journal of Computer Assisted Tomography*, **29**, 694-698, 2005
6) S. Mori, T. Obata, N. Nakajima, N. Ichihara, M. Endo: Volumetric perfusion CT using prototype 256MDCT Scanner: Preliminary study with healthy porcine model. *American Journal of Neuroradiology*, **26**, 2536-2541, 2005

Table 4. Specification of 4D CT (second model)

Scan mode	Cone-beam continuous rotation (4D) Helical cone-beam (precise 3D) Physiological signal
Detector	912 × 256
Scan time	0.5 s/rot (60 s max) Programmable
Reconstruction matrix	512 × 512 × 256
Contrast resolution	Less than 0.5 %
Reconstruction time	Less than 1 s
Scan Volume	13 cm thick × 50 cm diameter

5.2.2. Next generation PET project

Hideo Murayama, Ph.D.
Head of Imaging Physics,
Department of Medical Physics

Outline of research career:

Dr. Murayama received a Ph.D. from Osaka University in 1982 for his study on systems of scintillation detectors for radioisotope imaging. Since the mid 1970s he has continued to research instrumentation for nuclear medicine. In the 1980s, he was engaged in development of new detectors in order to construct PET scanners for head studies, and whole body studies for humans and animals. In the 1990s, he studied reconstruction methods and data correction techniques for SPECT and PET. In the mid 1990s, he proposed a new concept for a depth-encoding detector in order to achieve both high sensitivity and high spatial resolution in a PET scanner. To develop such a next generation PET system using the new detectors, in 2001 he established a new research group in cooperation with researchers from a wide spread range of companies and universities.

Contact point: mur@nirs.go.jp

Objectives:

This group does basic studies on instrumentation, image reconstruction and data corrections to improve image quality and quantity in nuclear medicine. Since the statistics of photon detection in radiation measurements causes fluctuations in reconstructed images, methodology for increasing sensitivity of full-3D imaging is an important research subject. Development and improvement of detector units for positron emission tomography (PET) has been done, and data processing techniques has also been studied from the viewpoint of increasing the signal component or reducing the noise component. Simulation techniques for modeling of the nuclear medicine imaging process have become an important and indispensable complement to experimental methods and clinical studies, and we have advanced to more accurate simulation studies about the physics and instrumentation involved in the process.

A next generation PET system with higher spatial resolution and higher sensitivity is under development with collaboration from both academic and industrial members. The next-generation PET system is expected to clarify biological functions such as the pathophysiology of psychoneurological disorders or the physiological functions of the brain, by using tracers in minute quantities.

Progress of Research:

1) Simple and reliable construction method for 4-layer DOI crystal blocks

The final design of the 4-layer DOI detector module for the jPET-D4 system was determined and we produced 120 of the DOI crystal blocks. The jPET-D4 detector module consists of four layers of 16 by 16 Gd_2SiO_5 (GSO) crystals and a 256 channel flat panel position sensitive photomultiplier tube (256ch FP-PMT). Two kinds of GSO crystals that show different scintillation decay time constants are used in the upper and lower two layers in order to distinguish these layers using pulse shape discrimination. Proper reflector insertion in the crystal block allows identification of detection crystals in each two layer part. For mass production of the DOI crystal block composed of 1024 crystal elements with the proper reflector arrangement, we used appropriate tools which promote simple construction as well as uniform configuration. The construction took only 3 hours per one crystal block. The 120 DOI crystal blocks produced were evaluated for their characteristics: pulse shape discrimination, energy resolution and full energy peak. The results show that misidentification in each GSO layer is less than 5% of the pulse shape discrimination, the average of energy resolutions for the central four crystals of the 1st (farthest from PMT), 2nd, 3rd and 4th-layers are 15.7 ± 1.0%, 15.8 ± 0.6%, 17.7 ± 1.2% and 17.3 ± 1.4%, respectively, and full energy peak variation among four layers is less than 5% on average.

2) Detector calibration acquisition system of the jPET-D4

The jPET-D4 has five detector rings with the ring

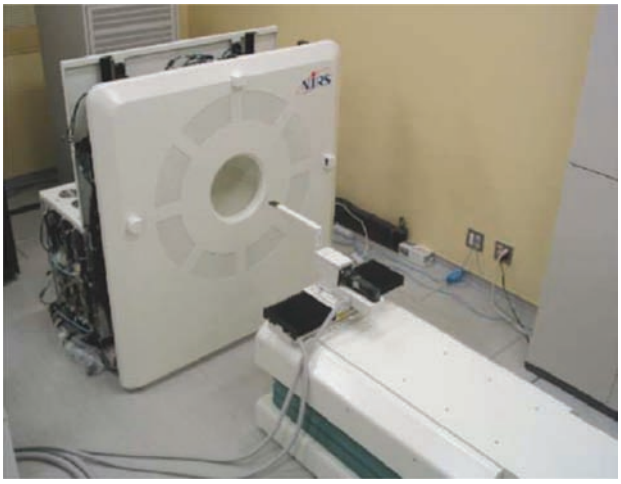


Fig 12. Photograph of the jPET-D4.

diameter of 390 mm and each detector ring consists of 24 DOI detectors. Axial length is 260 mm with five DOI detectors. A photograph of the jPET-D4 system is shown in Fig. 12. The gantry is very compactly designed and the bed has optionally programmable X- and rotation stages. The major specifications of the system are listed in Table 5.

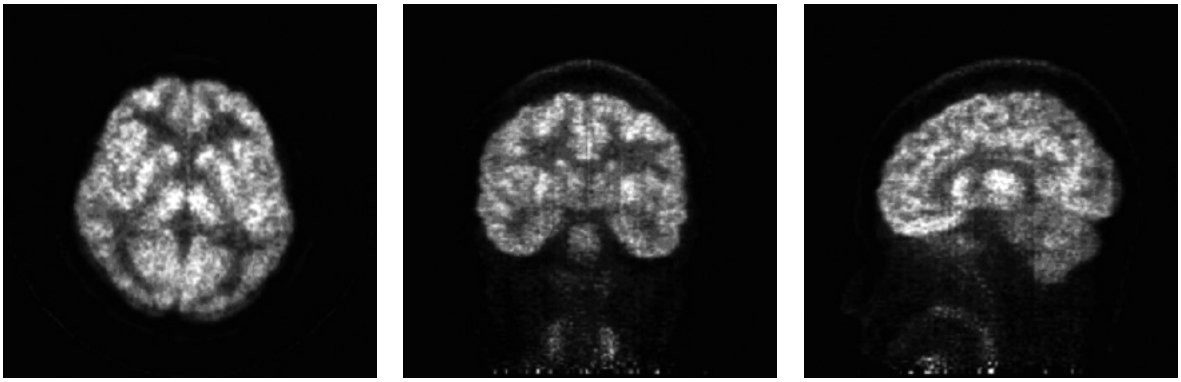
The DOI detector consists of 1,024 GSO crystals, which are arranged in four layers of 16 × 16 arrays, coupled to a 52mm square 256-channel flat panel PS-PMT (FP-PMT). The 256-channel anode outputs are reduced to 4 channels by a set of resistor chains for simple and fast processing. The crystals of the 1st, 2nd layers and 3rd, 4th layers are GSO doped with 0.5 mol% and 1.5 mol% Ce, respectively. The 4th layer is optically coupled to the FP-PMT. Detected events are classified into two groups corresponding to different Ce dopant crystals with pulse shape discrimination. Each group is projected on each 2D position histogram by an Anger calculation.

Four output signals from the DOI detector are fed to a position analyzer circuit. The 2D position signals X and Y are calculated from those outputs by the Anger calculation. Energy and timing signals are summed from those outputs. The 2D position signals and energy are digitized with 10-bit and 8-bit ADCs, respectively. For the DOI detector calibration routine, we obtained 2D position histograms and energy spectra at uniform irradiation of a 68Ge-68Ga line source. We create decay, position and energy Look-Up-Tables (LUTs) from the obtained data. The decay LUT identifies different light decay times of the scintillator layers with pulse shape discrimination. The position LUT converts location of 2D position histograms to crystal addresses using the Gaussian Mixture Model. The energy LUT corrects light output of each crystal. This energy LUT can correct non-uniformity of light output originating in crystal depth. Also, the energy LUT can attach an energy bit to list mode data and the energy bit has 3 bits for each coincidence event. Timing signal is digitized at 2 ns time resolution in 256 ns frame time to make a 7-bit time marker data. Detector block-based coincidence timing adjustment is achieved for each DOI detector.

The average energy resolution for 120 DOI detectors is optimized to 17 % ± 1.4 %. The scatter fraction for this system is 38 % with energy window of 400-600 keV. The sensitivity for point source is 126 kcps/MBq with a 250 keV LLD.

3) Reconstruction of first human brain image by the jPET-D4

This jPET-D4 is dedicated to brain scans, and the detector rings have a diameter of 390 mm. The basic idea for DOI discrimination is the coded reflector insertion that controls the distribution of scintillation light so that each position can be identified by the Anger type calculation. Four-layer DOI positions are identified based on this idea after upper and lower two DOI positions are separated by the pulse shape discrimination. In order to reduce computational cost while retaining the advantage of DOI information in iterative image reconstruction, we used (a) the DOI compression (DOIC) method which reduces data dimensions while suppressing resolution loss, and (b) the approximated system model which enables fast system matrix calculation while preserving image quality. In addition to the on-the-fly system matrix calculation, (c) a pre-computed system matrix scheme was newly proposed to speed up 3D image reconstruction. At this development stage, a histogram-based 3D OSEM was implemented. After evaluating basic imaging performance through phantom experiments, a normal volunteer was scanned (100 min past 104 MBq FDG injection, duration of 60 min) and the first human brain images were obtained. The maximum ring difference (mrd) was restricted to 54 (with no spanning) due to the computer memory limitation, 3D OSEM (8 subsets, 8 iterations), with 1.5mm × 1.5mm x 1.5mm voxels. Reconstructed images are shown in Fig. 13. These images show the excellent imaging performance of the jPET-D4: there are clear demarcations of thin gray matter from underlying white matter as well as fine visualization of the deep structures such as caudate nucleus, putamen and thalamus.



(A) Transverse section image (B) Coronal section image (C) Sagittal section image

Fig 13. Reconstructed human brain images of ^{18}FDG by the jPET-D4.

4) 8-layer DOI encoding of three-dimensional crystal array

An 8-layer DOI detector was designed on the basis of the technique we have developed for 4-layer DOI detectors. It attained 8-layer encoding by pulse shape discrimination (2-layer DOI encoding) and the proper reflector arrangement in a 3-dimensional crystal array (4-layer DOI encoding). Its capability was proved with an 8-layer, 10 × 10 Gd_2SiO_5 (GSO) crystal array coupled to a 256-channel flat panel position sensitive photomultiplier tube (256ch FP-PMT). The dimensions of each crystal element were 2.90 mm × 2.90 mm × 3.75 mm and intervals of 16 × 16 multi anodes in the 256ch FP-PMT were 3.04 mm. Two kinds of GSO crystals were used for pulse shape discrimination; GSO crystals of 0.5 mol% and 1.5 mol% Ce dopants that had 60 ns and 35 ns scintillation decay times, respectively. In the crystal array, layer-1, the farthest from the 256ch FP-PMT, layer-3, -5 and -7 were composed of 0.5 mol% GSO: Ce crystals; 1.5 mol% GSO: Ce crystals were in other layers. Performance of the 8- layer DOI detector was evaluated by irradiating 662 keV uniform gamma-rays. The results indicate capability for 8-layer DOI encoding. To prove the validity of the layer encoding, a fan-beam of 662 keV gamma-rays was irradiated onto the side face of each layer. The obtained 2D histograms showed the right structure in each corresponding layer clearly. The smallest light output was measured to be 62% of the largest in comparison of pulse height distributions for the central crystals in each DOI layers. Energy resolution was uniformly among eight layers and they were all about 15%.

5) Measurement of 32x8x4 LYSO crystal responses of DOI detector for small animal PET

The jPET-RD is designed to achieve high sensitivity as well as high spatial resolution by the use of four-layer DOI information of the detector. We have previously proposed the DOI encoding method that realizes four layer DOI identification using only a single kind of crystal element. The basic idea was tested by using Gd_2SiO_5, and the first prototype detector was developed using $Lu_{2(1-x)}Y_{2x}SiO_5$ (LYSO). We prepared a pair of jPET-RD prototype detectors composed of four layers of a 32 (transaxial) x 8 (axial) LYSO (Lu: 98%, Y: 2%) crystal block and a 256-channel flat panel position sensitive photomultiplier tube (256ch FP-PMT). The size of each crystal element was 1.46 mm x 1.46 mm x 4.5 mm. The crystal block (46.5 mm x 11.6 mm x 18.0 mm) was placed on the central area of the 256ch FP-PMT (49 mm x 49 mm useful area) and coupled with silicone rubber. First, we evaluated performance of the prototype DOI detector by uniform gamma ray irradiation. Then response functions of the prototype DOI detector were measured with collimated single gamma rays and finally coincidence responses were estimated with a pair of prototype DOI detectors in the experimental setup which simulated the jPET-RD system. In the performance evaluation, the energy resolution of all events was 14.7% and the time resolution was 0.66 ns. The response functions were 1.56 mm FWHM and 4.51 mm FWHM in average in transaxial and depth directions, respectively. The FWHMs of coincidence responses were 5.4 mm (non-DOI) and 3.7 mm (averaged DOI). We confirmed that the spatial resolution was improved by using DOI information.

Major publications:

1) Hasegawa, T., Ishikawa, M., Maruyama, K., Inadama, N., Yoshida, E., Murayama, H. : Depth-of-interaction recognition using optical filters for nuclear medicine imaging. *IEEE Trans. Nucl. Sci*., **52**(1), 4-7, 2005.
2) Orita, N., Murayama, H., Kawai, H., Inadama, N., Tsuda, T. : Three-dimensional array of scintillation crystals with proper reflector arrangement for a depth of interaction detector. *IEEE Trans. Nucl. Sci*., **52**(1), 8-14, 2005.
3) Inadama, N., Murayama, H., Watanabe, M., Omura, T. , Yamashita, T., Kawai, H., Orita, N., Tsuda, T. : Performance of a 256ch Flat Panel PS-PMT with small crystals for a DOI PET detector. *IEEE Trans. Nucl. Sci*., **52**(1),.15-20, 2005.
4) Yamaya, T., Hagiwara, N., Obi, T., Yamaguchi, M., Ohyama, N., Kitamura, K., Hasegawa, T., Haneishi, H., Yoshida1, E., Naoko Inadama, N., Murayama, H. : Transaxial system models for jPET-D4 image reconstruction. *Phys. Med. Biol*., **50**, 5339-5355, 2005.
5) Yamamoto, S., Takamatsu, S., Murayama, H., Minato, K. : A block detector for a multislice, depth-of-interaction MR-compatible PET. *IEEE Trans. Nucl. Sci*., **52**(1), 33-37, 2005.

