Preface

National Institute of Radiological Sciences (NIRS) has continued to facilitate an efficient, transparent, and competitive research atmosphere, which forms the essential principle for the Independent Administrative Institute (IAI). Our eventual aim is achievement of outstanding outcomes through research activities.

The fiscal year 2003 (FY2003) was the 3rd year after NIRS was reborn as an IAI in 2001. NIRS has been implementing its activities basically according to a mid-term (5-year) plan and annual plans.

We submitted our business report (including the financial report) and the achievement report of FY 2002 to the Ministry of Education, Culture, Sports, Science and Technology (MEXT) in June 2003, which was evaluated by the Evaluation Committee of MEXT. This evaluation process was the 2nd that we have experienced. We still need to get accustomed to this annual important event in order not to consume too much energy in this process.

In October 2003 "Heavy Ion Radiotherapy of Solid Cancer" was approved by the Ministry of Health, Welfare and Labour as a highly advanced medical procedure (HAMP). We treated 56 cancer patients as HAMP during the period from November 2003 to March 2004, in which each patient pays 3.14 million yen for heavy ion radiotherapy. Clinical research continues for the evaluation of safety and effectiveness of new irradiation techniques as well as new target tumors.

Research buildings for low dose radiation effects experiments and translational research were completed. The latter is to be used mainly for neuroscience study at present. A center for cutting edge gene expression research was newly established in order to facilitate application of the high coverage expression profile (HiCEP) technique.

NIRS continued research activities according to the mid-term plan, including 5 project studies, I frontier type study, 20 basic studies, and I brain function study. Almost all projects progressed as was planned. Additionally, I as president of NIRS, took initiative in granting 22 new research proposals after in house competition in order to cultivate research seeds. In FY2003, we produced 237 original papers, which is 1.2 papers per researcher on the average.

In order to support and promote the above mentioned research activities, the department of research promotion and division of information management were established. Division of planning strengthened its function by increasing the number of personnel from outside NIRS as well as collaborating researchers in NIRS.

Activities for public relationships, and international cooperation have been continuously enhanced.

It is our great pleasure to publish this annual report. In the rapidly changing society worldwide, we will continue our efforts as a center of excellence (COE) for radiological sciences utilizing advantages of IAI. We would like to ask for continuing support and constructive criticism from outside NIRS.

Yasuhito Sasaki

Yasuhito Sasaki, M.D., Ph.D.
President

1. Outline of Research Activities in 2003

This institute engages in original, advanced R & D activities. According to the mid-term plan, our research activities include 5 project studies (low-dose radiation effects research project, space radiation biological effects and protection project, clinical trials for heavy ion therapy, research on advanced imaging technologies supporting frontline medical care, studies on radiation emergency medicine), one frontier-type research project (radiation genomics (RadGenomics) project), one brain-functional study, and 20 basic studies.

In this financial year, almost all NIRS researchers performed their research activities very smoothly, because they have become familiar with new systems that were introduced when NIRS became an independent administrative institution in 2001. Although some problems interfered with research, such as budget shortages, we have overcome these difficulties.

The results for our research groups in 2003 fiscal year are shown in this text by research leaders. Judging from the number and quality of presentations at scientific meetings, and in research papers and reports, it can be concluded that our research was active, and that much progress was achieved this year. We hope you will recognize that our institute pursues high-level research activities after reading this annual report.

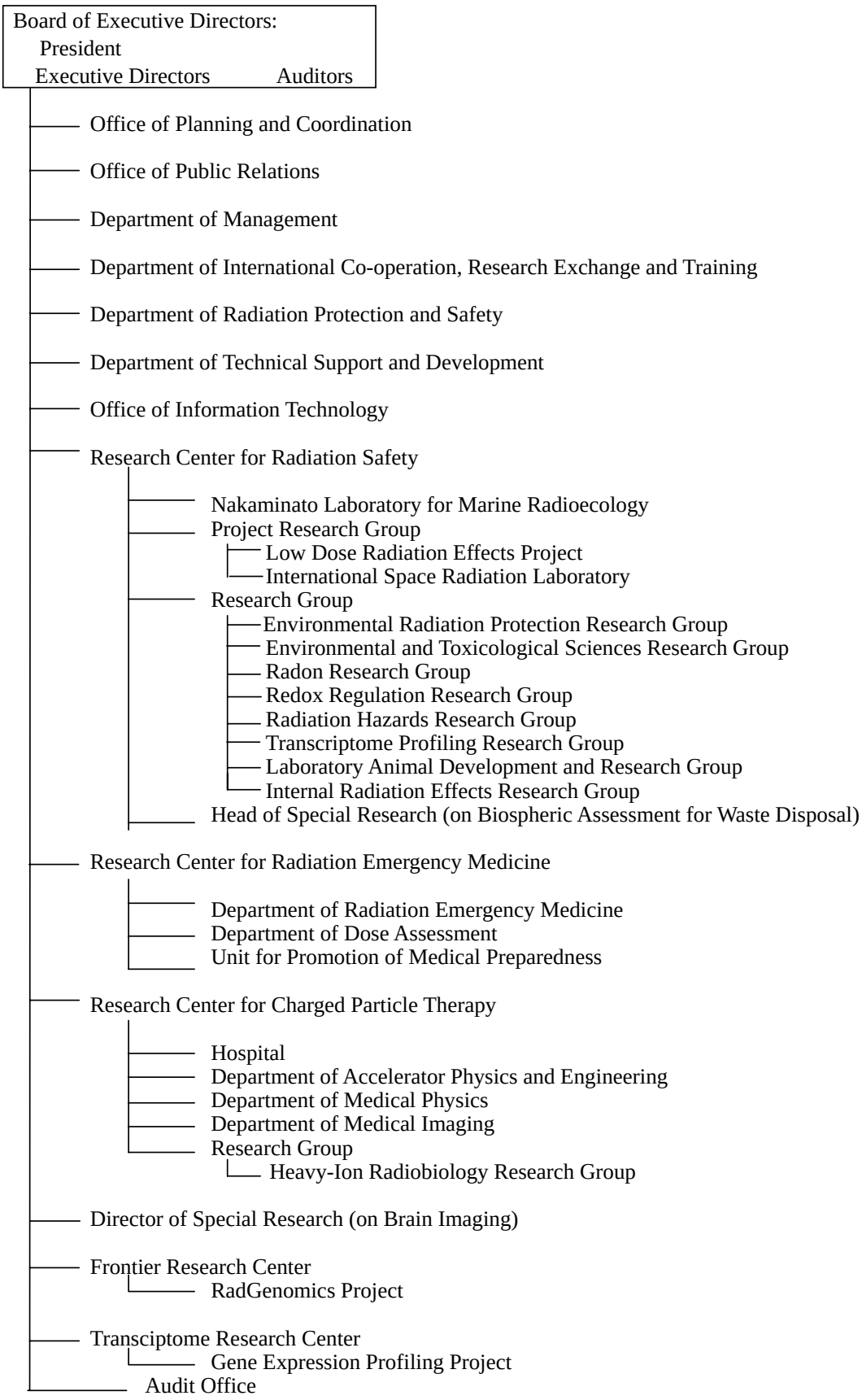
A total of 237 original papers have now been published by NIRS staff members, for an average of 1.2 papers per researcher.

This institute conducts comprehensive research and development, and returns the results obtained to society through collaboration and personnel exchanges with domestic and overseas research institutions, universities, and industries. For example, NIRS contributes to the international health physics community by sending experts to the meetings of UNSCEAR, ICRP or IAEA, and other organizations. We also organize many training courses on radiation protections and applications for researchers, engineers, medical workers, and disaster prevention personnel. We make efforts to update the curriculums into which new research results are incorporated, by employing feedback from our researchers.

Toshihiko Ozawa,Ph.D.
Executive Director

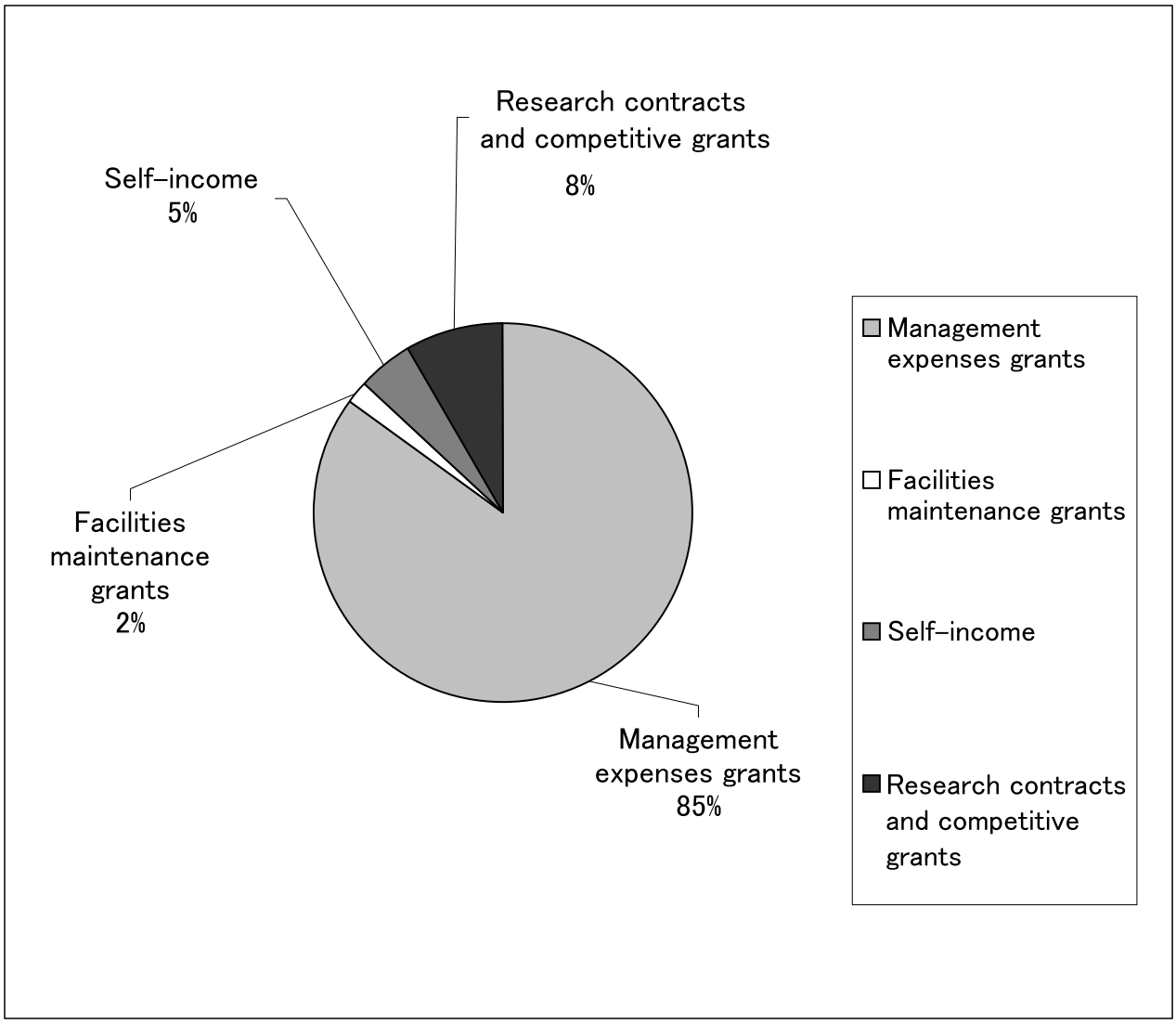
2. Organization Chart and Budget

(1) Organization



(2) Budget(2003.4~2004.3)

Total	16,110	million yen	%
Management expenses grants	13,700	million yen	85%
Facilities maintenance grants	323	million yen	2%
Self-income	761	million yen	5%
Research contracts and competitive grants	1,326	million yen	8%



3. Research Center for Radiation Safety

Sentaro Takahashi, Ph.D.
Supervisory Director

Outline of Research Career:

Dr. S. Takahashi graduated from Kyoto University in 1974, and after completing master course, started to work as a research scientist at the Division of Radiation Hazard, NIRS. He was at MRC Radiobiology Unit, UK as a visiting researcher between 1985 and 1986, and at Department of Radiation Oncology, University of Texas Medical Branch at Galveston, Texas as a visiting professor between 1996 and 1997. He is now the Supervisory Director, Research Center for Radiation Safety (from 2002) and the Supervisory Director, Advanced Transcriptome Research Center (from 2003, dual position) in NIRS.

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Objectives:

The Research Center for Radiation Safety was established on April 1, 2001, when the National Institute of Radiological Sciences (NIRS) was reborn as an Independent Administrative Institution (IAI). Although the Center is a new organization, its activities are underlined by the wide spread experiences and resources that former research divisions related to biology and environmental sciences have accumulated. The research fields covered by this Center are wide and ranging from environmental, biological to medical aspects of radiation hazards and safety. Concentrating research resources into research activity related to radiation safety, the Center aims at a safely utilizing radiation, advance in radiation safety sciences, understanding the basic mechanisms of radiation effects on humans and living organisms, and contributing to the related scientific fields. The development of advanced technologies related to this field, such as development of experimental animals and implementation of advanced measurement technology for ionizing radiation, is also an important objective of this Center. Support for regulation authorities, governmental committees, and international organizations is also provided by the Center. In addition to the research activities, training and education of students and young researchers are actively carried out.

Overview:

In this financial year, the Research Center for Radiation Safety performed all its research activities very smoothly, in part, because the stuffs were now familiar with the new systems which were implemented for the Independent Administrative Institution in 2001. Although some problems occurred, for instance, shortage of funding, reconstruction of laboratory facilities, and construction of a new building, we have overcome these difficulties. Judging from the number and quality of the presentations at scientific meetings and the research papers and reports, it can be concluded that the researchers were active and much progress were achieved this year. The number of original papers published by Center members reached as many as 120 papers, and many of them were published in international journals with good reputations. Proceedings of international or domestic scientific meetings included more than 40 papers from us and the number of oral presentations was more than 400. Some young researchers received prizes from scientific societies, such as the Japanese Society of Radiation Research and the Japanese Society of Radiochemistry. This year, we especially tried to present our research activities to newspapers and other media. As a result, 33 articles appeared in newspapers, and the name of our Center became known well to the public.

At present, the Research Center for Radiation Safety consists of two project research groups and eight fundamental research groups. The Center also operates two research promotion sections, and the Nakaminato Laboratory for Marine Radioecology. In the first project research, Research on the Health Effects of Low Dose Radiation, animal experiments on the induction of cancer by 10 MeV neutron was completed. The cancer induction ratio and relative

biological effectiveness (RBE) are being analyzed now. As to the modification of cancer risks, this project group focuses on the combined effects of radiation and other environmental agents, the effect of *scid* mutation on thymic lymphoma induction, and the effect of *Atm* mutation on leukemia induction. The second project research, Space Radiation Project, obtained many accomplishments in this year. The international comparison of measurements of space radiation (ICCHIBAN Project), the detection of bursts of solar flares, the determination of radiation dose during international flights, and the development of a new neutron detector are topics of this group. Biological study on the effect of space radiation was also carried out using heavy iron accelerator (HIMAC) operated by the Center for Heavy Ion Therapy, NIRS. It was found that a novel type of mutation was induced after the irradiation of heavy ions beams which mimics space radiation.

The fundamental research groups achieved much progress in their own research fields. The eight fundamental research groups were: the Environmental Radiation Protection Research Group, the Environmental and Toxicological Sciences Research Group, the Radon Research Group, the Redox Regulation Research Group, the Radiation Hazards Research Group, the Transcriptome Profiling Group, the Laboratory Animal Development and Research Group, and the Internal Radiation Effects Research Group. The Nakaminato Laboratory for Marine Radioecology also actively carried out the research. All the above obtained many new and significant scientific findings from the environmental, biological, and physical field to the medical field radiation. Research programs sponsored by agencies other than NIRS were also carried out. They included the Advanced Technology Development in Life Science (RR2002, Ministry of Education, Culture, Sports, Science and Technology), the Research Program for Preventing the Pollution of Global Environments (Ministry of Environment), the Monitoring and Measurements of Radiation and Radioactive Nuclides (Ministry of Education, Culture, Sports, Science and Technology), the Movement of Radionuclides in the Environment for Nuclear Disposal (Agency for Natural Resources and Energy).

Regarding personnel, the total number of workers was the same as in the last financial year; about 100 and 110 people for permanent stuff and part time assistant staff, respectively. The number of post-doctoral fellows was increased to 50. Since many collaborative research studies were preformed this year, mutual exchange of stuff members was frequent. About 150 persons worked as a visiting researcher or a trainee in the Center. The leader of the Environmental and Toxicological Research Groups, Dr. Y. Muramatsu, and the group leader of Internal Exposure Research Group, Dr. Y. Oghiso moved to Gakushuuinn University, and to the Environmental Science Technology Institute, respectively. For international collaboration, the Center sent many researchers to the foreign institutions and international scientific meetings. Especially, it should be noted that 40 scientists were dispatched to the International Congress of Radiation Research (ICRR) held at Brisbane, Australia in 2003.

Office of Biospheric Assessment for Waste Disposal

Shigeo Uchida, Ph.D., Head

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. It should be noted that environmental conditions, such as climate, vegetation, soil, affect on these parameters. Besides, agricultural products and food customs in Japan are different 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 (Kds), have been collected throughout Japan. The transfer model for predicting the radionuclide behavior in atmosphere-paddy soil-rice plant systems has been also developed.

3.1. Low Dose Radiation Effects Research Project

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

Outline of Research Career:

Dr.Shimada got Ph.D. in 1985 from University of Tokyo for a thesis entitled, "Unique characteristics of primordial germ cells to ionizing radiation in *Oryzias latipes*". As a post-doctoral fellow at Mizuo Biohoronics Project of JST (1985-1987) and a research fellow at Tokyo Metropolitan Institute of Gerontology (1987-1989), he worked on the activation of innate immunity for cancer therapy and the involvement of macrophages in aging of blood vessels, respectively. Since 1989 at National Institute of Radiological Sciences, major work has been focused on radiation carcinogenesis, including molecular and cellular mechanisms of T-cell lymphomagenesis and mammary carcinogenesis. Current research subjects are the dependence of carcinogenic pathways on genetic background and age at exposure, and the molecular alterations associated with ionizing radiation.

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Objectives:

The 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 subjects: 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 is obtained using animal models. For the neutron study, the final goal is to determine the energy dependence of the carcinogenic effects of neutron for each organ, and to provide insight into the factors influencing RBE. For the cancer risk assessment, we have 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, we have used a mega-sized DNA sequencing method to determine spectrum and the frequency of mutations in offspring after paternal irradiation.

Progress of Research ;

Biological effects of neutrons

After the accident at Tokai-mura in 1999, the cancer risks and fetal effects of low doses of neutrons became matters of concern. The main aim of this program is to investigate the biological effects of neutrons, and to make clear the relative biological effectiveness (RBE) for leukemia and RBE for fetuses, thereby assessing the risks of neutrons. Cyclotron 10 MeV neutrons were first used in this program. About 2660 SPF male C3H/HeNrs mice, a strain susceptible to radiation-induced myeloid leukemia, were divided into 13 groups of 150-250 each: one control group; six dose-groups (0.05-2 Gy) for neutrons; and six dose-groups (0.2-4 Gy) for gamma rays. Mice were treated with single whole-body radiation, and maintained over their life spans. Dead or moribund mice were pathologically examined. As of the end of March 2004, about 1,700 mice (67 percent) were autopsied. The incidence of leukemia increased depending upon radiation dose, to about 10 percent in the highest-dose groups. To study the effect of neutrons on fetal central nervous system, pregnant female C57BL/6 mice mated with male C3H/He mice were irradiated with neutrons (6 doses, at 0.05-1 Gy) or gamma-rays (6 doses, at 0.2-4 Gy) on day 13.5 p.c. Fetal brains at 24 hours after irradiation were used for analysis; the numbers of vital cells and apoptotic cells in a definite area of TUNEL-stained brain sections were examined under a microscope. Incidences of apoptotic cells increased with the doses of neutrons and of gamma rays. This study is still under way, to gather additional data. Since further experiments on the effects of 2 MeV

or more slow neutrons on a whole body are needed, the new building with the SPF animal facility, the electrostatic accelerator for neutrons, and other laboratories, were completed at the end of December 2003. The accelerator is now being conditioned, but we will be able to start some biological experiments in the near future.

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 is believed to be a result of interaction with these factors, and it is clear that the carcinogenic response of radiation could be influenced by these factors. The aim of this study is to determine the mode and mechanism of the combined effects of chemicals with radiation, especially at low- or threshold-dose range. The cancer models used in the current study are the murine T-cell lymphomas (TL) of B6C3F1 mice and the mammary cancer of SD rats. We have demonstrated that the dose-response curve of TLs after treatment of fractionated X-rays (4 times, at 0.2-2.0 Gy) and ethyl-nitrosourea (ENU; 50-400 ppm) was, respectively, sigmoid and linear, both with threshold doses. Molecular analysis has shown that the loss of heterozygosity on chromosome 11 and *Ikaros* mutations are associated with X-ray-induced lymphomas. For combined treatment, the synergistic effect was obvious for high-dose radiation, while effects were marginal for low- and threshold-dose radiation. It was notable that there was still a threshold for X-rays combined with ENU. Female rats were treated either with gamma-rays (0.5-2 Gy), methyl-nitrosourea (MNU; 20-40 mg/kg), or a combination of gamma-rays and MNU. It turned out that the combined treatment induced adenocarcinomas, but not fibroadenomas, more efficiently than gamma-rays or MNU alone. The H-*ras* mutation was not frequent in radiation-induced carcinomas, while it was characteristic of MNU-induced carcinomas. The mutation status of *Ikaros* and H-*ras* in TL and mammary tumors induced by combined treatment is currently being examined.

Cancer Risks of Genetically Susceptible Mice:

To clarify the genetic factors involved in radiation-induced carcinogenesis at low doses, we analyzed the dose-response relationship between radiation dose and the induction of thymic lymphomas (TL), using scid mice that had a mutation in the *DNA-PKcs* gene. Scid mice were highly susceptible to the development of spontaneous and radiation-induced TL, as compared with wild-type mice : at 0.25 Gy of gamma-rays, TL were significantly induced in scid mice, while there was no induction of TL in wild-type mice. This indicates that a defect in DNA-PKcs is responsible for susceptibility to the development of spontaneous and radiation-induced TL at a low dose, and suggests that the nonhomologous end-joining repair is involved in the suppression of radiation-induced TL. To analyze the pathways involved in the development of TL, we examined the sequence abnormalities of the breakpoints of rearrangements of Notch1 in TL of wild-type and scid mice. *Notch1* has been identified as a major oncogene responsible for TL induction. There were at least two pathways for the induction of *Notch1* rearrangements: one is the illegitimate V(D)J recombination pathway that operates at cryptic recombination-signal sequences in the *Notch1* locus, while the other is micro-homology mediated nonhomologous end-joining (MNHEJ), in which radiation-induced double strand breaks might be involved, and the processed end paired with another end at the micro-homology sequence, resulting in deletions. In the presence of the *DNA-PKcs* gene, the illegitimate V(D)J recombination functions as a major pathway for generating the deletion of *Notch1*, while in the absence of the *DNA-PKcs* gene the MNHEJ pathway acts as a major pathway. Because the illegitimate V(D)J recombination pathway occurs spontaneously, the MNHEJ pathway might be responsible for the significant induction of TL at a low dose in scid mice.

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 ($>10^7$ bp/dose) at a specific genomic loci and 150 STS in mouse offspring. Male mice irradiated with or without gamma-rays at 1-3Gy were mated with intact females 3 weeks later. This procedure could determine the genetic effects of radiation at the spermatid stage. DNA ($5x10^6$ bp, in total) from the offspring was analyzed. The mutation frequency of offspring from the male mice exposed to 3Gy gamma-rays was $1.4x10^{-6}$/bp, while spontaneous mutation was not detected ($< 1x10^{-6}$). Mutation was not detected in offspring derived from male mice irradiated with 1Gy of gamma-rays. These results suggest that the dose response for mutation induction is unlikely to be linear. One new mutation was also detected in offspring derived from male spermatogonia exposed to 3Gy of gamma-rays. Mutation frequency was calculated to be $2x10^{-7}$ /bp/Gy, which corresponds to one-eighth of the

mutation frequency observed in spermatid. Another mutation was detected from offspring derived from spermatid exposed to 0.5Gy of neutrons. The mutation frequency was calculated to be $2x10^{-7}$, and the RBE of neutron was estimated 5-6. Similar nucleotide sequence analysis of offspring derived from mouse spermatid exposed to 3Gy of X-rays was performed at the adenine phosphoribosyl transferase gene locus (3088 bp/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 1-3Gy of X-rays; dDynamic mutation was observed in 5-20 percent of these, according to irradiation dose.

Radiation Effects on Germ Cells

We have carried out mutation experiments in somatic cells and male germ cells from transgenic mice, after different doses (0, 1, 2.5, or 5 Gy) of ionizing radiation. The transgenic mice used for this were the gpt-delta strain, which carries 80 copies of the bacterial *gpt* gene per cell as targets for mutagenesis. Results are as follows:

- *Mutation frequencies in somatic cells:* The spontaneous *gpt* gene mutation frequencies in whole embryos and the spleens of adult mice were 1.1×10^{-5} and 1.2×10^{-5}, respectively. The mutation frequencies after exposure to 5 Gy of X-rays in whole embryos and adult spleens were 3.5×10^{-5} and 2.9×10^{-5}, respectively. When the mice were irradiated with 5 Gy of X-rays, the mutation frequencies in somatic cells increased about threefold over background.
- *Mutation frequencies in male germ cells:* Sperm cells were extracted 65-83 days after irradiation at various doses of X-rays, corresponding to the spermatogonia stage at the time of treatment. The spontaneous mutation frequency in male germ cells was 0.4×10^{-5}. The mutation frequency in male germ cells irradiated with 5 Gy of X-rays at the spermatogonia stage was 0.9×10^{-5}.