Table 5. Major specifications of jPET-D4 in comparison with other scanners

	jPET-D4	HRRT	G-PET	ECAT HR+
Crystal	GSO	LSO	GSO	BGO
Crystal size	2.9x2.9x7.5 mm	2.1x2.1x7.5 mm	4x4x10 mm	4.05x4.39x30 mm
Number of crystal	122,880	119,808	18,560	18,432
DOI	4	2	1	1
PMT	256ch FP-PMT	Round 19 mm PMT	Round 39 mm PMT	Round 19 mm PMT
Total number of PMT	120	1,120	288	1,152
Ring diameter	256 mm	350 mm	420 mm	824 mm
Axial length	260 mm	252 mm	256 mm	155 mm
Coincidence timing window	10 ns	6 ns	-	12 ns
Default energy window	400-600 keV	350-650 keV	411-665 keV	350-650 keV
Energy resolution	16 %	24 %	18 %	25 %
Sensitivity (Point source)	11 %	4.3 %	-	3.7 %
Scatter Fraction (NEMA 1994)	39.7 %	43.5 %	39 %	32.1 %
Maximum NECR	118kcps@9.3kBq/ml	99kcps@24.6kBq/ml	60kcps@7.4kBq/ml	-

5.3. R&D Studies of a Compact Accelerator for Carbon Therapy

Koji Noda, Ph.D.

Outline of Research Career:

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

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Objective:

Excellent clinical results for cancer therapy have been obtained with high-energy carbon beams at HIMAC. The primary aim of our research now is to design a compact accelerator facility for carbon therapy at a reasonable cost. R&D studies of key elements were completed by the end of FY2005. The construction of the compact therapy-facility project will be initiated in FY2006 at a site outside NIRS.

Progress of Research:

During this fiscal year, major activities of our group were concentrated on R&D studies of a compact carbon therapy accelerator.

1) Injector system

The compact injector system consisted of the 10 GHz ECR ion source, the RFQ linac and Alternating-Phase-Focused (APF) IH-DTL. The IH cavity was known to provide higher shunt impedance than that of conventional structures, such as Alvarez DTL. Moreover, use of the APF method for IH-DTL allowed us to employ a rather high operating frequency and hence to design a compact cavity. Although the APF IH-DTL has such attractive features, it has never been practically used until now. The reason is that the electromagnetic (EM) field could not be calculated with existing 2D field solvers and therefore it required lengthy and costly model studies to determine the final structure of the cavity. With recent developments in 3D field solvers, the EM field in the IH cavity can be directly calculated. To verify accuracy of the solver, we constructed a model cavity of the APF IH-DTL. Measurements of the electric field for the model cavity indicated that the measured field distribution could be reproduced well by the calculated one.

Based on the model cavity, the design of the high-power cavity of the APF IH-DTL has been developed. The construction of the APF IH-DTL was completed at the end of FY2005. Then, APF IH-DTL was installed in conjunction with the ECR ion source and RFQ linac. A schematic drawing of the compact injector system is presented in Fig. 14. The total length of the linac cascade was reduced to approximately 6 m, which is considerably shorter than that of existing heavy-ion linacs.

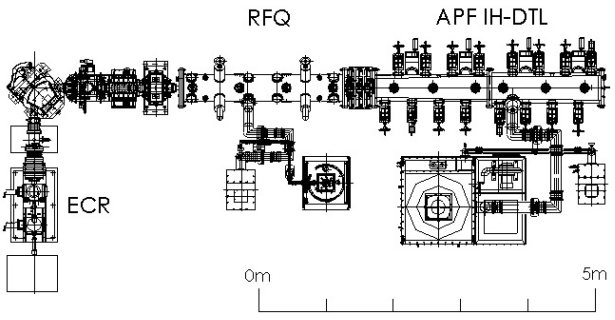

Fig 14. A schematic drawing of the compact injector. The total length of the linac cascade was 6 m.

After the installation, beam acceleration tests of the entire injector system were carried out. Carbon ions extracted from the RFQ linac were injected to the APF IH-DTL and successfully accelerated up to 4.0 MeV/u. The average value and width of the measured energy distribution were to be 4.0 MeV/u and ±0.4%, respectively. The beam intensity of

accelerated $^{12}C^{4+}$ ions from the APF IH-DTL was measured to be 380 eμA, which is twice that required for treatments. These results of the acceleration tests have proven the excellent performance of the proposed compact injector system.

2) RF cavity for synchrotron

We have developed a new RF acceleration system with Co-based amorphous cores, which have high permeability with a low Q-value of about 0.5. Especially, this core has about a 1.5-times higher μQf value than the FINMET FT-3M, which has been commonly used in the acceleration cavity. This is a very attractive point to realize a compact RF cavity with the required high shunt impedance. The fabricated core was made of 15 μm thick amorphous tape with a 1.5 μm SiO2 electric insulator. Based on the obtained property of the test core, the inner diameter, outer diameter, and thickness of the core for the cavity were 310 mm, 550 mm, and 30 mm, respectively. With these dimensions, twelve cores were fabricated. The cavity was composed of two acceleration gaps, and both sides of the gaps consisted of quarter-wave resonators. Since the total cavity length was as short as 1.5 m, the RF cavity was easily installed in the straight section in the HIMAC synchrotron as shown in Fig. 15.

Fig 15. Acceleration cavity installed in the HIMAC synchrotron.

The transistor amplifier was adapted instead of the commonly used tetrode to achieve the required acceleration voltage. This choice simplified the acceleration system, and we had no need to exchange the tetrode after a certain period of operation. To supply RF power from the transistor amplifier with an output impedance of 50 Ω, a transformer of 1:9 is attached to each resonator that have impedance of about 400Ω at maximum. With the maximum power operation of 2 kW, obtained RF voltage per one resonator was more than 1 kV in the required frequency range, which was high enough for the required voltage in the compact dedicated synchrotron. The maximum RF field in the core was calculated to be about 24 mT at 1 MHz, and its peak power consumption was 0.13 W/cm^3. This maximum RF field and the power density were below the values with which the core permeability decreased, i.e, about 50 mT at 1 MHz.

An acceleration test with the RF cavity will be carried out in FY2006.

3) Compact beam delivery system

A test bench for the compact irradiation port has been installed at HIMAC in order to verify the proposed irradiation methods for the compact therapy facility. The test bench consisted of a pair of wobbler magnets, a scatterer, a range shifter, a ridge filter, collimators and dose monitor system. The wobbler magnets were installed 5.5 m upstream from the iso-center. The maximum wobbler radius at the iso-center was 140 mm for 400 MeV/n carbon beam.

The wobbler radius was modulated to produce a uniform beam fluence at the surface. Under a constant angular velocity of the wobbling, the irradiated area expands with time in proportion to the wobbler radius. The wobbler radius should be proportional to the square root of time. The maximum wobbler radius depends on the irradiation field radius and the beam radius. To produce an irradiation field with a uniformity of 2.5 %, the maximum wobbler radius is written as $A = R + 2\sigma$, where R is the irradiation-field radius and σ is the 1 SD of beam radius assuming a Gaussian beam profile. This experiment employed the angular and radial frequencies of 59 Hz and of 23 Hz, respectively. The typical beam size was 25 mm (1σ) at the isocenter, which was spread by the scatterer. The dose profile at the isocenter was measured by a multi-channel ionization chamber with 64 sensors for the horizontal and vertical directions, respectively. The active area of the sensor was 3.7 x 3.7 mm and the interval the sensor was 4 mm. The measured dose profile is shown in Fig. 16. In the conventional wobbler-scatterer system, both the beam size and wobbler radius should be changed when changing the irradiation field size. In the spiral wobbler system, however, the beam size of 25 mm is fixed for each field size.

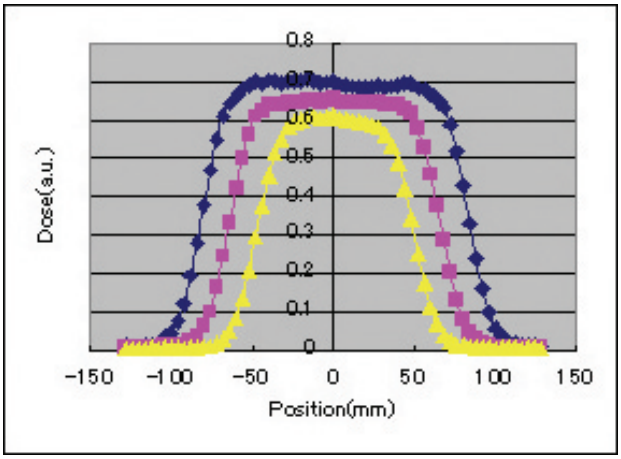

Fig 16. Dose profile of the irradiation field. The field sizes of 80, 130, 180 mm in diameter are plotted with yellow, red and blue, respectively.

4) Advanced Compact Accelerator Development Project

The Advanced Compact Accelerator Development Project was initiated in 2001 based on a report of the "Committee of Future Accelerators" organized by the National Institute of Science and Technology Policy. The project has been promoted as cooperative research with 8 universities and research institutes: Japan Atomic Energy Research Institute (presently known as Japan Atomic Energy Agency), The University of Tokyo, Hiroshima University, Kyoto University, High Energy Accelerator Research Organization (KEK), Osaka University, National Institute of Advanced Industrial Science and Technology, and Japan Synchrotron Research Institute (SP-8).

Major targets of this project are to develop key elements of very compact accelerators: a compact pulsed synchrotron for particle therapy, a FFAG accelerator for carbon therapy, a compact hard x-ray generator for medical diagnosis, and a high intensity hard x-ray generator for general use. The last two x-ray generators will use a high power laser source to generate hard x-rays through an inverse Compton scattering process with medium energy electrons. The secondary aim of this project is to educate young researchers through these R&D studies.

Major Publications:

1) T. Uesugi et al., Cool-stacking injection and damping of a transverse ion-beam instability at the HIMAC synchrotron, *Nucl. Instrum. Meth. A* **545** (2005) 45-56.
2) Y. Iwata et al, Alternating-Phase-Focused Linac with interdigital H-mode structure for medical injector, *Proc. PAC05*, pp.1084-1086, 2005.
3) T. Furukawa et al., Intensity Control in RF-knockout Extraction for Scanning Irradiation,*Nucl. Instrum. Meth. B* **240** (2005) 32-35.
4) A. Kitagawa et al, New medical irradiation technique by the permanent magnet system for the heavy-ion therapy, *Nucl. Instrum. Meth. B* **240** (2005) 78-82.
5) S. Hojo et al, Production of 11C-beam for particle therapy; *Nucl. Instrum. Meth. B* **240** (2005) 75-78.

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

Tatsuaki Kanai, Director of Department of Medical Physics

Outline of Research Career:

Tatsuaki Kanai received his B.S. degree from the Department of Science, Physics Course, Tokyo University of Education, in 1972 and completed the M.S. program there in 1974. He received the Ph. D degree in 1983 from Tsukuba University. In 1972, he joined NIRS as a researcher in the Physics Division. He was engaged in development and application of proton irradiation systems, using a scanning method. In construction of the HIMAC facility, he was engaged in development of the irradiation system and in establishment of the clinical dose system. He is now the director of the Department of Medical Physics.

Outline of Research:

The conformal irradiation system of HIMAC has been up-graded for a clinical trial using the layer-stacking method. After the acceptance and commissioning tests of this layer-stacking method, the clinical trial was started in June 2005. To date 20 ports of irradiations for 9 patients were successfully applied to clinical application. The eye-treatment using horizontal beam line has been clinically applied in the commissioning test of the system. Through development of the heavy-ion CT device, it was found that the relative stopping powers obtained by X-ray CT value and by the HICT agree within the deviation of 1.6 % for fat, muscle, and bone.

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Objective:

Heavy-ion radiotherapy has been expected to achieve good clinical results because of its good dose localization in the target and high biological effectiveness of the beam. On the whole, spatial and dose accuracy of irradiation under the present heavy ion treatments are considered to be 5mm and about 5%. In order to extend the treatment region in the patient body, and in order to get improvement over present clinical results, techniques, such as exact treatment planning, exact patient positioning, and exact irradiation, should be further developed. Research activities to improve the medical treatment accuracy of heavy ion radiotherapy will be accomplished under the 5-year fundamental research target.

Progress of Research:

1) Development of conformal irradiation system for heavy-ion radiotherapy using a layer-stacking method

The conformal irradiation system of HIMAC has been up-graded for a clinical trial using the layer-stacking method. The system has been developed to localize the irradiation dose to the target volume more effectively than is presently done. In the present passive irradiation method using a ridge filter, a scatterer, a pair of wobbler magnets, and multileaf collimator, the width of a spread-out Bragg peak (SOBP) in the radiation field cannot be changed. With dynamic control of the beam modifying devices during the irradiation, better conformal radiotherapy can be achieved.

After the acceptance and commissioning tests of this layer-stacking method, the clinical trial was started in June 2005. To date 20 ports of irradiations for 9 patients were successfully applied to clinical application.

2) Development of an irradiation system for eye treatment using a horizontal beam line

In order to avoid or reduce occurrence of glaucoma or damage to the retina, we plan to irradiate melanoma in the eyeball with two ports, horizontal and vertical beams. We are planning to develop a new irradiation system for eye melanoma.

A 170 MeV/n carbon beam was used for the eye-treatment by the horizontal beam line. Irradiation fields and ridge filters for the treatments using 170 MeV/n beam were designed and installed respectively in the irradiation system.

The treatment planning system used in the commercial treatment planning system, Xio, was newly developed. The whole process for eye-treatments was commissioned instead of the eye-plan treatment planning system, which is used for the vertical beam line.

A precise patient positioning system for the eye-treatment has also been developed. A flat panel imaging system has been used for the eye-treatment by the horizontal beam line which was clinically applied through the commissioning test of the system.

3) Development of dose estimation method

The monitor unit for treatment is determined at HIMAC using a measured dose under each irradiation condition in the treatments without a compensator. To assess this monitor-preset procedure for the treatment, it is desirable to estimate it by other methods.

It has been found that the dose calibration factors also depend on the field sizes. We found that the carbon beams could be well described using three Gaussian forms at the irradiation site in the pencil beam algorithm. The 2nd and 3rd components of the Gaussian form, which have widths much larger than the 1st component, are found to be fragmented particles produced in the up-stream beam modifying devices and in the water phantom.

4) Development of heavy-ion CT system.

In treatment planning for hadron therapy, information about the relative stopping power in a patient's body is used to calculate the range of incident ions. This information is obtained from computed tomography (CT) images using a conversion table from x-ray CT numbers into stopping powers relative to the stopping power of water. In treatment planning at NIRS, the conversion table has been created based on the polybinary tissue model. However, it has not been fully verified that the model is accurate enough for use in real animal tissues. In order to irradiate heavy ions more precisely in radiotherapy, we have to evaluate the accuracy of the polybinary tissue calibration in animal tissues. We have measured animal tissue samples with heavy-ion CT (HICT) and x-ray CT. The x-ray CT image was converted to an image of relative stopping power by using the table derived from the polybinary tissue calibration (polybinary-tissue-model CT image; PTCT). On the other hand, with HICT, the two-dimensional distribution of relative stopping power could be obtained directly. A comparison between PTCT and HICT images enabled us to verify the accuracy of the conversion table derived from the polybinary tissue calibration. Consequently, we found that the agreement between the relative stopping powers of PTCT and HICT was 1.6 % for fat, muscle, and bone.