Major publications

1)Yasushi Ohmachi, Yuka Ishida, Takeshi Hiraoka, Tsuyoshi Hamano, Shinji Fushiki, Toshiaki Ogiu: Postnatal changes in mice exposed *in utero* to fast neutrons. *Journal of Toxicologic Pathology*, 17, 63-68, 2004

2)Mayumi Nishimura, Shizuko Kakinuma, Daisuke Yamamoto,* Yoshiro Kobayashi,* Gen Suzuki,* Toshihiko Sado, Yoshiya Shimada: Elevated interleukin-9 receptor expression and response to Interleukins-9 and -7 in thymocytes during radiation-induced T-cell lymphomagenesis in B6C3F1 mice. *Journal of Cellular Physiology*, 198, 82-90, 2004

3)Kyoko Yasumura,* Isamu Sugimura,* Kazuei Igarashi,* Shizuko Kakinuma, Mayumi Nishimura, Masahiro Doi, Yoshiya Shimada: Altered expression of Tfg and Dap3 in *Ikaros*-defective T cell lymphomas induced by X-irradiation in B6C3F1 mice. *British Journal of Haematology*, 124, 179-185, 2004

4)Yoshiya Shimada, Mayumi Nishimura, Shizuko Kakinuma, Toshiaki Ogiu, Hirokazu Fujimoto,* Ayumi Kubo, Junya Nagai, Keizou Tano,* Shinji Yoshinaga: Genetic susceptibility to thymic lymphomas and K-*ras* gene mutation in mice after exposure to X-rays and N-ethyl-N-nitrosourea. *International Journal of Radiation Biology*, 79, 423-430, 2003

5)Hideo Tsuji, Hiroko Ishii, Hideki Ukai, Takanori Katsube, Toshiaki Ogiu: Radiation-induced deletions in the 5' end region of *Notch1* lead to the formation of truncated proteins and are involved in the development of mouse thymic lymphomas. *Carcinogenesis*, 24, 1257-1268, 2003

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

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Director, International Space Radiation Laboratory
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Outline of Research:

Dr.Fujitaka and his group continued discussions with an airline company on future collaborations in measurements of cosmic rays, in which Y.Uchihori was actively engaged. Also M.Takada paid a great effort to complete his Phoswitch detector to measure highly energetic neutrons, which could hold a large portion of cosmic radiation. H.Yamaguchi has supported these researches. In addition, N.Yasuda joined physics research group, where he was to count etch tracks on films that were on board a Russian satellite. H.Yasuda continued working as a member of planning section, but worked hours for the group and gave us useful information. And S.Kinbara calculated motions of highly energetic particles. Based on many low-level irradiation experiments, M.Suzuki showed that the mutation rate in human cells, which had been exposed to very low levels of high LET radiation, would depend on time-length after the pre-irradiation. It was one of the most useful information related to the radiation protection in the space. K.Nojima was interested in stress, which astronauts would meet, and had let mice swim in a water pool ("water maze" experiments), and examined whether they could or could not reach the target within a given time. They were previously irradiated by very low radiations. The mice could be good animal model for middle-aged men working in space. Significant results were expected. R.Okayasu was a competent leader in promoting and encouraging these works. He was engaging in his own cellular and molecular studies related to space environment. S.Fukuda and H.Iida have found that the rats experienced physical training showed less bone mineral loss, which could be applied to astronauts.

Objectives:

To find out the most effective detectors, both active and passive, ICCHIBAN project which compares detectors has been done. Also efforts were directed to avoid excessive exposure on air flights, based on estimated doses to any cities of the world. A Phoswich neutron detector was identified as the best for use in various fields. A by- product of this research was the development of automated imaging optical microscopy.

Long term analyses of exposure to high-LET particles can only be done under very limited conditions. HIMAC is basically a machine for medical purposes, which is free only during nighttime. Therefore, to repeat long time experiments, we have to overcome lots of difficulties. Every night (about 8h), we have to place an incubator with carbon dioxide at a point 45 degrees from the principal path of the beam. This gives an exposure level of about 1mGy/h, which is understood as space-like radiation.
Biological project objectives lie in research on cell or cellular mutations by exposure to radiation. More attention is being directed to the best use of the micro beam facility. Another important issue in this field is how much the animal brain is damaged after exposure of samples with very weak (about 1mGy/h) irradiation.

To solve another important issue, clarifying the alterations of calcium metabolism, a study of synergetic effects of radiation and simulated microgravity in rats has been done. This lead to a method to reduce radiation-induced damages, and to an examination of the beneficial effects.

Progress of Research:

1) Dosimetry of dose in space.

The ICCHIBAN project included many participants from abroad this year. This project will be continued in the future until all data are to converge. The experiments in space were implemented this year, and negotiations with the Russian participants were undertaken. Basic data on heavy ion response of TLDs and CR39 have been accumulated. A prototype of a compact Si detector was put into practical use, and development of the neutron Phoswich detector has been almost completed, though the power supply is still under review. Efforts to make a diamond detector to measure cosmic radiation is in progress. Material selection was based on its excellence in fundamental functions as well as ability to be used in the severe environment of space. For automated imaging microscopy, four patents have been filed in the U.S. and Europe regarding high speed image acquisition. Until recently, we have had neither rockets nor space vehicles. But Russia has very kindly given us an opportunity to use their vehicles. Then, under the auspices of NIRS, Russia, Austria and U.S. have joined together in the experiments. With the accelerator, we have irradiated some known amount of dose, and made data comparisons. Results are finely concentrated around the given dose with reasonable deviations.

2) Dose which we receive on board airplanes.

Measurements of air flight doses obtained by compact monitors (e.g. silicon detectors) and model Monte Carlo calculations, primarily those from Japan, can sustain practical curiosity. With regard to studies of radiation exposure in aircraft, negotiations with an air carrier are continuing. Data were accumulated largely on "route doses", mainly on flights to the US and Europe, and also model calculations by CARI-6 were repeated there. The results have shown that the annual dose received in flights seem unlikely to exceed 6 mSv.

A large solar flare confirmed existence of the Forbush decrease, which started in late October and continued until two weeks later. In this case, the occurrence of a geomagnetic disturbance resulted in decrease of the dose in an airplane. In this case, the magnetospheric boundary was suppressed inward, which refracted low energy components of cosmic rays, as predicted.

3) Cellular and in vivo effects.

We have found the LET dependence on the brain function in mice irradiated with heavy ions at HIMAC and at NSRL(National Space Radiation Laboratory; Brookhaven, NY; as collaboration). As to water maze experiments to examine brain memory, very low level irradiation down to 0.5Gy was used to simulate space. With carbon ion irradiation, the brain function was recovered to its normal level 20 weeks after irradiation, while with high LET iron ion irradiation, the function was not recovered even at 42 weeks post-irradiation. We also found LET dependence on the blood cells from mice irradiated with various heavy ion particles. Silicon ions (LET = 55 keV/um) seem to give the strongest biological effect so far. A rat model which shows susceptibility to renal cancer (Eker rat) was used to study the carcinogenic process associated with high and low LET radiation. We found high LET iron ions gave 1.6 times higher incidence of kidney cancer than the incidence with X-rays.

We have been studying the genomic instability phenomenon in normal human fibroblasts exposed to low doses of ionizing radiation. This year we irradiated cells with low-density carbon ions using faint beams in the HIMAC. The beam is about 1mGy/h, which is like space radiation. The genomic instability was examined by measuring cell killing and mutation induction in cells pretreated with low density carbon ions followed by irradiation with challenging doses of X-rays. The results showed that there was no enhanced effect on cell killing in low-density pretreated samples when compared to untreated cell populations. On the other hand, the frequency of mutation induction, which was measured as the induction of a 6-thioguanie resistant clone focused on hprt locus, of the low-density pretreated cells was much higher than that of untreated cells. These results suggest that the genomic instability was induced in the form of gene mutation by the pretreatment at a low level of about 1mGy/h carbon ions. This result is interesting from the viewpoint of future space trips.

We have also been studying the effect of high LET radiation using normal and radio-sensitive DNA double strand break (DSB) repair deficient cells. The DSB repair deficient cells showed an alteration in cell growth even after ~10 mGy of high LET background radiation. The cell survival with high LET radiation was similar to that with X-rays in the DSB defective cells. This made a great contrast to normal cells which showed a significantly reduced cell survival with high LET radiation when compared to X-rays. By examining the DSB repair process in these cells, we found that one form of DSB repair process called non homologous end joining (NHEJ) was severely compromised in cells irradiated with high LET

radiation. These results are also interesting from the viewpoint of aging which is related to long term space stays.

4) Effects on bone and its mineral components.

Also done was the effect of bone mass change due to irradiation associated with microgravity. The microgravity environment is realized by rotating an ingenious machine, a clinostat, by which the gravity is diverged for a long time. We observed the bone was rather strengthened when only radiation was left imposed. This phenomenon will be reviewed in the coming period.

Changes of bone mineral density after immobilization and irradiation, 0.5-2.0Gy, were observed within 2 weeks. As 0.5Gy is the dose which humans would experience in a round trip to Mars, it is very important. The shortening of life span has been observed for rats which were exposed to 0.75-1.0Gy at age of 12 months. Observations are still continuing.

Comparisons were made between the radiation exposure alone group and the group combined with radiation and simulated-microgravity induced by immobilization of the hind limb using neurolectomy. The results showed that alternations in bones were determined at an early stage after treatments. Alendoronate, which is used as a drug to prevent bone mineral loss in astronauts, has been found to have an optimum effect when the administration starts just after the irradiation. Experiments to examine radiation-induced cancer, shortened life, and bone damage by using young rats should be continued, and we have started to search for a model to examine individual differences in bone mass and genetic factors, and the effects of nutrient constituents in controlled diet supplementation.

Major publications:

1) Suzuki,M., Zhou,H., Gerad,C.R. and Hei,T.K.:, Effect of medium on chromatin damage in bystander mammalian cells, *Radiat.Res.,* 162, 264-269, 2004.
2) Takada,M, Kitamura,H., Koi,T., Nakamura,T. and Fujitaka,K.: Measured proton sensitivities of bubble detectors, *Rad.Prot.Dosim,* 11(2), 181-189, 2004.
3) Fukuda,S. and Iida,H.: Age-related changes in bone mineral density, cross-sectional area and the strength of long bones in the hind limbs and first lumbar vertebra in female Wistar rats, *J.Vet.Med.Sci.,* 66, 755-760, 2004.
4) Okada M., Saito S., Okayasu R.:Facilitated detection of chromosome break and repair at low levels of ionizing radiation by addition of wortmannin to G1-type PCC fusion incubation, *Mutat. Res.* 562, 11-17, 2004.

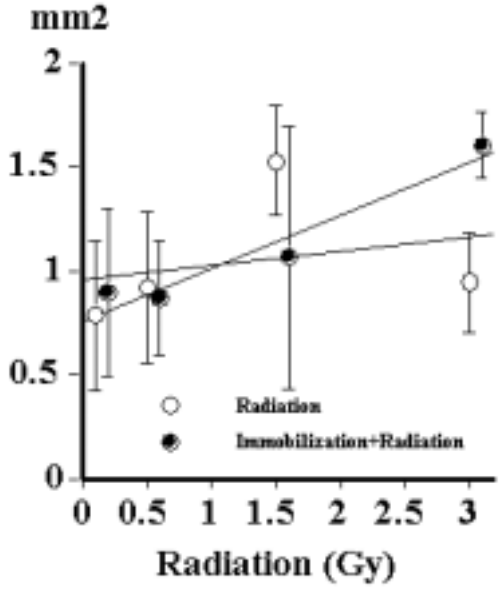

Fig.1.
Cross-sectional area of tibial proximal epiphysis of rats increased in the radiation combined with immobilization group (r=0.967) than in the radiation exposure alone group 22 weeks after heavy ion particle whole body irradiation.

3.3. Establishment of Radiation Protection System against Radioactive Materials Released into the Environment

Nobuhito Ishigure, Ph.D.,
Director, Environmental Radiation Protection Research Group

Outline of Research Career:

Dr. Ishigure received a Ph.D. from Nagoya University in 1979 for his study on energy loss of low-energy (keV) electrons in solids. He has had 25 years of experience in research and development on internal dosimetry at NIRS. Between 1985 and 1986 he was at the Medical Research Council, UK as a visiting scientist, where he studied microscopic distribution of enriched uranium within lungs using solid state nuclear track detectors. He has participated in the ICRP Committee 2 task group on internal dosimetry (INDOS) since 2001.

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Objectives:

The over 50 nuclear power plants operating in Japan provide one-third 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. In particular, this research group conducts marine studies at the Nakaminato Laboratory for Marine Radioecology. Furthermore, half of the research group members serve at the Research Center for Radiation Emergency Medicine, as 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 around the living environment

(K. Shiraishi, S. K. Sahoo and S. Kimura)

Using ICP-MS and TIMS, ultra-trace analysis is being conducted to develop a new method for specifying radioactive sources and to study relationships between trace elements and human health.

Precise uranium isotopic composition was determined for soil samples collected in the Chernobyl areas and special areas of Japan. The isotope ^{236}U was detected only in the Chernobyl samples. Ratios of $^{234}U/^{238}U$ and $^{235}U/^{238}U$ were also higher compared with natural abundance. Variation of the ratios could be used to detect the source origin. Whole diet samples are being collected to clarify the relationship between trace element intakes and diseases including cancer in the Chernobyl areas by duplicate portion studies. Approximately 20 radioactive and non-radioactive elements such as U, Th, I, Cs and Sr, have been analyzed for 100 samples. More samples must be analyzed to confirm the results. A dose estimation method by imaging plates was studied to develop a semi-quantitative analysis of radionuclides in contaminated areas. Several kinds of plants collected from the Chernobyl and JCO accident areas were used. It has been found that the sensitivity of photo-stimulated luminescence (PSL) depended on the content of fluorine. PSL had a significant energy-dependent sensitivity at low energy (60keV).

2) Behavior of radionuclides within the body

(Y. Nishimura, Y. Watanabe, S. Homma-Takeda and M. Yukawa)

Tritium dynamics in the reproductive organs and salivary glands were examined in Wistar adult male rats exposed to 3H-thymidine. While the uptake and retention of tritium in the testis and epididymis were similar to those of the liver and kidney, the amounts of residual tritium were high in the prostate and salivary glands, indicating that these organs may act as a radiation source after exposure to tritium.

The effect of long-term administration of a chitosan diet was studied in F-344 female rats. One group was fed a diet containing 5% w/w of chitosan while another group was fed a standard diet, and their survival rates were observed. The average life span was 867 ± 16.8 days in the standard diet group and 904 ± 22.8 days in the chitosan diet group. Thus life expectancy was extended in the chitosan diet group.

The effects of X-ray irradiation on cultured cells of Japanese cedar were investigated. Cell death in the cultured cells was increased drastically by X-ray irradiation at 5 Gy, which is the minimum dose inducing radiosensitive programmed cell death (apoptosis) in mammalian cells. This was accompanied by nuclear DNA fragmentation, which is typically observed both in apoptosis of mammalian cells and in hypersensitive programmed cell death observed in plant cells exposed to various environmental stresses.

3) Internal dosimetry for radiological protection

(N. Ishigure, T. Nakano, M. Matsumoto and H. Enomoto)

Recently developed biokinetic models of ICRP permit realistic description of the behaviour of radionuclides in the human body. This, however, has made the interpretation of bioassay data extremely difficult. Thus computer programs for implementing these models are in great demand, but very few are available. In the present work the personal computer-based software, MONDAL2 (monitoring to dose calculation ver. 2) has been developed, that enables users to estimate intake activity and the resulting effective doses from bioassay measurements for both workers and members of the public. This software runs on Microsoft Windows 95, 98, Millennium edition, 2000 or XP and it is distributed by NIRS free of charge.

To harmonize methodology for internal dosimetry throughout Japan intercomparison/intercalibration exercises among facilities are planned. Four sets of seamless BOMAB (bottle manikin absorption) Phantoms were constructed to use for intercalibration of whole body counters. Each set consisted of ten bottles made of polyethylene plastic. One set of them will be used for background counting by filling each bottle with water or KCl solution through a screw-type fill port. The other three sets will be filled with radionuclide in agar matrix. The radionuclides to be used are 60Co, 137Cs and 133Ba.

4) Radiation epidemiology and risk assessment

(Y. Yoshimoto, S. Yoshinaga and T. Tsukagoshi)

We have continued epidemiologic research for health effects of low-dose and/ or low-dose rate exposure of radiation and potential radiation risk of the public near a nuclear power plant (NPP) in Japan. Generally it is not easy to quantify cancer risk of medical radiological work. The mortality follow-up of Japanese radiological technologists showed a larger healthy worker effect in non-tumor diseases than in cancers and suggested association of cancers of lymphatic and haematopoietic tissue with radiation exposures in early periods. Superficial increase by ecological studies can raise a social concern even for small radiation risks due to NPP routine operations. Our recent analysis showed no increased risk for solid cancers or cancers of digestive organs in areas with a Japanese NPP. Excess risk of thyroid cancer has still been seen in the former Soviet Union following the Chernobyl accident. These findings were summarized as a publication of cancer risk assessment for low-level exposure including non-radiation occupational/ environmental circumstances. Cooperation with other research institutes in Japan or abroad has continued for studying health effects of occupational exposures. Besides, we took up effects of modification of radiation-induced cancers and exposures from radon in drinking water, We have accepted a Sri Lankan researcher as an exchange scientist.

5) Distribution of radionuclides in the ocean

(M. Yamada, T. Aono, J. Zheng, Z.L. Wang, T. Nakanishi, T. Sakuragi, M. Kawasaki, M. Oouchi, N. Takahashi and C. Oowada)

We reported an analytical method for ^{239}Pu and ^{240}Pu in marine sediment samples which uses quadrupole ICP-MS. To avoid the interference of uranium hydride in the determination of ^{239}Pu, a simple anion-exchange chromatography system was employed for the separation and purification of Pu from the sample matrix. A sufficient decontamination factor of 1.4×10^{4} for U was achieved. High sensitivity for Pu determination was obtained, which led to an extremely low concentration detection limit of *ca.* 8 fg/ml (0.019 mBq/ml for ^{239}Pu; 0.071 mBq/ml for ^{240}Pu) in a

sample solution or an absolute detection limit of 42 fg in 5 ml sample solution by using the shield torch system under normal plasma conditions. The method was validated by the analysis of $^{239+240}$Pu and ^{240}Pu/^{239}Pu ratio in IAEA 368 (ocean sediment) reference material, the analytical results indicated that the accuracy of the method was satisfactory. The developed method was successfully applied to a study on Pu behavior in the sediments from Sagami Bay, Japan. The observed high ^{240}Pu/^{239}Pu ratio in the sediment core indicated that there was additional Pu input derived from Bikini close-in fallout in addition to the global stratospheric fallout.

6) Mechanism of accumulation of radioisotopes by marine organisms

(T. Ishii, M. Nakahara, M. Matsuba, H. Kaeriyama and K. Oginuma)

We are studying about various factors controlling the bioaccumulation of radioisotopes. Information on feeding rate of fish in various environments is important for not only understanding fish ecology but also for getting basic parameters to rear fish under experimental conditions allowing evaluation of physiological characteristics including excretion rate of radionuclides. Traditional analysis of feeding rate of fish in actual environments includes counts, frequency of occurrence, volume or weight of individual prey items and gastric evaculation. These methods are time consuming and the estimates cannot be used for generalization if food consumption varies between days or seasons. Daily feeding rate of the bastard halibut Paralichthys *olivaceus* taken off the Pacific coast of Aomori Prefecture was estimated by a radioisotope method. The feeding rates were obtained by dividing the daily intake of ^{137}Cs by the concentration of ^{137}Cs in the food. The concentrations of ^{137}Cs of the bastard halibut and the stomach contents were measured and using these data together with previous information on the absorption and the retention of the ^{137}Cs in this species, the daily feeding rates were estimated. The radioisotope method gave the mean daily feeding rate of $3.7 \pm 0.4\%$ of the body weight for the bastard halibut during the period of October to December.

7) Assessment of impacts of radioactive substances released into the marine environment

(T. Watabe, S. Yokosuka, A. Kurosawa)

Marine organisms sometimes show a high affinity specifically to a chemical element or a radionuclide and accumulate it to levels high enough to be readily detected by ordinary measurement techniques. Such organisms have been often used as a "biological monitor" in an environmental surveillance program not only for just monitoring the releases of radionuclides but also for tracing the temporal and spatial changes of their distribution in the marine environment, since the level of radioactivity released under control is generally too low to be detected directly in seawater. In the present study, radioactivity measurements were carried out for marine organisms such as a common species of brown algae (*Sargassum thunbergii*) and mollusks including some species of gastropods of the family of Buccinum and squids (*Todarodes pacificus, Thysanoteuthis rhombus,* etc.) for exploring the marine environment background levels of ^{99}Tc (half-life: 2.111×10^5 y) and ^{108m}Ag (half-life: 418.21 y). The geographically wide distribution of the organisms made it possible to compare the background levels of radioactivity between coasts in Japan. In addition, the comparison of the specific activity of ^{108m}Ag in the viscera of the mollusks among the species inhabiting layers at different depths allowed a general trend of vertical distribution for the nuclide to be drawn.

Major publications:

1) Sahoo, S.K., Shiraishi, K. and Masuda, A.: Environmental Studies of Geochemical Behaviours of Artificially Produced Uranium Isotopes. *Geochim. Cosmochim.* Acta, 67, A407, 2003.
2) Homma-Takeda, S., Nishimura, Y., Watanabe, Y., Imaseki, H., and Yukawa, M.: Elemental Imaging of Rat Epididymis by Micro-PIXE Analysis. *Nucl. Instrum. Methods in Phys. Res.* B 210, 368-372, 2003.
3) Nishimura, Y., Sahoo, S.K., Kim, H.S., Honma-Takeda, S., Watanabe, Y. and Inaba, J.: Biokinetics of Radiotellurium in Rats. *Radiat. Protect. Dosimetry,* 105, 285-290, 2003.
4) Ishigure, N., Nakano, T., Matsumoto, M. and Enomoto, H.: Database of Calculated Values of Retention and Excretion for Members of the Public Following Acute Intake of Radionuclides. *Radiat. Protect. Dosimetry,* 105, 311-316, 2003.
5) Yamada, M. and Aono, T. : Vertical Profiles of $^{239+240}$Pu in Seawater from the East China Sea. *J. Radioanal. Nucl. Chem.,* 256, 399-402, 2003.

3.4. Environmental and Toxicological Sciences Research Group

Satoshi Yoshida, Ph.D., Team Leader

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

- Multi-element analyses of environmental samples (such as soil, plants, mushrooms, and earthworms) by ICP-MS and ICP-AES, with special emphasis on the chemical form of the elements.
- 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. For example, the burning of fossil fuels produces the sulfur and nitrogen oxides which cause acid rain, and also produce the carbon dioxide which causes global warming. The incineration of wastes produces dioxins which harm human health, and nuclear power generation produces radioactive wastes that must be safely stored for thousands of years. Unfortunately, there is no established method for discussing the impacts of different types of environmental toxicants together, and there are no methods for comparing the degree of their impacts each other. For example, scientific knowledge is insufficient to correctly compare the environmental impacts of thermal and nuclear power generation.

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 2003-2004.

Progress of Research:

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 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 technetium, plutonium, and

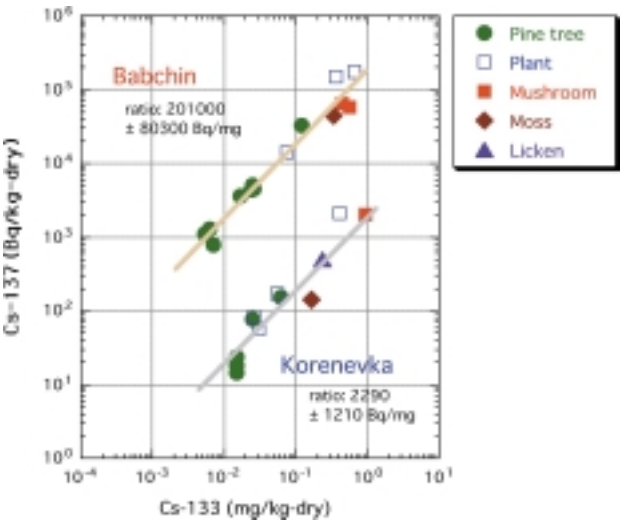

Fig.2 Relationship between stable Cs and ^{137}Cs in biological samples collected in two different forests, Babchin and Korenevka, in Belarus (Yoshida et al. 2004).

uranium, in environmental samples.

Forests are important ecosystems in the terrestrial environment, and are one of the team's research targets because they tend to accumulate radiocesium discharged into the atmosphere through nuclear weapons testing and nuclear accidents. As the chemical behavior of radiocesium is expected to be almost identical to that of stable Cs, analyses of stable cesium (Cs) and related stable elements should be useful in gaining an understanding of the long-term behavior of radiocesium and its equilibrium distribution. Fig.2 shows the relationship between ^{137}Cs and stable Cs in biological samples collected in 1998 in two forest sites with different contamination levels in Belarus. Even though several different species and parts of the same species were included, the concentration ratios of ^{137}Cs to stable Cs were fairly constant for samples collected at the same forest site. This finding suggests that ^{137}Cs, mainly deposited in forest ecosystems as a result of the Chernobyl accident in 1986, were well mixed with stable Cs within the biological cycle in the forest ecosystems by 1998. The transfer factor for each biological sample of ^{137}Cs was almost the same as that of stable Cs, when calculated based on concentrations in the organic soil layer. This suggests that the stable-Cs-based transfer factor could be used as equilibrium transfer factor of ^{137}Cs for many different types of biological samples in the forest.