Major Publications:

1) A. Kimura, S. Tanaka, T. Aso, H. Yoshida, N. Kanematsu, M. Asai, and T. Sasaki: Verification of the dose distribution with GEANT4 simulation for proton therapy, *IEEE Transactions on Nuclear Science*, **52**(4), 896-901, 2005
2) T. Inaniwa, T. Tomitani, T. Kohno and T. Kanai: Quantitative comparison of suitability of various beams for range monitoring with induced $\beta+$ activity in hadron therapy. *Phys. Med. Biol*. **50**, 1131-1145, 2005
3) T. Inaniwa, T. Kohno and T. Tomitani: Simulation for position determination of distal and proximal edges for SOBP irradiation in hadron therapy by using the maximum likelihood estimation method. *Phys. Med. Biol*. **50**: 5829-5845, 2005
4) Qiang Li, Y. Furusawa, M. Kanazawa, T. Kanai, A. Kitagawa, M. Aoki, E. Urakage, T. Tomitani, S. Sato, M. Yosimoto, Z. Wei: Enhanced efficiency in cell killing at the penetration depths around the Bragg peak of a radioactive 9C-ion beam. *Int. J. Rad. Oncl. Biol. Phys*. **64**(4): 1237-1244, 2005
5) S.Sato, A.Kitagawa, M.Kanazawa, E. Urakabe, T.Tomitani, M.Suda, Q.Li, T.Inaniwa, K.Hanawa, and K.Sato: A versatile control system for irradiation and measurement for secondary beam experiments in a heavy ion accelerator HINMAC: *Nucl. Instrum. Methods* **B240** 95. 2000.

5.5. Establishment of Dosimetry and Radiation Quality Measurements of Heavy-ion Beams

Tatsuaki Kanai, Director of Department of Medical Physics

Outline of Research Career:

Tatsuaki Kanai received his B.S. degree from the Department of Science, Physics Course, Tokyo University of Education, in 1972 and completed the M.S. program there in 1974. He received the Ph. D degree in 1983 from Tsukuba University. In 1972, he joined NIRS National Institute as a researcher in the Physics Division. He was engaged in development and application of proton irradiation system,s using a scanning method. In construction of the HIMAC facility, he was engaged in development of the irradiation system and in establishment of the clinical dose system. He is now the director of the Department of Medical Physics.

Outline of Research:

Spatial distributions of fragmented particles in water and in aluminum were experimentally obtained in order to discuss field size dependence of the dose calibration factor of the treatment. The effects of heavy ions on biological species were successfully explained by microdosimetric measurements obtained using the ROSSI counter. A clinical dose detector was developed for measuring the clinical dose directly.

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Objectives:

In order to perform the efficient heavy ion radiotherapy, it is necessary to estimate the biological effect of heavy ion beams, to find the kind of optimal heavy ion species for radiotherapy, and to establish the optimal irradiation schedule. For those purposes it is strongly required to measure radiation quality and dose of the heavy ions precisely. From the viewpoint of assuring quality of radiotherapy, it is very important to establish the traceability of the dosimetry for medical treatments including photon, electron, neutron, proton, and heavy ions to the national standard laboratory.

Research Project: Beam quality measurements and development of an effective method to evaluate biological effect

Purpose

Systematic evaluation of the radiation quality of heavy ion beams is required for the optimized treatment planning with heavy ions. Depth-dose distributions, depth-LET distributions, and particle kind distributions in water phantom, should be measured and summarized as a database for heavy-ion radiotherapy.

Progress of the Research

1) Measurements of spatial distribution of the beam quality

Field size dependence of the clinical dose in calibration of the monitor unit was found by researchers at HIMAC. In order to discuss this effect, spatial distributions were measured and the field size dependence of the monitor unit was evaluated. Additionally, the spatial distribution was investigated in a more microscopic way; each projectile fragment in a thick water phantom produced from a therapeutic carbon beam was measured with a set of scintillation counters and a LET counter. A simple model was developed to estimate the spatial distribution of fragments. This year, energy dependence and incident particle dependence of the spatial distributions of the fragments were experimentally obtained for examination of the simple model. Through the introduction of energy dependence of the parameters

in the simple model, we found the experimental results of the dose distribution can be reproduced within the error of 0.5 mm.

2) Analysis of clinical results using radiation quality of the heavy-ion beams

Clinical results of HIMAC treatments were analyzed using the estimated radiation quality of the therapeutic beam and the biological responses of the Human Salivary Gland tumor cell that is characterized by the LQ model. This year, clinical results of GSI treatments were also analyzed. A method for the conversion of the GSI GyE system to the HIMAC GyE system was developed. From this analysis, the RBE values of GSI and HIMAC were found to be about 20 % different for each other for the treatment of Chordomas.

3) Development of clinical dose detector

We are trying to determine the clinical dose by microdosimetric measurements. Using a Rossi counter, *z* distributions were measured for SOBP beams of various widths. The theory of the model developed by Hawkins was experimentally checked using the z distribution obtained by the ROSSI counter of sub-micron size. It was found that the surviving fraction of HSG cells exposed heavy ions, from proton to iron, can be explained by using this model.

In order to measure spatial distributions of the beam quality of the carbon ions, a small Si detector, 2mm in diameter, was developed and tested using therapeutic beams. Using this detector, we simultaneously obtained physical and clinical doses for the therapeutic beams.

Research Project: Development of calorimeter
Purpose

Dosimetry for heavy-ion beams is usually performed with an ionization chamber. IAEA tentatively recommends the dosimetry protocol for heavy-ion beams using ionization chambers. However required parameters for the ionization chamber dosimetry, *i.e.*, w-values, stopping power ratios and other quantities have not yet been satisfactorily examined for the heavy-ion beams. It is necessary to have a more direct modality of dosimetry in order to support ionization chamber dosimetry.

Progress of the research

We designed a graphite calorimeter for the dosimetry of heavy-ion beams. Tentative results for the fields of carbon beams were obtained and the detector showed good performance. We are continueing the measurements using this calorimeter for photon beams and other heavy-ion beams.

Major publications:

1) N. Matsufuji, M. Komori, E. Urakabe, A. Fukumura, T. Kanai, H. Sasaki, K. Akiu, M. Ohara, T. Inaniwa and T. Kohno: A simple model to describe spatial fragment distribution from pencil-like heavy-ion beams in a thick medium. *Proc. of the 43rd PTCOG Meeting* 2005.
2) N. Matsufuji, T. Kanai, T. Miyamoto, J. Mizoe, T. Kamada, H. Tsuji, H. Kato, M. Baba and H. Tsujii: Verification of RBE for Carbon Ion Radiotherapy at NIRS. *Proc. of the 42nd PTCOG Meeting* 2005.
3) N. Matsufuji, T. Kanai, T. Miyamoto, J. Mizoe, T. Kamada, H. Tsuji, H. Kato, M. Baba and H. Tsujii: Verification of RBE for Carbon Ion Radiotherapy against NSCLC at HIMAC. *Proc. of the 10th Workshop on Heavy Charged Particles in Biology and Medicine and 4th ENLIGHT Meeting* 2005.
4) Y. Kase, T. Kanai, Y. Furusawa, Y. Matsumoto and H. Okamoto: Response of Human Tumor Cells and Microdosimetry in Heavy-Ion Beams. *Proc. of the 4th JKMP Meeting* 2005.
5) M. Ohara, N. Matsufuji, M. Komori, E. Urakabe, A. Fukumura, T. Nishio, T. Kohno and T. Kanai: Study on the Spatial Distribution of Fragments Produced from Heavy Ion Beams. *Proc. of the 4th JKMP Meeting* 2005.

5.6. Studies Necessary for Promotion of Particle Radiotherapy

Tatsuaki Kanai, Director of Department of Medical Physics

Outline of Research Career:

Tatsuaki Kanai received his B.S. degree from the Department of Science, Physics Course, Tokyo University of Education, in 1972 and completed the M.S. program there in 1974. He received the Ph. D degree in 1983 from Tsukuba University. In 1972, he joined NIRS as a researcher in the Physics Division. He was engaged in development and application of proton irradiation systems, using a scanning method. In construction of the HIMAC facility, he was engaged in development of the irradiation system and in establishment of the clinical dose system. He is now the director of the Department of Medical Physics.

Outline of Research

The effective method of QA for particle radiotherapy is developed and is routinely practiced under the leadership of Office for the Quality Assurance of Radiation Therapy.

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Objective:

In Japan, there are many particle therapy facilities installed in or near hospitals. Good results of clinical trials on particle therapy are expected. The clinical results depend on the physical characteristics of the particle beams and also on the quality assurance and quality control of the treatment procedure. The quality control of the irradiation system is especially important. In order to expect good clinical results and to promote particle therapy, a standard guideline which establishes quality assurance/control of the irradiation system is needed. Moreover, it is very important to train medical physicists who can work in the field of particle radiotherapy facilities.

Research Projects:

1) Establishment of QA guideline for particle radiotherapy

Discussions between medical physicists at various particle therapy facilities about the QA/QC guideline for particle radiotherapy were summarized. The QA guideline for the particle radiotherapy was tentatively published.

This project was finished last year.

2) Development of an effective method of Quality Assurance for particle radiotherapy

(A) Acceptance test and commissioning of the newly developed eye-treatment system was conducted. Through this activity, the QA guideline was examined and discussed in detail.

(B) A CT system for the treatment planning of carbon beam therapy was renewed. The first Multi-Detector CT device (MDCT) was installed in the NIRS. Through the QA from using this MDCT in carbon therapy, a new protocol for QA standards for the MDCT was established.

(C) Office for the Quality Assurance of Radiation Therapy was opened in June 2005 in the Center of Charged Particle Therapy. Research activities of the QA process were sorted out and selected procedures are now routinely practiced under the leadership of the office.

5.7. Biological Effectiveness of Charged Particle Radiotherapy

Koichi Ando, D.D.S., Ph.D., D.M.Sc.
Director, Heavy-Ion Radiobiology Research Group

Outline of Research Career:

Dr.Koichi Ando has spent 35 years in research on high-LET radiation biology at NIRS. Between 1976 and 1979 he was at M.D. Anderson Cancer Center (Houston, TX) as a post doctoral fellow to study radiation effects on tumor metastasis, and in 1984 he was at Massachusetts General Hospital (Boston, MA) as a Visiting Lecturer. He served as Editor-in-Chief, Journal of Radiation Research between 2000 and 2003. Since 2001 he has been Director at NIRS, and Visiting Professor of Chiba University (Chiba, Japan) .

Doctorates and License:

1971: Doctor of Dental Surgery, National Board; 1976: Ph.D. Nihon University, School of Dentistry; 1985: Doctor of Medical Science, Tohoku University

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Objectives:

We are to clarify, through a basic and experimental approach, the most appropriate fractionation schedule of heavy ion therapy. Much effort is being spent to develop a method by which high-responder tumors that respond well to heavy ions can be distinguished from low-responder tumors. We want to achieve the following 2 goals by the start of Fiscal Year 2006: first, obtaining data necessary to understand mechanisms underlying (a) the LET-RBE relationship, (b) tumor controls, and (c) normal tissue damages; and second, developing a method to detect radioresistant tumors with hypoxic clonogens. Specific purposes for fiscal year 2005 included the following 5 items. (1) Comparison between carbon ions and X rays for gene expression profiles after 2 Gy-irradiation. (2) Effects of carbon ions on normal tissues. Significance of altered blood vessel density in functional damage of brain after carbon-ion radiation would be investigated. Expression of bFGF in gut after X-ray radiation would be compared with that after carbon-ion radiation. (3) Cellular damages caused by heavy ions. Dependence on oxygen of repair of DNA damage caused by heavy-ion radiation would be compared with that caused by X-ray radiation. (4) Biological comparison of therapeutic beams between domestic and overseas facilities. Acquiring data of biological effectiveness for carbon-ion beams at GSI would be completed. (5) Detection of radioresistant hypoxic cells in a tumor. An effective combination of nucleoside derivatives and hypoxic markers would be investigated using transplantable tumors.

Progress of Research:

We studied the relation between initial DNA double-strand breaks (DNA-DSB) and the rejoining kinetics of the strand breaks, as well as the OER (oxygen enhancement ratio) after low- and high-LET (linear energy transfer) radiations. CHO cells were exposed to 200 kVp X-rays or 80 keV/μm carbon ions under oxic and hypoxic conditions. DNA-DSB in the cells were analyzed by static-field gel electrophoresis (SFGE). The kinetics of the rejoining could be described by a sum of fast and slow components. The initialy released DNA after X-ray irradiation was higher for cells irradiated under an oxic condition than that under a hypoxic condition. The OER of DNA-DSB after X-ray irradiation was 5.7. This value decreased rapidly to reach 3.4 with the fast component in 15 minutes. On the other hand, the OER of DNA-DSB after carbon ion irradiation was 2.2, and this value was not changed by rejoining incubation (Fig.17). The OER values for cell killing were 2.8 and 1.8 after X-ray and carbon ion irradiations, respectively. These values matched the OER for DNA-DSB with complete rejoining. We conclude that the rejoining of DNA-DSB is an important factor in the mechanism of the oxygen effect.

In clinical use of carbon-ion beams, a deep-seated tumor is irradiated with a Spread-Out Bragg peak (SOBP) with a high-LET feature, whereas surface skin is irradiated with an entrance plateau, the LET of which is lower than that of the peak. The repair kinetics of murine skin damage caused by an entrance plateau of carbon ions was compared with that caused by photons using a scheme of daily fractionated doses followed by a top-up dose. Right hind legs of C3H female mice received local

irradiations with either 20 keV/μm carbon ions or γ rays. The skin reaction of the irradiated legs was scored every other day up to Day 35 using a scoring scale that consisted of 10 steps, ranging from 0.5 to 5.0. An isoeffect dose to produce a skin reaction score of 3.0 was used to obtain a total dose and a top-up dose for each fractionation. Dependence on a preceding dose and on the time interval of a top-up dose was examined using γ rays. For fractionated γ rays, the total dose linearly increased while the top-up dose linearly decreased with an increase in the number of fractions. The magnitude of damage repair depended on the size of dose per fraction, and was larger for 5.2 Gy than 12.5 Gy. The total dose of carbon ions with 5.2 Gy per fraction did not change till 2 fractions, but abruptly increased at the 3rd fraction (Fig.18). Factors such as rapid repopulation, induced repair and cell cycle synchronization are possible explanations for the abrupt increase. As an abrupt increase/decrease of normal tissue damage could be caused by changing the number of fractions in carbon-ion radiotherapy, we conclude that, unlike photon therapy, skin damage should be carefully studied when the number of fractions is changed in new clinical trials.