Experimental Model Ecosystem Research Team:

A common index applicable to ecological toxicity is needed for a comparative evaluation between the effects of ionizing radiation to environmental biota and ecosystem, and those of other environmental toxicants. Ecosystems consist of various kinds of organisms, and have various characteristics that can be used as endpoints for the evaluation of ecological effects. This team has proposed an index for the holistic evaluation of effects on various ecological parameters. 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. To demonstrate the usefulness of this index, we analyzed ecotoxicological data using the EEI for the effects of gamma-rays and other toxicants on a microcosm consisting of three microorganisms. The results showed that 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 for the microcosm (ED_{50}), at which the EEI became 50 percent, could be obtained for each toxic agent. In conclusion, the EEI can holistically represent the effects of toxicants on various endpoints in model ecosystems. Since the ED_{50} is a useful index for quantitative comparison of effects on model ecosystems between ionizing radiation and other toxic agents, it is expected that it will contribute to the comparative evaluation of effects on natural ecosystems.

In another study, the effect of toxic agents on the material flow in model ecosystems was investigated using a ^{13}C tracer. *Daphnia magna* was exposed to radiation and cultured in a medium containing phytoplankton, which was previously labeled with ^{13}C in the form of sodium bicarbonate. The concentrations of ^{13}C in the *Daphnia magna* exposed to radiation were lower than the control, which was considered to be due to a lower intake of phytoplankton by inactivated *Daphnia magna*. This result indicated that the material flow in an ecosystem could be affected by radiation, and that the change in the carbon flow could be used as an indicator of ecological function.

Environmental Toxicology Research Team:

This team is comparing the relative risks of radiation and other environmental toxicants, using colony-forming abilities and damaged DNA in animal cells as an index. It is now investigating heavy metals and chemicals responsible for environmental pollution, which are compared with the risks of radiation.

It has been reported that antimony and arsenite inhibit the repair of radiation-induced DNA double strand breaks (DNA-dsbs), but it is not well known whether or not antimony induces DNA-dsbs. DNA-dsbs are induced by radicals, whose generation is modulated by intracellular glutathione (GSH). It is not obvious whether antimony induces the generation of radicals. In the current study, the team investigated the effect of GSH depletion on the colony-forming ability and DNA damage of Chinese hamster ovary cells (CHO), by treatment with antimony and arsenite. The cytotoxicity of antimony evaluated by colony-forming ability was the same level as arsenite in cells in which the level of intracellular GSH is normal. In GSH-depleted cells induced by treatment with buthionine-sulfoximine (BSO), cytotoxicity was markedly intensified by antimony, but not by arsenite. The repair of DNA-dsbs in GSH-depleted cells was also inhibited by a lower level of antimony. These experimental results suggest that the cytotoxicity of antimony is more sensitive to changes in the intracellular GSH level than arsenite.

The effects of quinone (a metabolite of benzene) on colony-forming ability and DNA-dsbs in CHO and xrs-5 (DNA-dsb repair deficient mutant cell) were also investigated. Colony-forming ability was inhibited at a lower level of quinone in xrs-5 than CHO, and DNA-dsbs were induced by exposure of quinone.

In a number of studies, DNA damage-induced apoptosis has been reported to be dependent on p53. The team compared apoptosis induced by arsenite with radiation in the thymocytes of p53 knockout mice. Significant apoptosis was induced by irradiation in the thymocytes of normal mice. The extent of the apoptosis in p53 (+/-) mice was moderate, and no significant increase with radiation dose was seen in p53 (-/-) mutant thymocytes. Apoptosis induced by exposure to arsenite increased in p53 (-/-) mutant thymocytes as well as in normal mice. These findings suggest that DNA damage does not contribute to apoptosis in the cytotoxicity of arsenite.

Numerical Analysis and Computer Simulation Research Team:

The behavior of environmental toxicants and their effects on ecosystems are complicated and diverse, and cannot be fully understood using experiments and surveys of natural ecosystems alone. This team is developing a computer simulation model based on accumulated data on the behavior of toxicants in the environment, and their effects on ecosystems and living organisms. Another goal of the team is to contribute to protecting the environment from the effects of ionizing radiation, by developing a methodology for evaluating the radiation exposure of non-human species. It is also developing a mathematical model and computer simulation code to project the impact on the populations and communities of non-human biota.

The population dynamics, and mass and energy budgets, of an aquatic microbial ecosystems collected by other research teams are being simulated in a microcosm. 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. The goal in this is to define the protocols for determining the extent of the harm threatening whole species or creating imbalances between species, and thereby affecting the sustainability of the ecosystem.

Validity of this model is checked using data from the microcosm experiments. In the analysis, the intrinsic parameters of umbrella endpoints (lethality, morbidity, reproductive growth, mutation) are manipulated at the individual level, and the team is trying 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 a population's extinction. 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)T. Ban-nai, Y. Muramatsu: Transfer Factors of Radioiodine from Volcanic-ash Soil (Andosol) to Crops, *Journal of Radiation Research,* 44, 23-30, 2003.

2)R. Okayasu, S. Takahashi, H. Sato, Y. Kubota, S. Scolavino, J. S. Bedford: Induction of DNA double strand breaks by arsenite: comparative studies with DNA breaks induced by X-rays, *DNA Repair,* 2, 309-314, 2003

3)S. Fuma, N. Ishii, N. Tanaka, H. Takeda, K. Miyamoto, K. Yanagisawa, M. Saitou, Y. Ichimasa: Comparative evaluation of effects of gamma-rays and heavy metals on mobility of the water flea *Daphnia magna, Radioisotopes,* 52, 319-326, 2003.

4)S. Yoshida, Y. Muramatsu, A. M. Dvornik, T. A. Zhuchenko, I. Linkov: Equilibrium of Radiocesium with Stable Cesium within the Biological Cycle of Contaminated Forest Ecosystems, *Journal of Environmental Radioactivity,* 75, 301-313, 2004.

5)T. Sakashita, T. Hama, S. Fuma, M. Doi, Y. Nakamura, N. Ishii, H. Takeda: Effects of gamma-irradiation on CO_2 fixation and cellular proliferation of *Euglena gracilis* Z, *J. Radioanalytical and Nuclear Chemistry,* 254, 401-403, 2002.

3.5. 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 25 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 awarded for studies on air filter by Japan Health Physics Society in 1986 and Japan Association of Aerosol Science and Technology in 1997.

Contact point (E-mail): yj_yamad@nirs.go.jp

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:

Studies with different approaches to effects of radon exposure in the environments have been carried out so far. This year, research activity was focused on solutions to the problems relevant to dose evaluation of radon exposure. Particle size distribution of radon decay products is one of the most significant factors regarding the dose evaluation. In this subject, a quick measurement method with a newly designed system of a graded screen array was developed. The radon and thoron concentrations with their particle size distribution were investigated in the Chinese Loess Plateau where epidemiology studies have been conducted until now. Moreover, research on measurement of radon concentration in water was also carried out. To study on biological effects, an experiment with culture cells was carried out. Because quality assurance in the radon measurement is an important subject, an intercalibration experiment with an institute in Germany was performed to obtain international traceability. In addition, a study on development of advanced technology for a radon trap was carried out.

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

1) Particle size distribution of radon decay products

From the viewpoint of a dosimetric approach, the activity-weighted particle size distribution of radon decay products is one of the most important physical parameters for accurate dose evaluation of radon exposure. The National Research Council has demonstrated that the dose per unit exposure for inhaled unattached radon decay products is about 25 times higher than that for attached ones. A new system with a graded screen array was designed for measuring the particle size distribution of unattached

radon decay products. Use of fine wire mesh screens achieved both a high volumetric airflow rate and high alpha count rate. Consequently, this improvement produced both a high sensitivity and good precision in particle size distribution measurement for unattached radon decay products with an activity median diameter around 1 nm. From the radon/aerosol chamber experiments, the particle size distribution of unattached radon decay products was observed at around 1 nm as a narrow peak with the geometrical standard deviation of 1.1. (Fig.3)

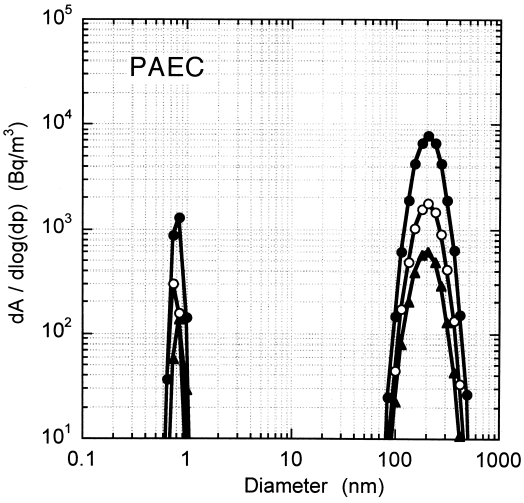

Fig.3. Particle size distributions of radon decay products. The concentrations are 150 ± 29 Bq m^{-3} (black triangles), 590 ± 45 Bq m^{-3} (open circles), and 2377 ± 68 Bq m^{-3} (black circles).

2) Field survey

Comprehensive natural radiation measurements were carried out in cave dwellings widely distributed in the Chinese Loess Plateau. Those dwellings are located in Gansu Province. Radon and thoron gas concentrations were measured using a passive integrating radon-thoron discriminative detector. Thoron decay products concentrations were estimated from their deposition rate measurements. In particular, the particle size distribution measurement was made using a diffusion battery in some houses. Fig. 4 shows a typical particle size distribution of ambient aerosols. Two peaks were often observed below 20 nm and around 100 nm in such dwellings though the number concentration was low with a few thousand numbers/cc. Since the dose conversion factor depends on the particle size of radon decay products, this fact implies that the dose could increase significantly with such a small particle size.

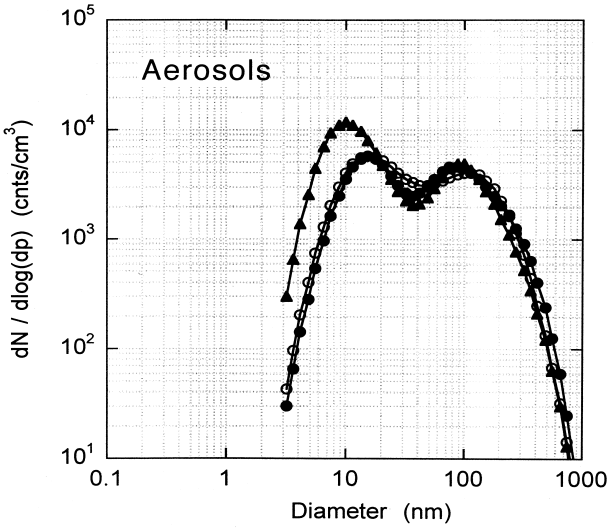

Fig.4. Typical pattern of particle size distribution of ambient aerosols in the cave dwellings.

3) Quality assurance in the radon measurements

For determining radon concentration in the atmosphere, there is no reference institute in Japan, and no method is set as a national standard regulated by the Japanese Industrial Standards. However, the gas storage ionization chamber method has been historically regarded as a standard method for radon measurements by many Japanese institutes.

The Physikalisch - Technische Bundesanstalt (PTB), the German National Institute for the Science and Technology is one European authority for metrology. Excluding France, many European institutes have traceability on radon measurements with the PTB directly or indirectly. We did a radon intercalibration experiment at the PTB. The PTB prepared radon gas in a chamber as the reference atmosphere and the NIRS estimated the radon concentration with the ionization chamber method. The intercalibration experiment provided important information on quality assurance of radon measurements at NIRS.

4) Radon trap technique

Radon is noble gas and chemically inert. However it seems that radon reacts with fluorine to form radon fluoride although the compound is not properly characterized. Based on the idea that radon can be adequately excited with a highly reactive property, radon might form some fluoric compounds. We confirmed of chemical reaction between radon and fluorine when a corona discharge was used as a promoter. The reaction was reversible, and the radon fluoride was stable only under the discharge field. Applying this phenomenon to a radon reduction technique, we developed a radon trap device using tetra-fluoric carbon (CF_4) gas. The trap efficiency of the device was over 99% at CF_4 of 5%. When the corona discharge was stopped, the trapped radon

was immediately released. The mass balance between trapped and released radon was reasonable and the trap performance was confirmed.

5) Radon in water

It has been reported that high radon concentrations can occur in water supplies from groundwater. Measurements of radon in water have been conducted by many investigators so far. While liquid scintillation counting is widely used for radon-in-water measurements in Japan, there are other available devices such as IM-fontactoscopes and atmospheric radon monitors with bubbling kits. In the present study, an intercomparison exercise was conducted for four devices for radon-in-water measurements. There was good agreement among the measured values (differences were within ± 3 %) for other devices than the IM-fontactoscope. The values measured with the IM-fontactoscope deviated from other measurement values. Since IM-fontactoscopes are used at some institutes in Japan even nowadays, it is necessary to check values measured with them for determination of radon-in-water concentrations.

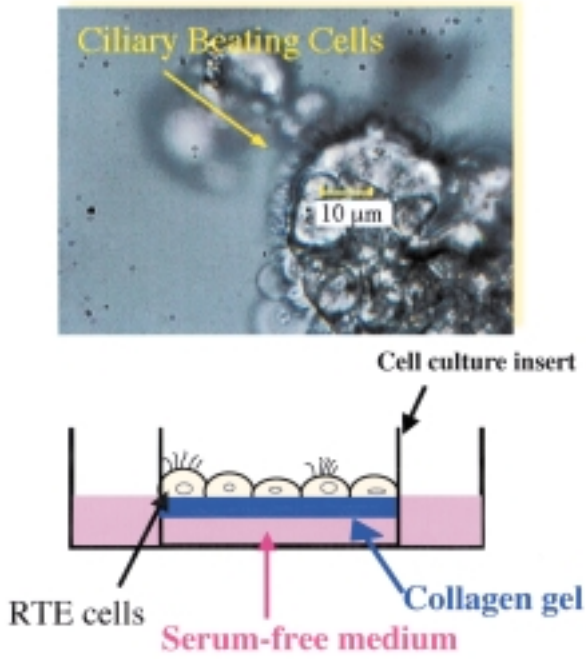

Fig.5. Photograph of rat tracheal epithelial (RTE) cells under the ALI culture (upper), and the cutview of the ALI culture (lower)

6) Exposure of cultured cells

One of the most important problems for evaluating biological effects of radon exposure is establish a method for estimation of the accurate absorbed dose. To consider the actual absorbed dose, exposure conditions for tracheal epithelial cells *in vivo* were reconstructed as an *in vitro* exposure system using an air-liquid interface culture (ALI culture). In the ALI culture, the apical surface of epithelial cells is not covered with culture medium. So the cells can be exposed to the short-range alpha rays of radon under the same conditions as in vivo. For rat tracheal epithelial cells, the dose response of ALI culture to X-rays proved to be the same as that for *in vivo* conditions. This result proved that ALI culture will be one of the most useful methods to facilitate future studies for investigation of the biological effects induced in tracheal epithelial cells by radon exposure.

Major publications:

1) Ishikawa, T., Yamada, Y., Fukutsu, K., Tokonami, S.: Deposition and clearance for radon progeny in the human respiratory tract, *Radiat. Prot. Dosim.,* 105, 143-148, 2003.
2) Tokonami, S., Furukawa, M., Yamada, Y. et al.: Characteristics of radon and its progeny concentrations in air-conditioned office buildings in Tokyo, *Radiat. Prot. Dosim.,* 106, 71-75, 2003.
3) Fukutsu, K., Yamada, Y., Tokonami, S., Iida, T.: A new graded screen array for radon progeny size measurements and its numerical verification, *J. Atmos. Electr.,* 23, 49-56, 2003
4) Ichitsubo, H., Yamada, Y., Shimo, M., Koizumi, A.: Development of a radon-aerosol chamber at NIRS - general design and aerosol performance -, *J. Aerosol Sci.,* 23, 49-56, 2003.
5) Fukutsu, K., Yamada, Y., Tokonami, S., Iida, T.: Newly designed graded screen array for particle size measurements of unattached radon decay products, *Rev. Sci. Instr.,* 75, 783-787, 2004.

3.6. 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) degrees from University of Tokyo. After working as a postdoctoral fellow (1976-1978) at Cornell University, he joined the Faculty of Pharmaceutical Sciences, Unversity of Tokyo as an Assistant professor in 1978. In 1982, he joined to the National Institute of Radiological Sciences. His research interest is the development of antioxidants and radioprotectors, and the elucidation of thier 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 vivo* when organisms are exposed to stresses from external factors such as radiation or ultraviolet light. The 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 group conducts studies on redox regulation research for biochemical effects 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 (・OH), peroxyl radicals (LOO・), and nitric oxide (NO) generated in vivo by radiation), studies on biological effects by radiation (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), and studies on redox regulation substances (development of antioxidants, radical scavengers, and radioprotectors from synthetic compounds, natural products, and medicines, and elucidation of their defense mechanisms against ROS, RNS, and free radicals).

Progress of Research:

The Redox Group consists of four teams, which investigate the following topics.

1) Studies on bioradicals generated by radiation.

We have detected *N-tert*-butyl- α-phenylnitrone (PBN)-CH_3 adduct in the bile of rats injected intraperitoneally with a dimethyl sulfoxide solution of PBN and irradiated with X-rays (Fig. 6). It was confirmed using a scavenger of hydroxyl radical (・OH) that the PBN-CH_3 adduct detected in the bile of the rats is derived from secondary methyl radical formed by the reaction of solvent dimethyl sulfoxide and ・OH. This method was applied to show the ・OH scavenging activity of cysteamine and bunte salt.

In vivo ESR signal intensity in the abdomen of mice injected with *N*-acetoxy-3-carbamoyl-2,2,5,5-tetramethylpyrrolidine (ACP) increased by the administration of sodium nitroprusside, a NO

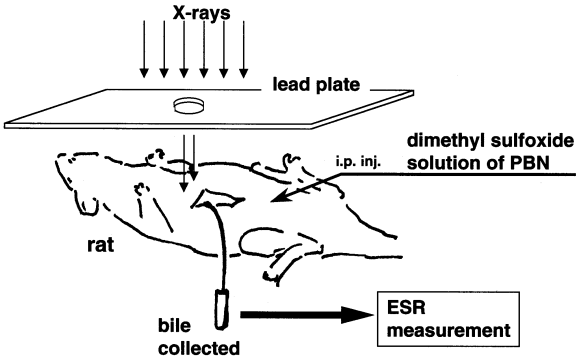


Fig.6
In vivo monitoring of hydroxyl radical generation caused by X-ray irradiation of rats using the spin trapping/EPR technique.

generator. This finding suggests that ACP may be applicable to *in vivo* detection of NO production.

Basic *in vitro* study of spin trapping with 5,5-dimethyl-1-pyrroline-*N-oxide* (DMPO) and 5-(diethoxyphosphoryl)-5-methyl-1-pyrroline-*N-oxide* (DEPMPO) revealed that only DMPO enhanced the formation of ・OH from $^1O_2$. Both DMPO and DEPMPO were proved to permeate through lipid bilayers. The ESR spin trapping technique and scopoletin fluorescence spectroscopy, respectively, demonstrated that ・OH and H_2O_2 were generated dose-dependently in aqueous solution by the irradiation of X-ray or heavy ion particles.

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

We focused on both responsive genes and an endogenous retrovirus, intracisternal A-particle (IAP) with H-type long-terminal repeat (LTR), that is an endogenous mutagen and is activated by damages caused by radiation and /or ROS. The kinetic analyses were done by the measurement of exact amounts of these cellular RNA levels. The exactness of the method to quantitate RNA based on real-time reverse transcription polymerase-chain reaction (rt-RT-PTR) that was established in the last year was compared to the quantitative Northern blot hybridization. Both methods gave closely related data on the mean levels of RNA. On the other hand, the rt-RT-PCR method showed advances on both convergence and reproduction of data with a standard deviation (SD) lower than 10%, though the Northern method gave the SD of approximately 20%. Using the rt-RT-PTR, we found that cysteamine, an antioxidative radioprotector, activated the expressions of both heme oxygenase 1 (HO-1) and junB gene in murine macrophage cell line RAW264.7. The quantitative rt-RT-PCR method was further improved for specificity as well as accuracy. Using the improved method, levels of RNA for the IAP with H-type LTR in the presence of closely related RNA fragments were successfully quantified. Selective and continuous activation of the IAP with H-type LTR in hematopoietic cells in C3H/He inbred mice was revealed. The cellular metabolic systems for ROS have potential to modify the radioresistance, since living cells are damaged by the reactive oxygens generated by low LET radiation. To study the effect of the metabolic enzymes on cellular damage by radiation, cDNAs for glutathione peroxidase (GPx)1, GPx4, super oxide dismutase (SOD) 2 and SOD3 were isolated. We constructed a series of expression vectors for these genes from modifications of amino acid sequences. Cell lines were established by the stable transfection of these vectors into the RAW264.7 cell line.

3) Radiation effects on endocrine systems.

We demonstrated previously that administration of NO scavenger or NO synthase inhibitor decreased the incidence of mammary tumors of rat irradiated with gamma-rays. Thus NO might participate in radiation-induced tumorigenesis. Subsequently, we examined the effects of ionizing radiation on the production and action of NO in the epithelium of mammary glands using a mouse mammary epithelial cell line (HC11). In the culture medium of HC11 cells, an elevation (3-5 fold) in the concentration of nitrite that appeared to be derived from the oxidation of NO produced by the cells was detected with Griess reagent after X-ray irradiation (~30 Gy) of the cells. However, this elevation was not inhibited by treatment with inhibitors of NO synthase (NOS), such as N^G-monomethyl-L-arginine (L-NMMA) and *S*-methyl- L-thiocitrulline (SMTC). Therefore, it is plausible that the nitrite is not derived from the NO produced by the iNOS mediated pathway in mammary epithelial cells, and/or that epithelial cells may not be a source of NO, and other populations, such as myoepithelial cells, may contribute to the production of nitrite following X-ray irradiation in the mammary gland.

On the other hand, to elucidate the role of NO in cellular and molecular events, we examined the effect of NO on the expression and localization of tight junction-associated proteins in a mouse mammary epithelial cell line (HC11). Continuous localization around the cell perimeter of occludin and ZO-1, components of a tight junction, was disorganized, and descending expression of these tight-junctional proteins was revealed in HC11 treated with NOC18, a NO donor. Tyrosine phosphorylation of several proteins was induced in a non-ionic detergent insoluble fraction of the cells incubated with NOC5, another NO donor. Furthermore, immunocytochemical observation for the phosphorylated proteins in the NOC5 treated cells showed distinct labeling at cell-cell junction sites. These results suggest that NO influences expression and localization of tight junctional proteins in mammary epithelial cells, and that the phosphorylation of these proteins may participate in functional modification of tight junctions.

4) Studies on damages of cellular components and dysfunction of proteins by radiation and ROS, and redox reguration substances.

To estimate the oxidative DNA damage by X-ray

irradiation, the level of 8-hydroxy-2'-deoxyguanosine (8-OHdG) in extracted cellular DNA was measured by HPLC with electrochemical detector. The formation of 8-OHdG increased dose-dependently in a range from 0 to 400Gy. The change of activity for antioxidative enzyme such as SOD and GPx by radiation was also investigated. The GPx activity (2 hours to 4 day) in C3H/He male mouse liver by whole-body irradiation (X-ray 15Gy) decreased compared with the non-radiation group, while there were no significant differences for SOD activity. This result shows that the radiosensibility of GPx is higher than that of SOD. The dysfunction of protein by peroxynitrite(PN) and the development of scavengers against PN were studied. It was demonstrated that nitration of cytochrome c by PN resulted in the suppression of the activity of apoptosome complex (caspase-9/Apaf-1/cytochrome c). The involvement of other apoptotic factors in nitration-dependent cytochrome c inactivation for the apoptosis-cascade execution was investigated, and Smac/DIABLO, another apoptogenic factor inactivating IAP (inhibitor of apoptosis), was found to be released from mitochondria after the continuous PN treatment, suggesting that Smac/DIABLO response was not modified after PN treatment, and was potentially apoptogenic. In the light of these results, it was suggested that cytochrome c nitration after continuous PN exposure affected the function of the apoptosome complex directly, and resulted in inactivation of the caspase-9 dependent caspase cascade.

An explorative investigation for PN scavengers was also performed, and it was found that several indole derivatives had a specific activity for the inhibition of nitration reaction by PN. This result implies that a new pathway of nitration by PN other than the caged radical pathway should be proposed.

The radical-scavenging mechanism of phenolic natural antioxidants has been investigated in O_2-saturated propionitrile at 203 K by means of electron spin resonance. Artepillin C, a major component of Brazilian propolis, was found to scavenge cumylperoxyl radical *via* a one-step hydrogen atom transfer. On the other hand, the scavenging reaction of cumylperoxy radical by (+)-catechin or quercetin proceeds *via* an initial electron transfer followed by proton transfer.

One-electron oxidation potentials of (+)-catechin and quercetin determined by the second-harmonic alternating current voltammetry indicated that the more negatively shifted the one-electron oxidation potential was, the faster the radical-scavenging reaction becoame.