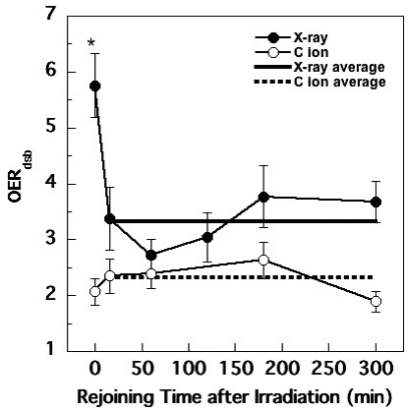

Fig 17. Time dependence for OER of DNA-DSB induction by irradiation with X rays and carbon ions. A significant difference (P<0.002) between X rays and carbon ions was detected at 15 min of irradiation.The solid and dotted lines represent the averaged values excluding data at t=0.

Major Publications:

1) Hirayama,R., Furusawa,Y., Fukawa,T. and Ando,K.: Repair Kinetics of DNA-DSB Induced by X-rays or Carbon Ions under Oxic and Hypoxic Conditions. *J. Radiat. Res*. **46**:325-332,2005.
2) Ando, K., Koike, S., Uzawa, A., Takai, N., Fukawa, T., Furusawa, Y., Aoki, M. and Miyato, Y.: Biological gain of carbon-ion radiotherapy for the early response of tumor growth delay and against early response of skin reaction in mice. *J. Radiat. Res.* **46**:51-57,2005.
3) Ando,K., Koike, S. and Hori, N.: Early growth of experimental lung metastasis in mouse. *J. Radiat. Res.* **46**:289-292,2005.
4) Ando,K., Koike, S., Uzawa,A., Takai,N., Fukawa,T, Furusawa,Y., Aoki, M. and Miyato, Y.: Tumor induction in mice locally irradiated with carbon ions: a retrospective analysis. *J. Radiat. Res.* **46**:185-190,2005.
5) Li, Q., Furusawa, Y., Kanazawa, M., Kanai, T., Kitagawa, A., Aoki, M., Urakabe, E., Tomitani, T., Sato, S., Yoshimoto, M. and Wei, ZG: Enhanced efficiency in cell killing at the penetration depths around the Bragg peak of a radioactive ^{9}C-ion beam. *Int. J. of Radiation Oncology Biol. Phys.* **63**: 1237-1244, 2005
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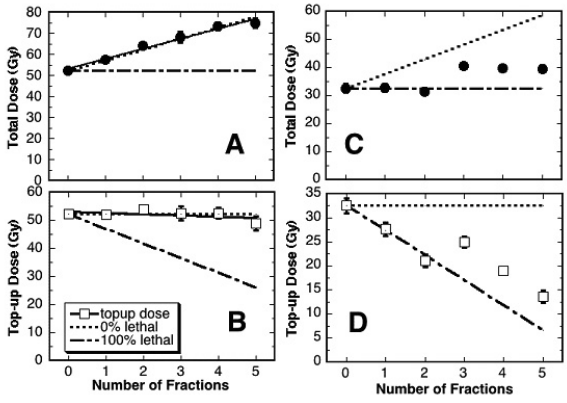

Fig 18. Total and top-up doses for the daily irradiations with 5.2 Gy followed by a top-up irradiation. Total doses (A, C) and top-up doses (B, D) for γ rays (A, B) and 20 keV/μm carbon ions (C, D) were calculated from dose responses for daily irradiation of 1 through 5 times followed by graded top-up doses 1 day after the final 5.2 Gy. The mean values with 95% confidence limits for total doses (●) and top-up doses (□) are plotted against the number of daily doses. Dotted and chain lines are for theoretical values of 100 and 0 % repair, respectively, while the solid line is for experimental data.

5.8. Information Processing for the Clinical Evaluation of Charged Particle Therapy

Yutaka Ando, M.D.
Head, Medical Information Processing Office

Outline of Research Career:

Yutaka Ando graduated from the School of Medicine, Keio University in 1976. He received the M.D. from Keio University in 1984. From 1978 to April 2004, he belonged to the Department of Radiology, Keio University. He was Assistant Professor and the Vice-director of Clinical Radiology Department. Since May 2004, he has been head, Medical Information Processing Office, Research Center for Charged Particle Therapy. He has specialized in radiological information systems and radiation oncology. He has researched tele-radiology systems, PACS and the electronic storage of medical information. He is a member of the Japan Radiological Society (the Vice-chairperson of the Committee of Electronic Informatics Science), the Japanese Society for Therapeutic Radiology and Oncology (Councilor), the Japanese Society of Nuclear Medicine, and the Japan Association of Medical Informatics (Councilor), and the Japanese College of Radiology (member Board of Directors).

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Objectives:

By using image information, responses and toxic effects, we quantitatively evaluated charged particle therapy. To reach an advanced therapy, we prepared a database of clinical data, standardized the information and managed the database. In our hospital, we used all kinds of image data (for example; CR, CT, MRI, PET, SPECT etc.), integrated these image systems and extracted suitable parameters for evaluation of clinical therapy and toxic effects. In the future, we are planning to establish a tele-conference system between hospitals that have heavy particle therapy devices and we want to share therapy results among them.

Progress of Research:

It is very important to enter data into a database system at the information source and also to eliminate data manipulation. We revised the function of automatic generation of documents (history of the disease, confirmation sheet of the protocol, sheet of informed consent) for the ethics committee. We could not make the documents before, but we could format a suitable document for the disease history.

We improved the coordination among several database systems (Hospital Information System, Therapy Plan Database, Therapy Schedule Management System and PACS). 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 are preparing 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 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.

We improved the functions of retrieval and statistics. We can automatically generate summary documents for the evaluation committee and network committee. We will examine the value of the documents in the future. We also developed the retrieval function for basic patient information,

treatment method, tumor information, tumor responses and toxic effects. The results of retrieval can be transformed to a value-separated format. We implemented the web analysis system using the syntax file of the SPSS. This system provides the client with the SPSS analysis function.

We studied how to get fusion images among temporal series image. We evaluated the size of a lung tumor in a series of PET and CT images of a patient with lung cancer. We read a paper at the academic meeting of the Japan Society of Medical Physics and Japanese Society of Nuclear Medicine concerning the results.

We evaluated the security of the tele-conference system and overcame its problems. There is room for further improvement (sharing pointer and conversation) in this system.

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.

The NIRS hospital information system is shown in Fig.19.

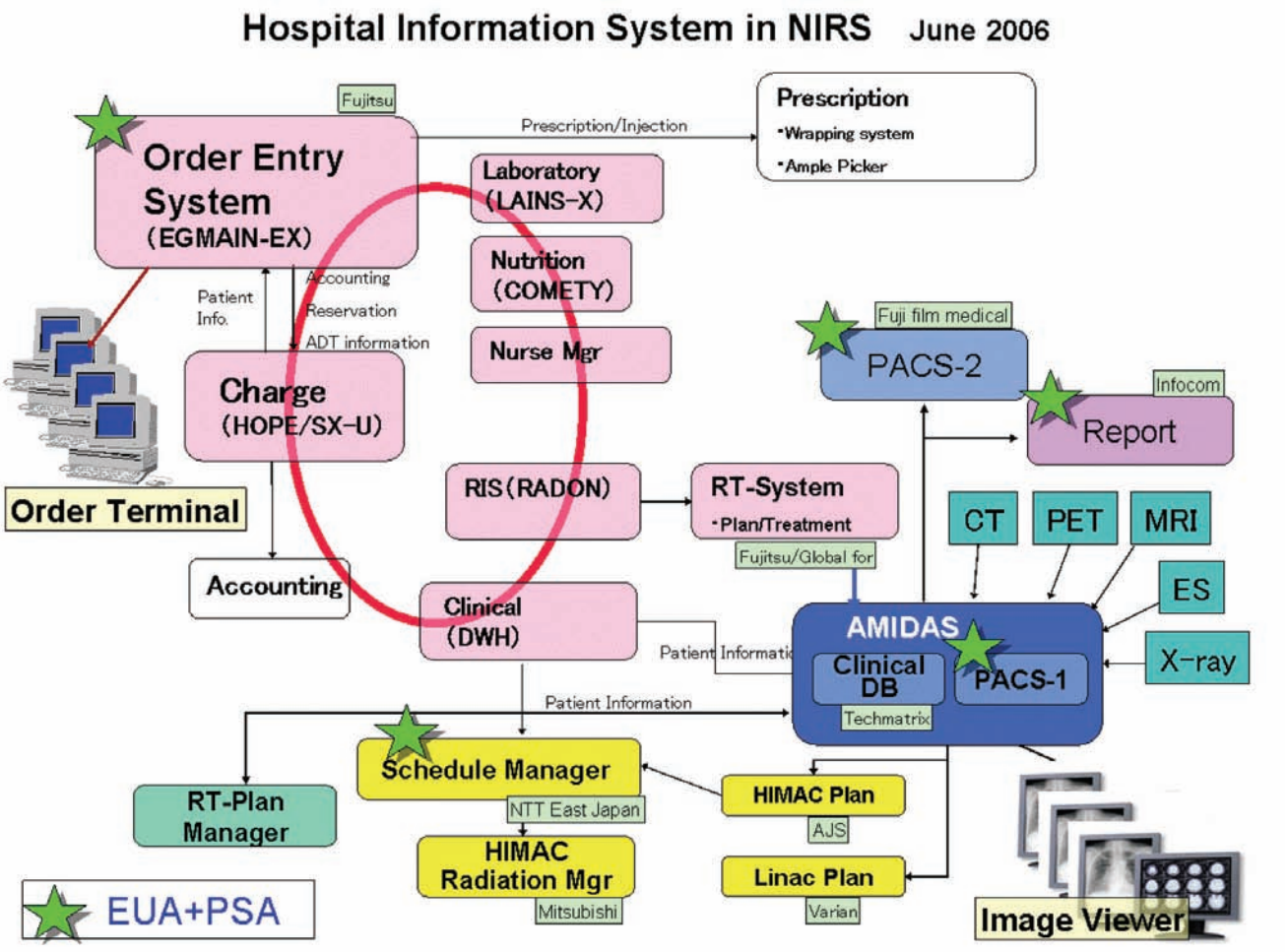

Fig 19. Hospital information system in NIRS June 2006

5.9. Medical Imaging Research and Associated Mission

Shuji Tanada, M.D.
Director, Department of Medical Imaging

Outline of Research Career:

Dr. Shuji Tanada received a doctor of medical sciences from Kyoto University in 1988 for his study on the role of positron emission tomography in evaluation of cerebral perfusion and metabolism in various pathological conditions in the human brain. He has had 29 years of experience in clinical research and practice on radiology, nuclear neurology and molecular nuclear medicine at Kyoto University, Ehime University and NIRS. Between 1985 and 1987 he was at the Johns Hopkins Medical Institutions, USA as a research fellow where he studied neurotransmission function using positron emitting radiopharmaceuticals and dedicated counting instruments. He has participated in the IAEA/RCA projects on nuclear medicine since 1998.

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Objectives

Medical imaging research and associated missions have been continuously conducted since the medical-use cyclotron was installed in the early 1970's and the first PET scanner was developed by NIRS in 1979. The major purpose of the research and missions is to contribute to the promotion of cancer radiotherapy and biological functional imaging with respect to neuroscience, oncology and cardiovascular science.

The purposes of the medical imaging research on PET/SPECT and NMR are development of molecular imaging technology for the visualization of biological functions and promotion of clinical applications.

In the field of PET/SPECT, different types of synthesis units coupled to the multi-purpose automated synthetic module were developed and a wide variety of PET radiopharmaceuticals labeled with ^{11}C, ^{13}N, ^{15}O and ^{18}F were synthesized automatically with the synthesis units. As new PET radiopharmaceuticals, ligands of [^{11}C]NMPA (dopamine D2), [^{18}F] FEtSPA-RQ(NK1), [^{61}Cu]Cu-ATSM (hypoxic cancer cells), [^{18}F]FEP4A(acetylcholine esterase), [^{18}F]FEP4MB (butylcholine esterase) [^{11}C]DAA1097, [^{11}C]EDAA1097, and [^{11}C]MDAA1097, [^{11}C]Ac5216 (peripheral benzodiazepine), [^{11}C]MTEP (mGluR5), [^{11}C]5Et-4HQ, [^{11}C]5I-4HQ (NMDA/glycine binding site) have been developed. By use of these ligands, the pathophysiology of neuro-psychological diseases such as dementia, schizophrenia and mood disorder as well as tumor was investigated. The feasibility to detect non-invasively a remodeling of myocardium after an incident of myocardial ischemia was verified using In-111 labeled anti-tenascin-C monoclonal antibody. This could be important for evaluation of the prognosis of patients with coronary heart disease. As a new attempt, we have started to survey lead compounds for *in-vivo* imaging of oxidative stress. In clinical research, a new project has been launched to visualize amyloid deposition in the brain of patients with Alzheimer's disease using ^{11}C-PIB (Pittsburgh Compound).

In the field of NMR, research and development have been conducted toward elucidation of pathophysiology in the brain, cancers and bone and soft tissue. ^{31}P-MR spectroscopy has been conducted in skeletal muscles of patients with non-hypoxaemic chronic obstructive pulmonary disease. In order to promote higher quality of measurements, we have developed a high-radiation-sensitive polymer gel for MRI 3D-dosimetry. In order to contribute to micro-imaging research, we have optimized the T_2-weighted sequences for surface coil microimaging of the human eye.

Regarding support for research conducted in the Medical Imaging Building and Cyclotron Facility, the production and quality assurance evaluations of short-lived PET radiopharmaceuticals have been continued for both clinical and animal experiment uses.

Progress of Research:

1) PET and SPECT related research

1.1) ^{11}C-labeled compounds

Three novel PET ligands, [^{11}C]DAA1097, [^{11}C]EDAA1097, and [^{11}C]MDAA1097 were synthesized by reaction of the precursor with [^{11}C]$(CH_3)_2$CHI, [^{11}C]CH_3CH_2I, and [^{11}C]CH_3I. These ligands were evaluated using the peripheral benzodiazepine receptor in the brain. Of these ligands, [^{11}C]MDAA1097 displayed a promising potential as an agonist for the receptor in the brain.

1.2) Excitation function measurement for the production of ^{76}Br and ^{124}I

Excitation functions were measured for the production of ^{76}Br and ^{124}I using natural Se and Te. Thin layer targets of Se and Te were prepared on thin Al foils by the vacuum evaporation method with Se and Te powder. Irradiation was performed on the stacked foils with 5 - 65 MeV protons from the NIRS AVF 930 cyclotron. Preparation methods of Se and Te alloys for the practical production of ^{76}Br and ^{124}I were also investigated.

1.3) Studies on development of new radiopharmaceuticals to measure biomolecular functions by using PET/SPECT

(A) In development of ^{18}F-radiopharmaceuticals targeting acetylcholinesterase (AChE) in the brain as a more convenient probe, a promising candidate probe, N-[^{18}F]fluoroethylpiperidin-4-ylmethyl acetate, was evaluated in monkey, which demonstrated the feasibility for estimating enzyme activities in the cortex by kinetic analysis.

(B) Concerning the development of PET radiopharmaceuticals to measure butyrylcholinesterase in the brain, new probes were selected which were hardly metabolized in lung on the basis of results of clinical studies of two known ^{11}C-radiopharmaceuticals.