Major publications:

1) Anzai, K., Aikawa, T., Furukawa, Y., Matsushima, Y., Urano, S. and Ozawa. T.: ESR measurement of rapid penetration of DMPO and DEPMPO spin traps through lipid bilayer membranes, *Archives of Biochemistry and Biophysics,* **415**, 251-256, 2003.
2) Nakanishi, I., Ohkubo, K., Miyazaki, K., Hakamata, W., Urano, S., Ozawa, T., Okuda, H., Fukuzumi, S., Ikota, N. and Fukuhara, K.: A Planar catechin analogue having a more negative oxidation potential than (+)-catechin as an electron-transfer antioxidant against a peroxyl radical. *Chem. Res. Toxicol.,* **17**, 26-31, 2004.
3) Nakagawa, H., Takusakawa, M., Arima, H., Furukawa, K., Kinoshita, T., Ozawa, T. and Ikota, N.: Selective scavenging property of the indole moiety for the nitrating intermediate of peroxynitrite. *Chem. Pharm. Bull.,* **52**,146-149, 2004.
4) Ishihara, H., Tanaka, I., Wan, H., Nojima, K.and Yoshida, K.: Retrotransposition of limited deletion type intracisternal A-particle elements in the myeloid leukemia cells of C3H/He mice. *J. Radiat. Res.* **45**, 25-32, 2004.
5) Saito, K., Takeshita, K., Anzai, K. and Ozawa, T.: Pharmacokinetic study of acyl-protected hydroxylamine probe, 1-acetoxy-3-carbamoyl-2,2,5,5-tetramethylpyrrolidine, for *in vivo* measurements of reactive oxygen species, *Free Radic. Biol. Med.,* 36, 517-525, 2004.

3.7. Basic Study of Radiation Hazards

Isamu Hayata, Ph.D.
Director, Radiation Hazards Research Group

Outline of Research Career:

Dr. Hayata worked for three years at Roswell Park Memorial Institute in New York State as a research fellow. He received a Ph.D. from Hokkaido University in 1976 for his study on unusual Ph1 translocation in human chronic myelocytic leukemia. His major works at NIRS during 28 years are: 1) Development of cytogenetical methods and of automated system to detect the effects of low dose radiation, 2) International collaborative studies on chromosome aberrations in high background radiation areas, 3) Multidisciplinary research and management under Nuclear Cross-over Research Project in collaboration with other six national institutes, 4) Biodosimetry of the accidentally exposed persons such as those in JCO Tokaimura criticality accident, 5) Cytogenetical study on the genesis of radiation-induced mouse leukemia.

Contact point (E-mail): hayata@nirs.go.jp.

Objectives:

This research group aims at the overall investigation of radiation hazards 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.

First team

The analysis of radiation-induced DNA damage, including chromosome aberrations, produces 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. Recently, we constructed a more cost-effective and flexible metaphase finder system than before. This system is indispensable for automated chromosome analysis.

Second team

The most remarkable effects of radiation can be detected in hematological tissues. Adaptive response and bystander effect are two important phenomena among radiation effects on embryogenesis in radiobiology with a critical impact on novel bioresponse mechanisms and risk estimates. The second team has been analyzing hematological changes in irradiated mice and effects of radiation in irradiated mouse fetuses.

Third team

The third team studies molecular mechanisms underlying radiation hazards, with the aims of establishing a scientifically justified risk assessment of radiation and of further improving radiation medicine.

Fourth team

The fourth team elucidates the mechanism of the effects of radiation on the proliferation and differentiation of mammalian cells at cellular and molecular levels.

Fig.7.
Metaphone finder system

Progress of Research:

First team

Chromosomes of lymphocytes of the residents in a high background radiation area (HBRA) in the southern China, where the level of natural radiation is 3 to 5 times higher than a control, were studied in collaboration with the Chinese National Institute for Radiological Protection, Chinese Center for Disease Control and Prevention. The effect of radiation was detected in the yield of dicentrics but not in that of translocations. Since dicentrics and translocations are equally induced by radiation, it can be concluded that the effect of radiation 3 to 5 times higher than the normal level is not significant compared with that of other clastogens such as chemicals and metabolic factors (active oxygen species) that affect the human body under normal living circumstances. Further study on the effect of smoking as one clastogen is being conducted.

For biological dosimetry by counting chromosomes aberrations, automation techniques are required to process a large number of sample preparations at low dose radiation exposure. Metaphase Finder is an optical microscope system, which automatically scans and finds metaphase cells on the slide glass, and relocates metaphase cells to the center of the field of view of the microscope to observe chromosomes in high magnification. There are several commercial products of metaphase finders, but these dedicated-system products are usually expensive and inconvenient for fitting to the variety of conditions of sample preparations.

Now, we have constructed an improved system by assembling each component of the system, such as the microscope, automated stage and computer, by selecting from commercially available products, instead of purchasing one dedicated system. The new system has high cost-effectiveness and high flexibility in adapting to the new staining methods, such as chromosome painting.

This Metaphase Finder system consists of the following components: an optical microscope, a motorized sample stage, an auto-focusing unit and two CCD cameras for focusing and for image acquisition. These components are controlled by a personal computer. The image recognition software for detecting metaphase cells from the microscope image was developed on the programming environment provided by general-purpose image analysis software.

The processing speed of this Metaphase Finder system is 20 to 30 minutes per slide glass (typical scan area is 20 mm x 50 mm), which is sufficiently acceptable for practical use and remarkably improved from the speed of our previous model of 1993. The algorithm for detecting metaphase cells has also been improved to adapt to the variety of conditions of sample preparation.

This new system is scheduled to be distributed to several laboratories in Japan, where it will be tested for practical use.

Second team

The evidential correlation and interaction between two phenomena of adaptive response (AR) and bystander effect (BE) were observed in cultured limb bud cells. AR was induced by conditioning irradiation (0.3 Gy) of the E11 cells resulting in a significant protective effect against the occurrence of apoptosis, inhibition of proliferation and differentiation induced by a challenging dose of 5 Gy on the next day. Both protective and detrimental BE were observed, namely, irradiating 50% of the E11 cells with 0.3 Gy led to a successful induction of the protective effect, and irradiating 70% of the

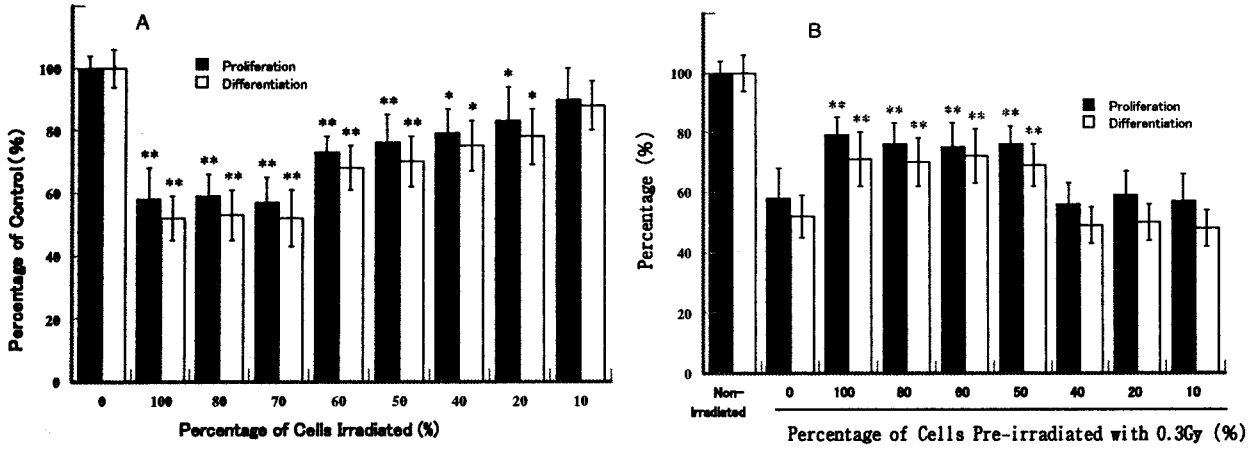


Fig. 8.
Survival rates of cultured limb bud cells showing a detrimental bystander effect (A) and a protective bystander effect (B).

E12 cells with 5 Gy produced an equal detrimental effect when 100% of the cells were irradiated. Further, the BE was markedly vanished by blocking the gap junction-mediated intercellular communication. These results indicated that the BE played an important role in both the induction of a protective effect by the conditioning dose and the detrimental effect of the challenging irradiation (Fig. 8).

Third team

GADD45a gene is regulated by p53 after ionizing irradiation. Recently it was shown that p53-dependent activation of genes in human and mouse cells requires additional transcription factors such as Sp1, GKLF, Ets1, and IRF-1. To examine the possible involvement of cooperating factors in transcriptional regulation of the *GADD45a* gene by ionizing radiation, we comprehensively searched for the X-ray-inducible binding locus of nuclear factor throughout the upstream region (-2244 bp / +89 bp) and the third intron (+1389 bp / +2488 bp) of the *GADD45a* gene by EMSA using 136 probes. The X-ray-responsive binding of nuclear factors was detected at eight loci in human myeloblastic leukemia ML-1 cells. Oct, NF-κB, HNF, NF-AT, and KLF family transcription factors were identified by the competition assay. An EMSA revealing activation of a transcription factor Oct is shown in Fig.9 as an example. We conclude that these transcription factors are activated by ionizing radiation in ML-1 cells. It is possible that some of these factors cooperate with p53 to mediate transcriptional regulation of the *GADD45a* gene after ionizing irradiation.

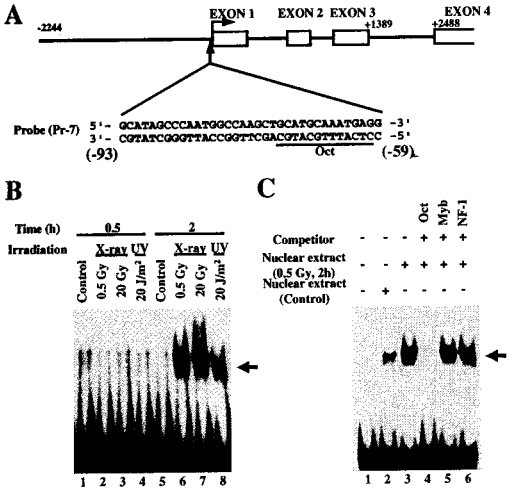


Fig.9.
Irradiation at doses of 0.5 and 20 Gy of X-rays and 20 J/m^2 of UV stimulates the binding of Oct-related factor to the GADD45a gene promoter 2 h after irradiation.

Fourth team

To clarify what factors derived from keratinocytes are involved in regulating the proliferation and differentiation of epidermal melanocytes in pigmented spots long after the cessation of UVB irradiation, granulocyte-macrophage colony-stimulating factor (GMCSF) was supplemented to melanoblasts and melanocytes in keratinocyte-depleted cultures. GMCSF induced the proliferation and differentiation of melanocytes in keratinocyte-depleted cultures. Anti-GMCSF antibody supplemented to the media inhibited the proliferation of melanoblasts and melanocytes as well as the differentiation of melanocytes from UVB-induced pigmented spots of irradiated mice, but not from non-irradiated mice. Enzyme-linked immunosorbent assay of culture media revealed that GMCSF secreted from irradiated keratinocytes was much greater than that secreted from non-irradiated mice. These results suggest that GMCSF is one of the keratinocyte-derived factors involved in regulating the proliferation and differentiation of mouse epidermal melanocytes from UVB-induced pigmented spots (Fig.10).

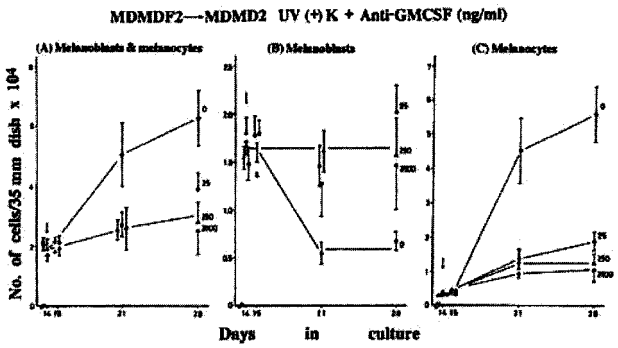


Fig.10.

Kinetics of the proliferation of epidermal melanoblasts and melanocytes derived from the control mice co-cultured with the UV-irradiated keratinocytes [UV(+)K] and the anti-GMCSF antibody. Pure melanoblasts/melanocytes in melanoblast-proliferation medium (MDMDF2) were cultured with UV-irradiated keratinocytes with melanocyte-proliferation medium (MDMD2) plus rabbit-IgG (○, control) or MDMD2 plus an anti-GMCSF antibody (●, 25; △, 250; ▲, 2500 ng/ml). In the anti-GMCSF antibody-treated culture, the number of melanoblasts and melanocytes (A) and melanocytes (C) dramatically decreased. However, the number of melanoblasts (B) did not decrease.

3.8. Analysis of Gene Networks in Response to Ionizing Radiation

Kouichi Tatsumi, M.D., Ph.D.,
Director, Transcriptome Profiling Research Group

Objectives:

We have developed a high performance gene expression profiling technique called HiCEP and in 2003 we focused on achieving high throughput with this method. We also identified genes of interest.