(C) PET radioligands for NMDA receptors are being developed. The first human trial of [^{11}C]AcL-703, a glycine site ligand, indicated insufficient BBB permeability for PET imaging. Several C-11 labeled analogs of L-703,717 have been designed and evaluated to develop a high-affinity PET ligand with high BBB permeability. It was found that introduction of a basic amino group into L-703,717 reduces the unfavorable protein bindings in blood and therefore shows higher BBB permeability than [^{11}C]L-703,717.

(D) We have proposed that SPECT imaging by using radio-labeled anti-tenascin-C antibody is promising for molecular imaging of tissue remodeling based on studies using model rats for myocardial disorders. For enhancement of potency in the labeled- anti-tenascin-C antibody related to availability and safety in clinical applications studies for lowering molecular size of the antibody have been continued. One single strand Fv of anti-tenascin-C antibody (4F10), which was prepared previously, was confirmed for biding ability, and then was chemically modified to be labeled with radio-nuclides for SPECT.

(E) We have studied development of a tracer rationale and lead compounds for *in vivo* imaging of oxidative stress and found one promising lead compound. The relationship between the chemical structure and the kinetic behavior *in vivo* was investigated to provide us with a valuable basis for the design of effective radiotracers.

1.4) Studies on kinetic analysis of PET data and on clinical application in assessment of bio-functions with PET radiopharmaceuticals

(A) Related to establishment of quantitative image analysis in ^{11}C-MP4A and ^{11}C-MP4P /PET, the characteristics of the two methods were comprehensively elucidated for reliability (precision and certainty) in estimation of the local enzyme activity among different brain regions with a diverse enzyme activity.

(B) The clinical research studies using ^{11}C-MP4A/PET have been continued for assessment of the cholinergic alteration in the brain of demented patients and the therapeutic effect of AChE inhibitor on Alzheimer's disease. We can estimate IC50 of donepezil, a therapeutic Alzheimer drug, as efficacy of the action by assessment of the drug concentration in blood. A method was developed for preclinical evaluation of the efficacy of AChE inhibitors as a therapeutic Alzheimer drug using ^{11}C-MP4A/PET and monkey.

2. NMR related research

2.1) ^{31}P-MRS study in skeletal muscles of patients with non-hypoxaemic chronic obstructive pulmonary disease

An alteration of high energy phosphate metabolism in muscles may contribute to exercise intolerance. The objective of this study was to clarify the changes in high energy phosphate metabolites in muscles during exercise in patients with non-hypoxaemic chronic obstructive pulmonary disease (COPD), which influences the impairment of

muscle metabolism. Calf muscle energy metabolism was studied in eight stable non-hypoxaemic COPD patients and eight control subjects, using ^{31}P-magnetic resonance spectroscopy (MRS). MRS spectra were acquired at rest, during exercise at two levels of intensity, and during recovery. The control subjects exercised under both normoxic and hypoxic conditions. The intensity of exercise was standardized by the maximal isometric voluntary contraction (MVC) of the calf muscle and the cross-sectional area (CSA) of calf muscle.

MVC and CSA were lower in COPD patients. No significant differences in intracellular pH, inorganic phosphate/phosphocreatine ratio or percentage recovery in inorganic phosphate/phosphocreatine ratio was observed between the two groups in muscles at rest, during exercise or during recovery. Muscle metabolites, during exercise standardized by muscle CSA and MVC, did not differ between non-hypoxaemic COPD patients and control subjects. MVC, CSA or both, were assumed to be closely related to muscle metabolism, as no difference in high energy phosphate metabolites was observed for COPD patients compared to control subjects when the load was standardized for MVC and CSA. This suggests that high energy metabolites are consumed to a similar extent in the same muscle volume in non-hypoxaemic COPD patients and control subjects.

2.2) Study of functional network in the prefrontal cortex during episodic memory retrieval

A recent consistent finding in neuroimaging studies of human memory is that the prefrontal cortex (PFC) is activated during episodic memory retrieval. To date, however, there has been no direct evidence to explain how activities in the right and left PFC and in the anterior and posterior PFC are functionally interconnected. The goal of the present study was to obtain such evidence by event-related functional magnetic resonance imaging (MRI) and the functional connectivity method. Subjects were first asked to try to remember a series of associate-word lists outside the MRI scanner in preparation for a later recognition test. In the MRI scanning phase, they were asked to make recognition judgments in regard to old words, semantically related lure words, and unrelated new words. The analysis of functional connectivity revealed that the posterior PFC in each hemisphere had strong functional interconnections with the contralateral posterior PFC, whereas the anterior PFC in each hemisphere had only weak functional interconnections with the contralateral anterior PFC. No strong functional interconnections were found between the anterior and posterior PFC in either hemisphere. These findings support the hypothesis of an associative contribution of the bilateral posterior PFC to episodic memory retrieval and a dissociative contribution of the bilateral anterior PFC.

2.3) Development of high-radiation-sensitive polymer gel for MRI 3D-dosimetry

We developed a high radiation sensitive polymer gel by modifying the amounts of the gel components and the temperature for the gel preparation. We evaluated its relaxation time linearity against dose and compared the measured dose distribution with the calculated one. For the relaxation time-dose linearity, irradiations were carried out with a linear accelerator using 6MV photons and doses ranging from 0-5.0Gy. The relationship between dose and R_2 value (reciprocal of T_2 relaxation time) was measured and it had good linearity over a wide range (0.3-5Gy). The measured dose distributions were in good agreement with calculated ones. Since the present gel has higher sensitivity and it is synthesized more easily at lower cost than conventional polymer gels, we expect to see improved three-dimensional (3D) dosimetry using it.

2.4) Time course evaluation of reparative cartilage with MRI after autologous chondrocyte implantation

The aim of this study was to evaluate the qualitative change in reparative cartilage after autologous chondrocyte implantation (ACI). Ten knees of 10 patients were studied. The signal intensities of reparative and normal cartilage were evaluated by fat-suppressed three-dimensional spoiled-gradient recalled (FS 3D-SPGR) MR imaging. The signal intensity (SI) index (signal intensity of reparative cartilage divided by that of normal cartilage) was defined and the change in SI index was investigated. Histological and biochemical evaluation was done at the second look arthroscopy. The SI index was at its lowest level immediately after ACI and increased with time to 9 months thereafter. After 9-12 months, the SI index was maintained at that value for at least 2-3 years postoperatively. The average of the SI indexes after 12 months to the last examination was 74.2 ± 4.6 (range 64.2-82.8), which means signal intensity of reparative cartilage was maintained at a value lower than that of normal cartilage. The total ICRS score was 11.6 ± 2.3 points (mean ± SD). The GAG concentration was 107.9 ± 17.0 μg/mg (mean ± SD) in normal cartilage and 65.9 ± 9.4 μg/mg in reparative cartilage. The quality of reparative cartilage as hyaline cartilage was inferior to that of normal cartilage. In the present study, the time

course change in the SI index indicates that the major maturation process of implanted chondrocytes neared completion in 9-12 months. Minor changes, such as matrix remodeling with reorganization of the collagen fibers in reparative cartilage, may continue, but an almost identical condition seemed to be maintained during the first 2-3 years of follow-up. SI index does not always reflect all properties of reparative cartilage but may be a useful parameter for noninvasive evaluation.

2.5) Optimizing T_2-weighted sequences for surface coil microimaging of the eye

To acquire high-resolution magnetic resonance (MR) images, we developed a new blinking artifact reduced pulse (BARP) sequence with a surface coil specialized for microscopic imaging (47 mm in diameter). To reduce eye movement, we ascertained that the subjects' eyes were kept open and fixated to the target in the 1.5-T MR gantry. To reduce motion artifacts from blinking, we inserted rest periods for blinking (1.5 s within every 5 s) during MR scanning (T_2-weighted fast spin echo; repetition time, 5 s; echo time, 100 ms; echo train, 11; matrix, 256 x 128; field of view, 5 cm; 1-mm thickness x 30 slices). Three scans (100 s x 3) were performed for each normal subject, and they were added together after automatic adjustment for location to reduce quality loss caused by head motion. T_2-weighted MR images were acquired with a high resolution and a high signal-to-noise ratio. Motion artifacts were reduced with BARP, as compared with those with random blinking. Intraocular structures such as the iris and ciliary muscles were clearly visualized. Because the whole eye can be covered with a 1-mm thickness by this method, three-dimensional maps can easily be generated from the obtained images. The application of BARP with a surface coil of the human eye might become a useful and widely adopted procedure for MR microimaging.

Major Publications:

1) M-R Zhang, J Maeda, T Ito, T Okauchi, M Ogawa, J Noguchi, T Suhara, C Halldin, K Suzuki: Synthesis and evaluation of N-(5-fluoro-2-phenoxyphenyl)-N-(2-[^{18}F]fluoro methoxy-d2-5-methoxybenzyl)acetamide:a deuterium-substituted radioligand for peripheral benzodiazepine receptor. *Bioorganic & Medicinal Chemistry;* **13**: 1811-1818, 2005.
2) T Okamura, T Kikuchi, A Nagamine, K Fukushi, Y Arano, T Irie : An approach for measuring in vivo cerebral redox states using the oxidative conversion of dihydropyridine to pyridinium ion and the metabolic trapping principle. *Free Radical Biology and Medicine;* **38**: 1197-1205, 2005.
3) T Shiraishi, T Kikuchi, K Fukushi, H Shinotoh, S Nagatsuka, N Tanaka, T Ota, K Sato, S Hirano, S Tanada, M Iyo, T Irie: Estimation of plasma IC50 of donepezil hydrochloride for brain acetylcholinesterase inhibition in monkey using N-[^{11}C]methylpiperidin-4-yl acetate ([^{11}C]MP4A) and PET. *Neuropsychopharmacology;* **30**: 2154-2161, 2005.
4) T Hamaoka, H Ikehira, T Obata, S Tanada, Y Sasaki, et al : Metabolic activity in skeletal muscles of patients with non-hypoxaemic chronic obstructive pulmonary disease studied by P-magnetic resonance spectroscopy. *Respirology;* **10 (2)**: 164-170, 2005.
5) T Obata, K Uemura, H Nonaka, M Tamura, S Tanada, H 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**: 97-101, 2006.

5.10. Electron Density Measurements with Dual-Energy X-ray Computed Tomography

Masami Torikoshi, Ph.D.,
Department of Accelerator Physics and Engineering.

Outline of Research Career:

Dr. Torikoshi received a Ph. D. from Tohoku University in 1983 for his study in nuclear spectroscopy of the pion-photo-production reaction in carbon. He has had 11 years experience at NIRS in research and development on the accelerator and irradiation systems of HIMAC and research on medical applications of synchrotron radiation.

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Objective:

Electron density distribution in a body is indispensable for treatment planning of radiotherapy for cancer. More precise treatment planning requires more accurate electron density. At present, a CT-number obtained in CT-scanning is converted to the electron density under the assumption that the CT-number is proportional to the electron density. It should be, however, noted that the beam-hardening effect and deviation from the proportionality inevitably give rise to an error of a few percent in the electron density. Instead, direct measurement of the electron density using monochromatic x-rays could remove the error from the electron density.

Progress of Research:

1) Progress during five years

We proposed a CT-scanning method using dual-energy x-rays generated from synchrotron radiation, and started a feasibility study of the dual-energy X-ray CT (DXCT) in 2001. The first study was aimed at proving that the electron density could be precisely and quantitatively measured in DXCT. For this we developed a one-dimensional scanning system that had a much wider dynamic range than a conventional imaging device. In 2002, we proved that the electron densities of phantom materials were measured at about 1 % accuracy in experiments carried out at Spring-8 and KEK PF-AR. We also set about developing a two-dimensional CT system with a high frame rate scintillator array. During 2002 and 2003, many biological samples, rats and porcine organs, were used for experiments carried out at Spring-8. These experiments provided many images. There are three kinds of images: one as a linear attenuation coefficient, one as an electron density and one as an effective atomic number. In particular, the last image is one of features of DXCT, it is a by-product obtained when reconstructing the electron density image. We found that the image included interesting information on the object, which differed from that of the electron density image. This means that a thing seen in the electron density image is invisible in the effective atomic number image, and vice versa. There seemed to be a potential for this as a new method for not only medical diagnosis, but also other fields. From 2003 to 2004 a filtration technology was developed for the DXCT scanning to obtain more quantitative information. In 2005 we successfully formed a vertically magnified radiation field employing the asymmetry crystal method to scan a large sample. Eventually, we obtained a radiation field of about 50 mm × 250 mm. This technique required very careful tuning, so it took a while to obtain the field we expected. More technical developments are needed to use this method in practical applications.

A study of multi-energy x-ray CT (MXCT) has been running in parallel with the DXCT study. MXCT is an extension of DXCT and it is essential to realize a practical system. From 2001 to 2003, we were developing a method we proposed in 2000 that used mixed energy beams instead of dual-energy x-ray beams. This concept has been extended to MXCT. In the study we used synchrotron radiation beams consisting on a few energy components. We started study of MXCT in 2004 with a 64-channel CdTe detector array which had an

ability for energy resolving. The experiments were carried out at KEK PF-AR. We obtained promising results in the MXCT but at the same time we found several technical problems to be solved.

2) Annual Progress

In the study of DXCT we produced a magnified radiation field to take images of large samples. We employed an asymmetric Bragg geometry which was formed using a pair of silicon crystals, one had a symmetric reflection plane and the other had an asymmetric reflection plane. In this method a line like radiation field was vertically magnified by about six times for a 40 keV x-ray beam and about three times for 70 keV. Finally the radiation fields of 50 mm × 250 mm and 30 mm × 250 mm for 40 keV and 70 keV x-ray beams, respectively, were obtained. These fields helped us take images of the whole body of a sample in a short time. But it took time to tune the crystals and careful manipulation was required. The system of the DXCT was mentioned in the annual report of 2004. A few kinds of porcine tissues were used as samples: brains, kidneys and eyes. Fig.20 shows three dimensional CT images of porcine eyes; the upper drawing shows the electron density image and the lower drawing shows the atomic number image. The former clearly depicts the edge of the eyeball.

Since synchrotron radiation needs a large light source, it is not suitable for installation in a hospital. If the information on photon energy is taken during CT scanning, the polychromatic x-rays can be regarded as a set of many monochromatic x-rays. We have proposed a photon counting method with the 64-channel CdTe array for the MXCT. In the method many monochromatic x-rays were separately detected in CT-scanning and CT images were reconstructed using counts collected in individual energy regions. Therefore, two scannings were not necessary. The experiments were carried out at KEK PF-AR. A few physical and biological samples were used to verify the validity of the method. Physical samples such as water, ethanol and a solution of chemical compounds indicated that the MXCT had a potential to provide not only quantitative information about the electron density but also more extensive information on chemical structure of an object. We showed experimentally that the photon counting method could be valid for MXCT and the energy resolution was one of the most important factors. We concluded that the method we proposed and developed was feasible for MXCT.

Major Publications:

1) Torikoshi, M., Tsunoo, T., Endo, M., Noda, K., Kumada, M., Yamada, S., Soga, F. and Hyodo, K.: Design of synchrotron light source and its beamline dedicated to dual-energy x-ray computed tomography, *J. Biomed. Opt.* **6**, 371-377, 2001.
2) Torikoshi, M., Tsunoo, T., Sasaki, M., Endo, M., Noda, Y., Ohno, Y., Kohno, T., Hyodo, K., Uesugi, K. and Yagi, N.: Electron density measurement with dual-energy x-ray CT using synchrotron radiation, *Phys. Med. Biol.* **48**, 673-685, 2003.
3) Tsunoo, T., Torikoshi, M., Sasaki, M., Yagi, N. and Uesugi, K.: Distribution of Electron Density Using Dual-Energy X-Ray CT, *IEEE Trans. on Nucl. Sci.*, **50**, 1678-1682, 2003.
4) Ohno, Y., Torikoshi, M., Tsunoo, T., and Hyodo, K.: Dual-Energy X-ray CT with CdTe Array, *Nucl. Instrum. Meth., A* **584**, 72-77, 2005.
5) Torikoshi, M., Tsunoo, T., Ohno, Y., Endo, M., Natsuhori, M., Kakizaki, M., Nobuhiko Ito, N., Uesugi, K., and Yagi, N. : Features of dual-energy x-ray computed tomography, *Nucl. Instrum. Meth., A* **584**, 99-105, 2005.

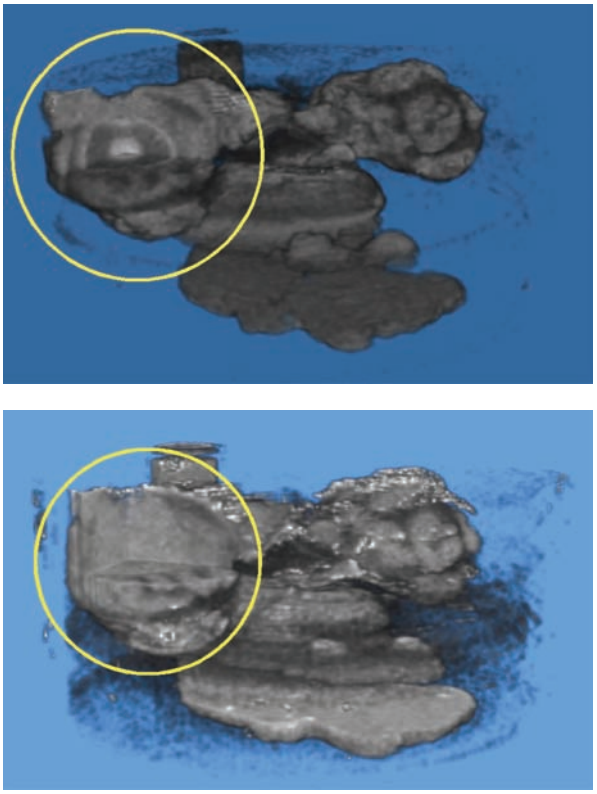

Fig 20. Three-dimensional images of porcine eyes. The top shows the electron density image and the bottom shows the effective atomic number image. The edge of the eyeball is clearly seen in the left image.

5.11. Study of Dose Estimation and Protection of Patients and Medical Staff from Medical Radiation

Kanae Nishizawa, Ph.D.
Head of medical exposure assessment section, Department of medical physics, Research Center for Charged particle Therapy

Outline of Research Career:

Dr. Nishizawa received a Ph.D in 1985 for her study on dose estimation of patients in X-ray examinations. She has 29 years of experience in research and development on dose estimation in medical exposure and occupational exposure while on the medical staff at Kyorin University and at NIRS. In 1996, she was at the Radiation Protection Institute of Sweden as a visiting scientist where she studied dose measurement in mammography and CT examinations.

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Objectives:

It is a fundamental standpoint of ICRP that there is no dose limit for medical exposure because of the direct merit for patients irradiated. However, optimization is not always enough. There must be an optimized dose balancing image quality and exposed dose in diagnostic examinations. In addition, the technical progress in peripheral equipment and techniques can reduce the optimized dose. From this point of view, the purposes of our study were to estimate the doses of patients from medical exposure in investigating the optimized dose range, and to reduce the doses of medical staff. In FY2005, we estimated the doses of patients from multi-row CT (MDCT) examinations progressing multiplication of detector-rows and their applications in radiology. A nationwide survey on radiation therapy was also made. We have continued to study the exposure estimation method of patients and staff in Interventional Radiology. We received co-operation from many medical facilities for exposure measurements and surveys concerning the use of medical radiation.

Progress of Research:

1) Dose estimation and protection against medical radiation

The organ doses of patients from various MDCT devices having no less than 4 detector-rows were measured using adult and child phantoms made of tissue equivalent materials. The development and spread of MDCT has been remarkable, and more than 2,600 machines were already in used by autumn of 2005. Presently, 45% of MDCT devices are 4 detector-rows CT machines. However, there is a tendency for use of 16 detector-rows CT to increase, and 64 rows and 256 detector-rows CT have begun to be sold. Various combinations of irradiation condition parameters are possible, so that exposures of patients could differ. We studied clinical needs, optimized image qualities and doses with the cooperation of staff at many medical facilities. For dose measurements, small dosemeters (glass and TLD) were used. Based on the measured data, effective doses of patients were estimated. It has been a long time since X-ray CT machines were used for chest mass screenings for the first time, and the cases using MDCT in the screenings have been increasing recently. A manual concerned with QA/QC of MDCT was prepared three academic associations related to medical radiation to establish an adequate examination method for mass screening in which many healthy persons would be examined. In the process of making the manual, we contributed to establishment of the dose estimations part. The fundamental experiments of CTDI for applying MDCT have been continued. To estimate doses of patients using CTDI, computer simulations have also been continued using PMMA and voxel phantoms, and quantitative data on various conditions were obtained.

2) Survey of medical exposure

In FY2005, a nationwide survey concerned with

radiation therapy was done. There are 800 medical facilities having a radiation therapy section, and all of them were targets of the survey. Sex, age, therapy target region, radiation quantity and so on of the patients receiving radiation therapy using irradiation instruments (sealed radioisotopes such as Ra needles) or equipment (X-ray, Cobalt and Linear accelerators) were investigated for one month and totaled for the year by mailing a questionnaire to the facilities. Among 800 facilities, about 60% replied.

3) Results

The doses of the patients in X-ray CT examinations depend on the machine used and conditions. In fact, the doses can vary by several times for the same kind of machines. In mass screening healthy persons are also examined, so lower doses and good image qualities are required. The same problem exists in MDCT examinations which are being introduced into mass screening. To confirm the differences of doses among the same kind of MDCT machines, we measured the does of three 4-rows CT as mostly distributed machines in mass screening. The difference in introduction year into screenings of these machines was 3 years. The conditions of the measurements are shown in Table 6. Condition 1 was used in general chest examinations, and 2 was used in mass screenings. The differences were current and pitch. Table 7 shows the doses of main organs for each condition. The doses for the mass screening condition were reduced to be about one fifth those for the general condition for each machine. But, organ doses for the general condition differed 30 − 35% between A and C machines, resulting in 3% difference of effective doses. The tendencies were similar for both conditions 1 and 2. It is difficult to interpret the difference among machines as not significant. It could be explained as improvement of machines, however, the improvement should be considered for machines which have already been introduced.

Table 6. Conditions of Chest Exam.

	Condition	1	2
Voltage	kV	120	120
Current	mA	200	30
Exposure time	sec/rot	0.75	0.75
Feed	mm/rot	20	27.5
Total scan time	sec	14.2	11.25
Beam width	mm	16	20
Pitch		1.25	1.375
Detector	mm x rows	4mm x 4	5mm x 4
Exposure area	All lungs	30cm	30cm

Table 7. Comparison of Organ Doses (mGy)

	Condition	1			2		
Organ	Machine	A	B	C	A	B	C
Red bone marrow		7.79	7.14	5.74	1.02	0.92	0.74
Lungs		23.7	21.2	16.9	2.92	2.43	1.97
Stomach		22.4	17.0	14.5	3.07	2.15	1.74
Breast		22.5	15.0	12.1	2.33	1.99	1.47
Liver		22.5	16.9	13.7	2.85	1.99	1.69
Esophagus		23.3	19.0	16.3	3.00	2.54	1.91
Thyroid		30.9	30.2	22.2	3.76	3.93	2.83
Effective Dose (mSv)		13.3	11.2	8.99	1.72	1.41	1.12
Mean skin dose		23.8	19.1	15.0	3.28	2.49	2.11

6. Brain Imaging Project

Tetsuya Suhara, M.D., Ph.D.
Director, Department of Molecular Neuroimaging, 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 began to work at NIRS in 1989. In 1992-1993, he studied in the PET group of the Department of Clinical Neuroscience, Karolinska Hospital, Sweden. He has researched on brain functional imaging for a long period. He serves as a visiting professor in the Department of Neuropsychiatry, Nippon Medical School from 2004, and in the Graduate School of Medicine, Yokohama City University from 2006.

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Objectives:

1.Neuroimaging Research

1) Clinical research: The mechanism of mental disorders
   Abnormal inter-regional connectivity has been reported in neurophysiological studies of schizophrenia. Dopamine systems interact with several other neurotransmitter systems with direct or indirect synaptic connections, and aberrant interactions among different neural networks could lead to an unusual inter-regional dopaminergic tone.
2) Neuropsychopharmacological research
   Studies on imaging of neurotransmission were conducted in search of molecular interactions that critically modulate the release of dopamine in the striatum.
3) Generation of animal models of neuropsychiatric disorders
   Our aim in establishment of *in vivo* systems modeling neurological and psychiatric conditions was to construct an experimental paradigm for comprehensive investigations of neurodegenerative disorders including Parkinson's disease, on pharmacological, behavioral and histopathological bases.
4) Development of novel PET tracer
   Exploitation of imaging agents included radiosynthesis and characterization of [^{18}F]SPA-RQ, a newly produced radioligand for visualizing neurokinin 1 receptors, which are major binding sites for substance P neuropeptide in the brain. The primary focus of the present assessment was elucidation of diversity in the pharmacokinetics and pharmacodynamics of the radiotracer among species ranging form small rodents to non-human primates. Additionally, evaluation of radiolabeled agonist for dopamine D2 receptor, was also planned to be performed by using animal PET.

2.Neurogenetic Research

A genetic screen for mutations, which were induced by ENU (N-nitroso-N-ethylurea) or X-rays in the medaka (Oryzias latipes), has identified many mutants that exhibit deformities in the brain morphogenesis and abnormalities in behaviors. These mutants are thought to have mutations in the genes that play important roles in the brain formation and brain functions.

3.Brain Toxicological Research

The studies have been performed to elucidate the mechanisms of irradiation-induced brain damage and to find protective methods (compounds) against this damage.

4.Imaging Research of Gene Expression

We have studied the methodology to detect iNOS gene expression in cellular and individual animal levels using an expression vector containing the iNOS promoter sequence and the dopamine D2 receptor gene.

Progress of Research:

1.Neuroimaging Research

1) Clinical research

Connectivity of regional D2R in schizophrenia

A number of morphological and neurochemical abnormalities have been found to characterize schizophrenia. In particular, the dopamine D2 receptor has been investigated extensively, since the chronic use of amphetamine can cause psychotic symptoms and dopamine D2 receptor antagonists are the most widely used drugs for the treatment of schizophrenia. On the other hand, abnormal inter-regional connectivity has been reported in neurophysiological studies of schizophrenia. Dopamine systems interact with several other neurotransmitter systems with direct or indirect synaptic connections, and aberrant interactions among different neural networks could lead to an unusual inter-regional dopaminergic tone. In this study, we investigated the connectivity of regional dopamine D2 receptor binding in PET data from 10 drug-naive patients with schizophrenia and 19 healthy controls. We applied a structural equation method to evaluate the connectivity of regional D2 receptor binding in schizophrenia patients and normal controls. By this method, the inter-regional correlations of D2 receptor binding were decomposed to assign numerical weights (path coefficients) to the anatomical connections. This computational method allows for the assessment of changes in the inter-regional associations of entire systems. The results indicated that the network models of the patients and normal subjects were significantly different. As to the individual path coefficients, (a) connectivity between cortical regions was different between groups; (b) connectivity from the prefrontal cortex, parietal cortex, and thalamus to the anterior cingulate differed from that in controls; and (c) connectivity from the prefrontal cortex to the anterior cingulate and thalamus via the hippocampus was observed in normal subjects but not in patients. These results suggest that a systems-level change reflected in the connectivity of D2 receptor binding is present in schizophrenia.

Appropriate dosage setting of antipsychotics by PET research

Conventional antipsychotics tend to elicit extrapyramidal symptoms at clinical doses, but dose optimization could reduce the risk of such side-effects. *In-vivo* receptor-binding studies have suggested that 70-80% of dopamine D2 receptor occupancy provides the desired antipsychotic effects without extrapyramidal symptoms (EPS). In terms of dose optimization based on the occupancy, there has not been enough supporting data regarding the clinical doses of the respective antipsychotics.

Although two conventional benzamide antipsychotics, sulpiride and sultopride, are prescribed at similar doses (300-1200 mg), and their clinical potency is considered to be equivalent, sultopride has been reported to induce more EPS than sulpiride.

In this study, we measured extrastriatal dopamine D2 receptor occupancy of sulpiride and sultopride using PET, to investigate the rationale of their clinical dose.

Subjects were 21 male healthy volunteers. PET scans were performed with [11C]FLB 457 before and after a single administration of several doses of sulpiride or sultopride. Quantification of dopamine D2 receptor binding potentials was done with the simplified reference tissue model. Dopamine D2 receptor occupancies were calculated using binding potential. Although dopamine D2 receptor occupancy increased as the dose increased for both drugs, the doses required to obtain similar receptor occupancy (70-80%) were quite different: 1010-1730 mg for sulpiride but 20-35 mg for sultopride. In terms of dose, sultopride has about 50 times greater potency than sulpiride based on dopamine D2 receptor occupancy. The calculated optimal dose range for sulpiride overlapped with the upper range of the registered clinical doses. On the other hand, the registered clinical doses of sultopride were about 10 times higher than the calculated optimal doses. The present results suggest that a much lower dose of sultopride would be sufficient to treat psychotic symptoms.

Appropriate dosage setting of conventional antipsychotics based on dopamine D2 receptor occupancy would be helpful for rational antipsychotic therapy.

2) Neuropsychopharmacological research

More reliable measurement of endogeneous striatal dopamine by novel D2 agonistic PET tracer

Radiolabeled agonist for dopamine D2 receptor was employed to quantitatively monitor alterations in the release of endogenous dopamine subsequent to administration of potential direct and indirect modulators of dopaminergic neurotransmission. Measurements were done by performing PET scans for awake monkeys and rats, and then estimating specific binding of the radiotracer to the striatal D2 receptors.

In addition, changes in the radioligand binding in these animals after administration of methamphetamine, a potent modifier of the dopamine release, were detected in a reproducible

manner. Hence, the new agonistic tracer was conceived to facilitate reliable estimation of endogenous dopamine present in the synaptic cleft.

3) Generation of animal models of neuropsychiatric disorders

Prediction of dopaminergic dysfunction in the animal model of Parkinson's disease with PET

A new experimental system for quantifying presynaptic and postsynaptic dopaminergic neurotransmission in nigrostriatal neurodegeneration recapitulating Parkinson's disease was constructed by carrying out PET scans with [^{11}C]raclopride (antagonistic radioligand for dopamine D2 receptor) and [^{11}C]PE2I (radioligand for dopamine transporter) in conjunction with behavioral tests for the same rat in the time course following unilateral injection of 6-OHDA into the medial forebrain bundle. Alterations of dopamine transporter and D2 receptor, as assessed by the binding of the radiotracers, were tightly correlated with the dose of 6-OHDA administered to each rat, while the dopamine transporter was more vulnerable to lesioning than was the D2 receptor, producing a partial discrepancy between presynaptic and postsynaptic changes in pathophysiological circumstances. Methamphetamine-induced rotational behaviors, which reflects laterality of dopaminergic functions, was observed in the rats injected with 6-OHDA at relatively high doses, and was thus indicated to emerge as a consequence of severe impairments in the presynaptic elements of dopaminergic neurotransmission. There revelations provide a mechanistic basis for motor deteriorations in Parkinson's disease, and clarify the utility of PET studies on multiple components of neurotransmission combined with behavioral assays.

4) Development of novel PET tracers

Establishment of two novel tracers

Protocols to robustly synthesize [^{18}F]SPA-RQ and an agonistic radioligand for dopamine D2 receptor were established, and pharmacological evaluation of these tracers by applying them to PET and autoradiographic measurements for brains of rodents and non-human primates is currently going on. Radioligand for noradrenalin transporter was also successfully produced in a series of pilot experiments, and several remaining technical issues, which are relatively minor, are being figured out.

2.Neurogenetic Research

We have started positional cloning of several medaka mutants in order to identify these genes and to understand the gene functions. The selected mutants were who (white out), tac (tacobo), act (albino with cloudy tectum), and gac (growing act). All of the mutations were genetically mapped at each chromosome, and several candidate genes were isolated. We found that who mutant, which shows a hypochromic anemia and an unusual swimming behavior at later stages, was caused by a mutation in the gene for δ-aminolevulinic acid dehydratase (ALAD). This is the first successful positional cloning of the medaka induced mutants. who mutants represent a model for the human disease, ALAD-deficiency porphyria. Another mutant, tac, which exhibits a short body length and smaller brain subdivisions, was caused by a mutation in the gene lamγ1, which plays a role in laminin formation. The mutants, act and gac were genetically mapped at linkage groups (LG), LG 15 and LG 14, respectively.

3.Brain toxicological Research

The protective effects of a free radical scavenger on brain tissue injury induced by heavy-ion irradiation were investigated. The left cerebral hemispheres of Sprague-Dawley rats were irradiated at a dose of 100Gy with charged carbon particles (290 MeV/nucleon, 5mm spread-out Bragg peak). Some rats were administered with a free radical scavenger, MC-PROXYL, just before irradiation. After irradiation, a conventional behavioral test and histological examination of the brain were done. The results showed that behavioral changes in walking patterns and rotation when suspended by their tail were observed at 8 week after irradiation, and the distinctive histological changes like necrosis, vascular dilation and tissue swelling at the irradiated region were also induced around 8 weeks after irradiation. Irradiation-induced histological and behavioral changes were mitigated in most rats that were injected with the free radical scavenger.

4.Imaging Research of Gene Expression

Two types of expression vector were prepared: iNOS promoter + D2 receptor and iNOS promoter + D2 receptor + EGFP. They were transfected to rat glyoma cells (C6) and macrophage cells (Raw264.7) and the clones responding to LPS and INF-γ were selected. The EGFP expression in Raw264.7 cells measured by fluorescent microscopy and flow cytometry showed that the fluorescence intensity increased 2-5 times after stimulation with LPS and INF-γ. In contrast, expression of D2R mRNA and protein in C6 cells measured by RT-PCR and Western blotting, respectively, was not significantly affected by the stimulation. These findings suggest that C6 cells transfected with the construct containing D2R receptor sequence are not suitable

for *in vivo* PET detection of iNOS expression in rats.

Major Publications:

1) Inaji M., Okauchi T., Ando K., Maeda J., Nagai Y., Yoshizaki T., Okano H., Nariai T., Ohno K., Obayashi S., Higuchi M., Suhara T. Correlation between quantitative imaging and behavior in unilaterally 6-OHDA-lesioned rats. *Brain Res,* **1064**:136-145, 2005.
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3) Takano A., Suhara T., Yasuno F., Suzuki K., Takahashi H., Morimoto T., Lee Y.J., Kusuhara H., Sugiyama Y., Okubo Y. The antipsychotic sultopride is overdosed - a PET study of drug-induced receptor occupancy in comparison with sulpiride. *Int J Neuropsychopharmacol,* **9**:1-7, 2005.
4) Yasuno F, Suhara T, Okubo Y, Ichimiya T, Takano A, Sudo Y, Inoue M. Abnormal effective connectivity of dopamine D2 receptor binding in schizophrenia. *Psychiatry Res,* **138**:197-207, 2005.
5) Yamamoto N., Ishikawa Y., Yoshimoto M., Xu H-G, Bahaxar N., Sawai N., Yang C-Y, Ozawa H., Itou H. A new interpretation on the homology of the teleostean telencephalon based on hodology and a new eversion model. *Brain Behav Evol,* in press.

7. Frontier Research Center
RadGenomics Project

Hajime Murata, M.D., Ph.D.
Supervisory Director

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

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Takashi IMAI, Ph.D.
Director

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. Since 1994 he has been a senior researcher at NIRS. In 2001 he was named project leader of the RadGenomics Project.

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Objectives:

Cancer patients vary considerably in normal tissue reactions after radiotherapy. Several observations have indicated that certain genetic factors play important roles in this variability. It has been hypothesized that the clinical radiosensitivity of normal tissues should be regarded as a so-called complex trait dependent on the cumulative effect of many minor genetic determinants. Thus single nucleotide polymorphisms (SNPs) on certain genes may somehow associate with the severity of normal tissue reactions after radiotherapy. It is important to uncover a molecular basis underlying radiation sensitivity of normal tissues for further investigation of 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 1,834 patients who were registered between 2001 and 2006 included 699 breast cancer patients, 251 cervical cancer patients, 324 prostate cancer patients, and 268 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.

Optical detection system for allele-specific extension of oligonucleotides immobilized on a plastic chip

Single nucleotide polymorphisms (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 are selected in advance in large scale association studies.

A novel optical detection system for on-chip allele-specific primer extension was developed to conveniently genotype multiple SNPs. This method used selective incorporation of biotin-modified deoxynucleotide by allele-specific extension reaction with oligonucleotides immobilized on a plastic chip and provided simplification of experimental procedures and reduction of reaction time to as short as 10 minutes at a constant temperature of 65 ^{o}C. The methodology is easily carried out at reasonable running cost with regular laboratory instruments.

Inter-strain variance in late phase of erythematous reaction or leg contracture after local irradiation among three strains of mice

To gain insights into inter-strain differences in radiosensitivity, mice of inbred strains, A/J, C57BL/6J, and C3H/HeMs, were irradiated at graded doses ranging from 20-60 Gy. Skin reaction and leg contraction were observed for a period of 230 days and between 175-350 days, respectively. Gene expressions in leg skin tissue were quantified by quantitative RT-PCR assay at 1, 12 and 72 hour after 30 Gy irradiation. The three strains showed various degrees of susceptibility to irradiation as evaluated by skin scores. Large inter-strain differences were also detected in the lengths of contraction. Expressions of several genes such as Per3 and Rad51ap1 displayed inter-strain differences. We concluded that the continuum model of tissue injury revealed that genetic factor, which varies among strains, is one of the causes of variances in severity of damage after irradiation.

Strain-dependent differences in locomotor activity after local brain irradiation with 30 GyE of carbon ions

This study investigated strain differences in brain damage among male A/J, C57BL/6JNrs and C3H/HeNrs mice after local brain irradiation. Whole brains were irradiated with a single dose of 30 GyE carbon ion beams and then locomotor activity was determined as body heat of each animal. The daily locomotor activities of untreated mice differed among strains. Non-irradiated C57BL/6JNrs mice were more active than A/J mice. This variance became more obvious immediately after irradiation, when the activity of A/J and C3H/HeNrs mice diminished, whereas that of C57BL/6JNrs mice increased at the beginning of the active phase and remained elevated for three days after irradiation. The altered activities of all three strains of irradiated mice gradually recovered to normal within three to four days.

DNA repair capacity measured by high throughput alkaline comet assays in EBV-transformed cell lines and peripheral blood cells from cancer patients and healthy volunteers

We collected peripheral blood (PB) from 556 patients with various types of cancer who had undergone radiotherapy and from 81 healthy volunteers. We exposed whole PB and Epstein-Barr virus-transformed lymphoblastoid cell lines (EBLs) derived from the PB mononucleocytes to X-ray irradiation (5 Gy). Using the alkaline comet assay, we measured the immediate DNA damage and, at 15 min, the % residual damage. In PB, the immediate damage was similar in patients and healthy volunteers while the % residual damage (mean +/- S.D.) was significantly higher in patients with breast (54.3 +/- 23.9), cervical (54.7 +/- 23.9), head/neck (56.8 +/- 24.4), lung (60.1 +/- 23.5), or esophageal cancers (59.5 +/- 33.7) than in healthy donors (42.9 +/- 19.6) ($P < 0.05$). We did not observe such differences in the EBV-transformed cell lines. Thus, radiation sensitivity of fresh PB cells measured by the alkaline comet assay was related to cancer status.

Gene expression profile changes correlating with radioresistance in human cell lines

To identify gene expression profiles specific to radioresistance of human cells, global gene expression profiles of a total of 15 tumor and normal fibroblast cell lines were analyzed using DNA microarrays and statistical clustering methods. Initially, six of the cell lines were categorized into radioresistant (RG) or nonradioresistant (NRG) groups according to the radiation dose required to reduce their survival to 10% (D_{10}). Genes for which expression was specific to each group at 1 or 3 h after irradiation were identified using statistical procedures including analysis of variance and a two-dimensional hierarchical clustering method. The remaining nine cell lines were subjected to the k-nearest neighbor pattern classification. The nine test cell lines were successfully classified by their D_{10} value using 46 and 44 genes for which transcription levels had significantly changed at 1 and 3 h after irradiation, respectively. Of these genes, 25 showed altered expression at both time points in the NRG or RG, but independently it was not possible to classify the test cell lines. These results suggested that radioresistant cell lines showed certain radiation-induced changes in gene expression profiles that are different from the profile changes of the more-sensitive cell lines.

Potential in a single cancer cell to produce heterogeneous morphology, radiosensitivity and gene expression

Morphologically heterogeneous colonies were formed from a cultured cell line (KYSE70) established from one human esophageal carcinoma tissue. Two subclones were separated from a single clone (clone13) of KYSE70 cells. One subclone (clone13-3G) formed mainly mounding colonies and the other (clone 13-6G) formed flat, diffusive colonies. X-ray irradiation stimulated the cells to dedifferentiate from the mounding state to the flat, diffusive state. Clone 13-6G cells were more radiosensitive than the other 3 cell lines. Clustering analysis for gene expression level by oligonucleotide microarray demonstrated that in the radiosensitive clone13-6G cells, expression of genes involved in cell adhesion was upregulated, but genes involved in the response to DNA damage stimulus were downregulated. The data demonstrated that a single cancer cell had the potential to produce progeny heterogeneous in terms of morphology, radiation sensitivity and gene expression, and irradiation enhanced the dedifferentiation of cancer cells.

Radiation sensitivities of 31 human esophageal squamous cell carcinoma cell lines

The purpose of this study was to determine the radiosensitivities of 31 human oesophageal squamous cell carcinoma cell lines with a colony-formation assay. A large variation in radiosensitivity existed among 31 cell lines. Such a large variation may partly explain the poor results of radiotherapy for this cancer. One cell line (KYSE190) demonstrated an unusual radiosensitivity. Ataxia-telangiectasia-mutated (ATM) gene in these cells had five missense mutations, and ATM protein was truncated or degraded. Inability to phosphorylate Chk2 in the irradiated KYSE190 cells suggests that the ATM protein in these cells had lost its function. The dysfunctional ATM protein may be a main cause of unusual radiosensitivity of KYSE190 cells. Because the donor of these cells was not diagnosed with ataxia telangiectasia, mutations in ATM gene might have occurred during the initiation and progression of cancer. Radiosensitive cancer developed in non-hereditary diseased patients must be a good target for radiotherapy.

A fast, simple method for screening radiation susceptibility genes by RNA interference

Radiotherapy can cause unacceptable levels of damage to normal tissues in some cancer patients. To understand the molecular mechanisms underlying radiation-induced physiological responses, and to be able to predict the radiation susceptibility of normal tissues in individual patients, it is important to identify a comprehensive set of genes responsible for radiation susceptibility. We have developed a simple and rapid 96-well screening protocol using cell proliferation assays and RNA interference to identify genes associated with radiation susceptibility. We evaluated the performance of alamarBlue-, BrdU-, and sulforhodamine B-based cell proliferation assays using the 96-well format. Each proliferation assay detected the known radiation susceptibility gene, PRKDC. In a trial screen using 28 shRNA vectors, another known gene, CDKN1A, and one new radiation susceptibility gene, ATP5G3, were identified. Our results indicate that this method may be useful for large-scale screens designed to identify novel radiation susceptibility genes.

Major publications:

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2) Mayumi Iwakawa, Miyako Gotou, Shuhei Noda, Masashi Sagara, Shigeru Yamada, Naohito Yamamoto, Yoshihiro Kawakami, Yoshifumi Matsui, Yukimasa Miyazawa, Hideya Yamazaki, Hiroshi Tsuji, Tatsuya Ohno, Junetsu Mizoe, Hirohiko Tsujii, Takashi Imai: DNA repair capacity measured by high throughput alkaline comet assays in EBV-transformed cell lines and peripheral blood cells from cancer patients and healthy volunteers. *Genetic Toxicology and Environmental Mutagenesis : A Section of Mutation Research,* **588(1)**:1-6, 2005.
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5) Atsushi Tsuji, Hitomi Sudou, Aya Sugyo, Marika Ohtuki, Makoto Miyagishi, Kazunari Taira, Takashi Imai, Yoshinobu Harada: A Fast, Simple Method for Screening Radiation Susceptibility Genes by RNA Interference. *Biochem. Biophys. Res. Commun.*, **333**: 1370-1377, 2005.

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

Masumi Abe, Ph.D.
Supervisory Director
Transcriptome Research Center
(HiCEP Center)

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.

Aims in 2005 were:

1) Developing a high throughput system for the HiCEP reaction and for the information analysis

a) Reaction steps (RNA prep, cDNA synthesis, HiCEP reaction and PCR): Development of a experimental automatic machine ver2 for the HiCEP reaction, which enables us to perform 96 reactions / 3 days.

b) Step for the information analysis: Development of software to compare expression profiles comprehensively, rapidly and efficiently.

2) Developing a procedure for the analysis using a small number of cells: an analytical method for 50 to 100 eukaryotic cells and a routine system using 1,000 cells.

Results

1) High throughput system

a) We made a HiCEP protocol for an automatic reaction using a machine and then made a test machine, Version2, in which the protocol was implemented.
The version2 machine is superior to the version1 machine in terms of the following points.
- more efficient reaction with a shorter period
- Easy changing of the program for machine controlling
- Down sized

b) Step for the information analysis:
We succeeded in preparing an algorithm for making a one-on-one correspondence in peaks between different analyses.

2) Developing a procedure for the analysis using a small number of cells:
We succeeded in HiCEP analyses using mouse 8 cell stage embryos and using 50 cells of cultured cells. A routine analysis using 1,000 eukaryotic cells also became possible.

9. Progress report of the single particle irradiation system to cell (SPICE)

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

Outline of Research Career:

Dr. Imaseki received the Ph.D. from Tohoku University in 2005 on development of the droplet PIXE analyze system. He has been developing accelerator techniques for biological and environmental sciences, and working as the manager of the radiation facility and shared units in NIRS. Now, he is also the manager head of SPICE developing group consisted of three teams, accelerator development, radiation detection, and biological research.

Objectives:

At National Institute of Radiological Sciences (NIRS), we constructed a microbeam system in 2003, named Single Particle Irradiation to Cell, SPICE. From the beginning of 2005, we redesigned it to improve the stability of the optical alignment of the system, and obtained an ensured reduction rate of the beam size proportional to the openness of the objective slit in the vertical line. As a result, SPICE is now capable of producing a beam size of approximately 10 micron in diameter, and the numbers of particles are controllable to intensity as low as single particles per second, and single particle irradiation has been succeeded. Moreover, these conditions can be easily reproduced with a routine everyday procedure. We describe in detail the modifications of the beam line and results indicating the improvements. In addition, the result of our first biological experiments is shown.

Progress of Research:

Single cell microbeam irradiation systems are of increasing interest, and have become a significant tool in the field of radiation biology. The major characteristics of microbeam irradiation systems are a very narrow beam of radiation, micron or submicron size, corresponding to cellular of sub-cellular dimensions. This is one of the advantages compared to conventional irradiation, such as broad beam irradiation, which enabled one to solve the problems of conventional irradiation with low dose, where targets are traversed by a Poisson-distributed number of particles.

Over 10 years has passed from the first development of proton and alpha particle microbeam irradiation systems by the Gray laboratory, and by Columbia University. Recently many microbeam systems with different types of radiation have been developed. These include soft X-ray of Gray laboratory, heavy charged particles of SNAKES, and heavier charged particles of GSI and electron microbeam of PNNL. Also, in Japan a monochromatic X ray microbeam of PF-KEK and a heavy charged particle microbeam of TIARA are currently available for biological experiments.

The single particle irradiation system to cell (SPICE) of National Institute of Radiological Sciences (NIRS) generates 3.4 MeV proton and 5.1 MeV alpha particle, and is the only microbeam irradiation system in Japan with low-LET particles irradiation. There are two defining characteristic of SPICE: one is that the particles are irradiated vertically from beneath the cells, and therefore biological samples can be placed on the sample stage horizontally, like those under the conventional culturing condition. Another is that the SPICE

focuses its beam by mono-bloc triplet quadrupole lens to produce a beam with a very sharp energy spectrum, which cannot be obtained with collimated micro beam system. For these specifications, SPICE may become the standard microbeam irradiation system for biological research in Japan, which enables to compare with those preceding studies of proton and alpha particle irradiation held in other microbeam facilities.

2. Modified specifications and current results

a. Improvements of beam line

The previous design concept of SPICE was to construct a vertical beam line with the same optical configuration of the scanning micro PIXE beam line and to isolate the beam line from environmental vibration by four air suspensions installed between the inner and outer frames, which consist of the vertical beam line. With this configuration, we were only able to minimize the beam diameter to several hundred micrometers, and its proportional relation with the openness of the objective slits was not seen at below several hundred micrometers. Therefore, further improvements in the mechanical alignments and the structure were considered to be necessary.

The modifications of the beam line are shown in figure 21. To begin with, the four air suspensions were removed, because of their flexibility affected the alignments of the beam ducts, Q-triplet lens, and microscope. Instead of these suspensions, four spacers equipped with vibration-removing rubbers installed (Fig 21A). In this way, high-frequency vibrations were inhibited, and the beam line was kept practically stable. Secondly, fixation apparatuses were installed at three different sections of the beam line at the position of the object and the emittance slits, and a bellows duct, as shown in figure 21B. This apparatuses have adjustable bolts that push the beam duct from three different angles to the center, which enabled us to fixate the beam duct with an inner frame. Thirdly, the inner frame was also fixated at two different sections of the outer frame by adjustable bolts as shown in Fig 21C. Finally, the beam exit duct and Q lens were separated and reconstructed to be independently controllable, which made beam alignment easy (Fig 21D). These four modifications stabilized the beam line to approximately less than 1 μm range at the beam exit. The current results are described as follows.

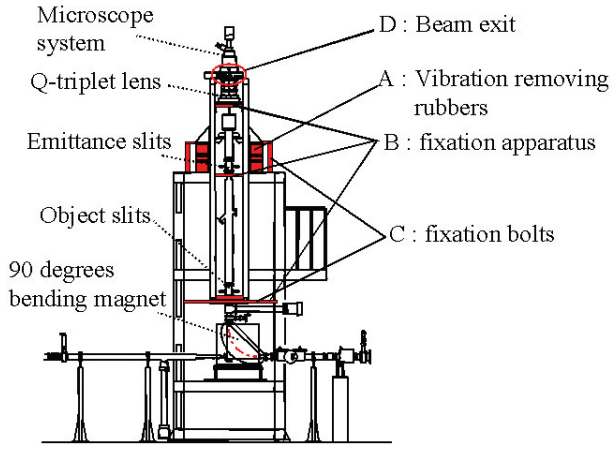

Fig 21. Schematic drawing of the SPICE beamline and its modifications. A is the vibration-removing rubber. B is the three apparatus for fixation of inner frame and the beam duct. C is the adjustable bolts to fixate the inner and outer frames.

b. Beam measurements

To obtain a microbeam, mainly three parts of the vertical beam line were adjusted: objective slits, emittance slits, and Q lens. During these adjustments, the beam size at the sample position was confirmed by observing the scintillation from the 100 μm thick plastic scintillator. This plastic scintillator was attached to the metal cell dish, which enables us to determine the beam size at the sample position. This scintillation image of the beam was captured by a microscope system. The size of the single image (1344×1024 pixels) was captured with 100× magnifications.

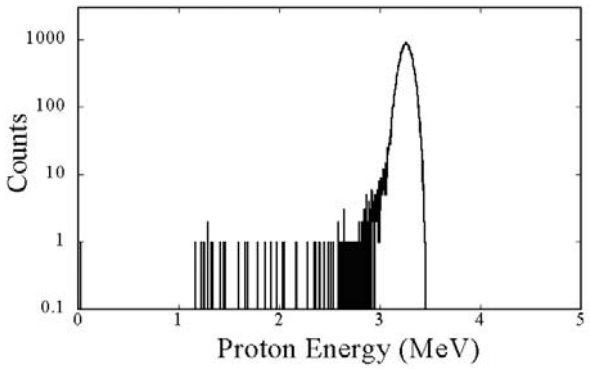

Fig 22. Typical example for the energy spectrum of the proton microbeam at the beam exit.

The actual beam size was determined by irradiating a plastic track detector, CR-39 (HARTZLAS TD-1, Fukuvi chemical industry). CR-39 of 5 mm×5 mm size and 1 mm thick was attached to the metal cell dish and set on the XY-stage. The beam intensity was controlled to approximately 1500 protons per second by adjusting

the objective slits installed in the horizontal line. The beam deflector installed upstream of the 90-degree bending magnet was controlled to give a pulse width of 50 msec for the beam to be irradiated. The number of protons irradiated to the CR-39 was estimated to be nearly 70, and 70% of the protons were in this 10 μm×10μm area. The energy spectrum of protons at the beam exit showed a clear proton peak of FWH=145 keV as shown in Fig 22 and the detection efficiency of our proton counting system showed an accuracy over 90% as shown in Fig 23.

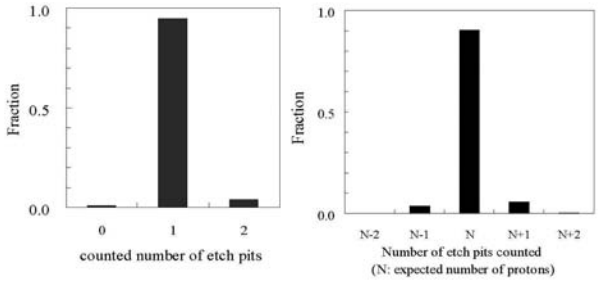

Fig 23. Counting accuracy of the single particle irradiation system measured by CR-39 detector at the cases of preset value (number of protons to be irradiated) N=1 and arbitrary number N (N>1). At N=1, 95.1 +4.9 8.1 %, and At N>1 90.1 ±5.1%.

c. Design of Cell Dish

Figure 24A shows a schematic drawing of the cell dish. A Si_3N_4 plate consisted of 7.5×7.5 mm frame of 200 μm thick with 2.5×2.5 mm area of extremely thin portion of 1 μm thick at the center. This Si_3N_4 plate was attached to the metal dish with Vaseline at the center of the dish, where there is a 3mm diameter hole. Therefore, particles from the beam exit will travel through a 1.2 mm air gap, 1 μm thick Si_3N_4, cells, 2 μm thick polypropylene film, and finally to enter the scintillation counter. Image of the Si_3N_4 plate attached cell dish is shown in Fig 24B. The edge of the Si_3N_4 plate (Fig 24C), a boundary of thick and thin portions, can be seen very clearly, and the upper left edge was used as a datum point to accord with the beam position for a latter experimental procedure with irradiated cells. Two hamster cell lines (V79, CHO-K1) and three human cell lines (HSG, HeLa, AG1522) were cultured on the Si_3N_4 plates and there were no significant differences with the conventional plastic dish.

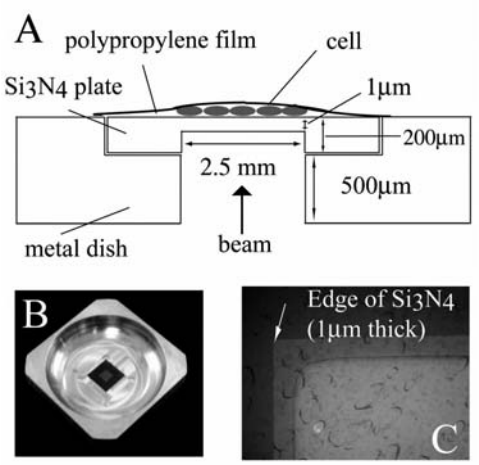

Fig 24. A is a diagram of a cell dish especially designed for SPICE and B is a photograph of the cell dish. B shows the boundary of 200 μm and a 1 μm thick portion of the Si_3N_4 plate. The upper left edge is defined as the datum point

3. Preliminary biological result

The purpose of this preliminary experiment was to determine whether the targeted cell is actually irradiated by protons. We visualized the DNA double-strand breaks (DSBs) induced by the traversals of protons through the cell nucleus using phosphorylated histone H2AX (γ-H2AX) as a marker for DNA DSBs.

CHO-K1 cells were cultured in α-MEM (supplemented with 10% FBS, 100 U/ml penicillin, 0.1 mg/ml streptomycin) and incubated under 37 degrees with 5%CO_2/95% air until the irradiation and prepared on Si_3N_4 plates. Cell suspensions of 20 μl containing approximately 1×10^4 cells were inoculated on the Si_3N_4 plate for 5 hours before irradiation. Approximately 30 minutes previous to irradiation the cell nuclei were fluorescent stained by incubating in media containing 1 μM Hoechst33258. Just before irradiation, 2.5 ml of media containing 10 mM Hepes buffer to prevent a variation of the pH, and 6 μm thick polypropylene films was floated on the surface of the media. The solution was removed slowly, so that the polypropylene film would cover the cell-attached area to prevent the cells from drying.

For irradiation, the beam intensity was reduced to approximately 10^3 per second by slits installed in the horizontal line, which can control the amount of protons supplied to beam exit without changing the beam profile. The number of protons to be irradiated to the targeted cells was preset at 500. Cell images of the targeted cell were captured by a microscope system just before irradiation, and the

coordinates of the sample stage were recorded to define the targeted cell for a latter observation after an immuno -fluorescence assay. Up to now, the automatic recognition of cell nuclei is not complete. Therefore, cells were identified from its fluorescence, moved to the beam position by controlling the X-Y stage, and then finally irradiated. This so called "move and shoot" procedure is laborious and protracts the time and also affects the cell conditions by the massive dose of hazardous UV-light exposed to cells during the procedure. Therefore, an automatic cell recognition system is necessary and will be developed and installed in SPICE by the end of 2006.

After irradiation, the cells were incubated at 37℃ with 5% CO_2 /95% air for 30 minutes for the phosphorylation of H2AX to reach its maximum and then the cells were fixed with 4% paraformaldehyde. An immuno-fluorescent assay was held using anti-γ-H2AX antibody and secondary anti-rabbit Alexa 488 antibodies. Fig 25 represents the cell image captured by the microscope system. Fig 25A is an image of cell nuclei stained with Hoechst 33258 and B is the fluorescence of Alexa 488 secondary antibody, which indicates induced DNA double strand breaks. As can be seen in B, the cells in the targeted position showed fluorescence of γ-H2AX, and unfortunately only one neighbored cell also showed γ-H2AX fluorescence. Smaller beam size is required for single cell (nucleus) irradiation.

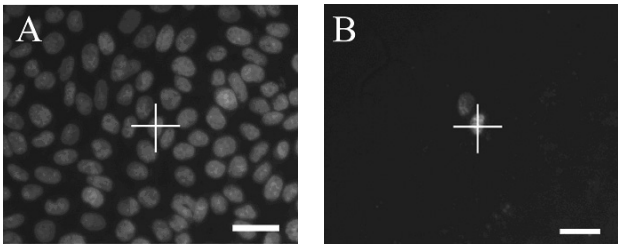

Fig 25. A represents the image of cell nuclei stained by Hoecst 33258, and B is a fluorescent image of γ-H2AX. The targeted positions indicated in + were irradiated by 500 protons. Bar size, 20 μm

Major Publications:

1) H. Imaseki, et al., "Progress report of the single particle irradiation system to cell" *Nuclear Instruments and Methods in Physics Research B,* (2006) accepted.
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10. List of Original Papers

This list includes main publications by the staff members issued during the period from April 1, 2005 to March 31, 2006

****Outside Co-research***

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

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Study of dose estimation and protection of patients and medical staffs on medical radiation

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RadGenomics Project

1. Atsushi Tsuji, Hitomi Sudou, Aya Sugyou, Marika Ohtuki, Makoto Miyagishi*, Kazunari Taira*, Takashi Imai, Yoshinobu Harada: A Fast, Simple Method for Screening Radiation Susceptibility Genes by RNA Interference, Biochemical and Biophysical Research Communications, 333, 1370-1377, 2005
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