Specific tasks:

1.Preparing a peak database
2.Achieving high throughput
3.Establishing a knockout mouse preparation system

Progress of Research:

Preparing a peak database: We decreased the number of false positive peaks from over 50% in standard AFLP to under 5%, enabling us to efficiently isolate peaks of interest and determine the relationship between peak and gene unequivocally. We began preparing a HiCEP peak database for the mouse embryonic stem (ES) cell line, detecting about 38,000 peaks and sequencing about 15,000 of them.

Achieving high throughput: HiCEP analysis consists of six steps:

1.RNA preparation
2.cDNA synthesis
3.Preparation of HiCEP template
4.PCR
5.Separation by capillary electrophoresis
6.Data analysis using bioinformatics

By refining these steps, we achieved a 10-fold improvement in performance.

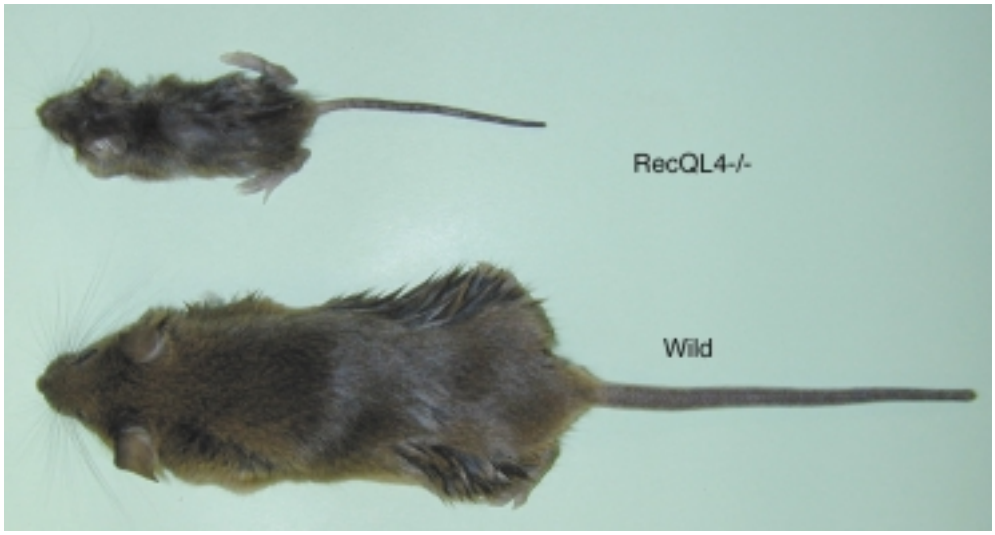
*RNA preparation: Using an automatic RNA elution system six samples can be treated simultaneously, allowing us to elute the RNA fraction from up to 48 samples. The quality of RNA fraction obtained by this procedure was good enough to use for analysis.

*cDNA synthesis and Preparation of HiCEP template: If magnetic beads are used for DNA handling, HiCEP analysis can be carried out by machine. We made a prototype automated HiCEP analyzer that can analyze three reaction plates of 96 wells apiece per week. The reproducibility is extremely good, and we are now testing the machine.

*PCR: This step requires a highly controlled PCR machine, and the variation in temperature should be less than 0.2° C. Few available PCR machines can satisfy this requirement, so we are making our own prototype.

*Separation by capillary electrophoresis: We improved the throughput of this step by a factor of ten by using a 16 capillary sequencing machine. Now we are trying to achieve a throughput of 384 capillaries.

Establishing a knockout mouse preparation system:We created knockout mice for RecOL4 and RecOL1. The RecOL4 knockout mouse exhibits glowth retardation and premature aging. This is the first example of a knockout mouse for a RocO helicase gene that represents early aging phenotype as shown in the following pictures.



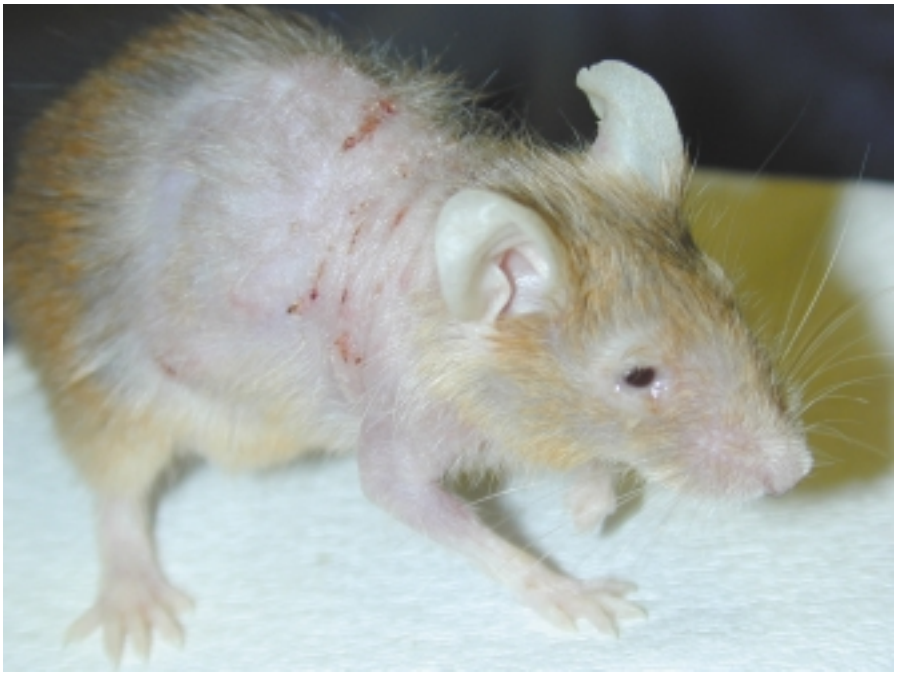


Fig.11. RecQL4-1-mice

3.9. 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 studies in the field of laboratory animal sciences. Major works are concerned with research for infectious diseases of mice and rats, pathological and physiological research for the 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 considering 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 ;

Contact point (E-mail):matu_sat@nirs.go.jp

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) ・Establishment of techniques of intracytoplasmic sperm injection (ICSI) to apply for production of transgenic mice and cryopreservation of sperm.
・Development of reproductive biotechnology such as in vitro fertilization, 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 attempts were made in the year 2003.

1)To establish the techniques of ICSI to apply for production of transgenic mice and cryopreservation of sperm.
2)To develop reproductive biotechnology such as in vitro fertilization and oocyte maturation, using inbred mice.
3)To screen mutant medaka at the third generation for their sensitivity to radiation.
4)To establish diagnostic antigens using recombinant viruses in developing a highly specific serodiagnostic method for lactic dehydrogenase virus (LDV) infection, which is one of the major virus infectious diseases in small laboratory animals.
5)To complete the compilation of data on the sensitivity of 10 strains of mice bred at this institute to bacteria（cilia-associated respiratory bacillus）, causing chronic respiratory diseases, to clarify the disease characteristics in laboratory animals used in the study of the effects of radiation.

Progress of Research:

Fiscal year 2003 is the third year in the Middle Range Reseach Plan; to date we have published ten original papers and made steady progress in this project. The followings are our research accomplishments in the year 2003.

1)Attempt was made to apply ICSI for injection of dormant sperm cryopreserved without any cryoprotectant. Comparison was made for development of ICSI embryos injected with sperm stored for 3 months and 1 year at various temperatures (-20, -80℃ and in liquid nitrogen). For 3 months storage, developmental ability of ICSI embryos after embryo transfer was approximately 20% and temperatures during storage has no significant effect. However, for 1 year of storage developmental ability of ICSI embryos injected with sperm stored at -20℃ (2%) was significantly lower than with sperm stored -80℃ (15%) and in liquid nitrogen (19%). These results indicate sperm

cryopreservation at -80℃ and in liquid nitrogen is appropriate for long (> 3 months) period of storage.

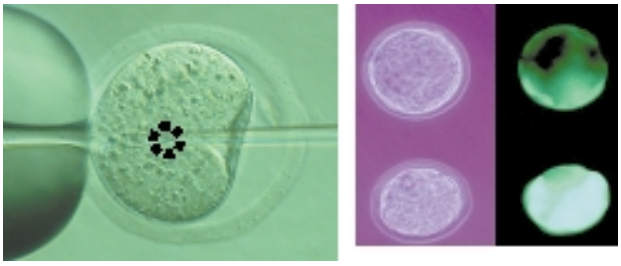


Fig.12.
Intracytoplasmic sperm injection (ICSI) in mice
(Left) Sperm head (dotted circle) is directly injected into the cytoplasm of an unfertilized ovum. Exogenous DNA can be injected with a sperm head to produce transgenic mice. (Right) In vitro cultured mouse blastocysts derived from ICSI embryos injected with DNA coding green fluorescence protein (GFP).

2)Effect of aging in vivo and in vitro on developmental competence of ICSI embryos was examined. Ova were injected with fresh sperm at 13, 16, 19 and 22 h after injection of human chronic gonadotropin (this hormone induces ovulation). In vitro development to blastocyst stage 120 h after ICSI was between 55-88% and there was no significant differences among aging periods tested both in vivo and in vitro.

3)Conditions of in vitro fertilization (IVF) were studied to improve fertilization in BALB/c mice. Attempt was made to improve in vitro capacitation of sperm. We found that isotonic osmotic pressure (305 mOsmols) and elimination of lactate results in good fertilization. Furthermore, Ca^{2+} was shown to have no significant effect on sperm capacitation unlike sperm penetration through the zona pellucida, which need high Ca^{2+} (>2.5 mM).

4)For the mutagenesis in medaka, male fish 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 treated males were pair-mated with untreated females to produce F_1 fish. Each F_1 fish was mated with an untreated partner to produce F_1 family (F_1 founder fish and the F_2 progeny). When the F_2 fish grew to adult stage, several single-pair crosses between siblings were performed for each F1 family to produce F_3 progeny. The mutations for radiation sensitivity were screened in the F_3 progeny by exposing them with X-irradiation at the dose of 2Gy. No effect has been found in normal medaka embryos at this exposure dose. We have completed the screening of 63 pairs from nine F_1 families. It was found for one F_1 family that approximately 25% of the embryos of the pair died following 2Gy X-ray irradiation. This medaka strain is considered to be a candidate mutant strain having a high sensitivity to radiation.

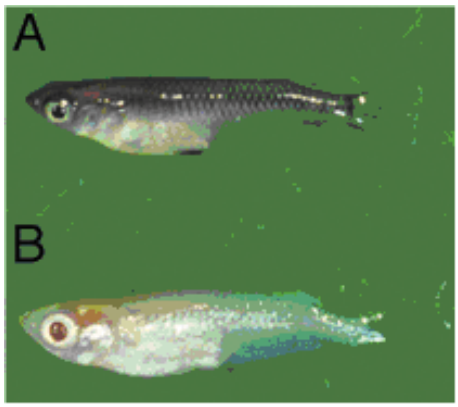


Fig.13.
Medaka inbred strains: A) HNI strain B) i3 strain.

5)To establish a highly specific serodiagnostic method for LDV infectious disease, we carried out virus core protein and envelope protein expression studies using various expression systems such as Escherichia coli, insect cells and animal cells. The expression of LDV M/VP-2 was possible in insect expression systems using recombinant vacuolar viruses. The expressed M/VP-2 protein can be harvested in the soluble state and shows properties similar to those of the M/VP-2 protein originating from a virion; it is considered to be a useful antigen for diagnosis.

6)Regarding the collection of pathological data from laboratory animals, three strains of mice (B10, B10-Thyl.1, and B10.D2) bred at this institute were inoculated with cilia-associated respiratory(CAR) bacillus, and all strains of the inoculated mice presented with moderate sensitivity to the bacterium. The collection of pathological data from the 10 strains of mice bred in this institute was completed. Furthermore, we compared histopathological changes with time after infection between mice with high sensitivity (BALB/*c-nu*/+ mice) and mice with low sensitivity (A/J mice). Compared with A/J mice, the attachment of the bacilli to the epithelial cells and the development of severe lesions in the airways in BALB/*c-nu*/+ mice were observed in early stages.

7)Collaborative studies with the Transcriptome Research Center and the Transcriptome Profiling Group have been promoted. Experiments for the

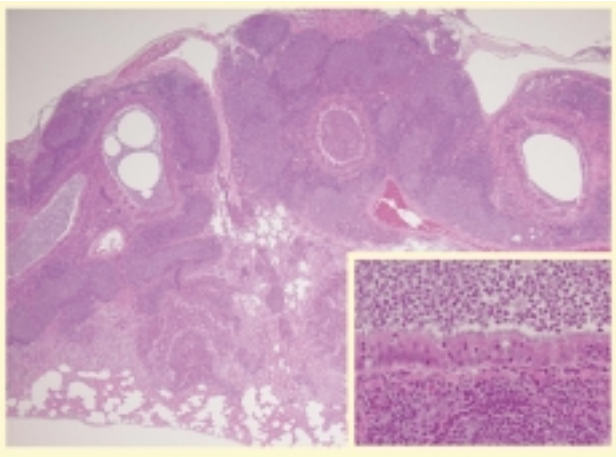


Fig.14.
Cuffing pneumonia in the lung infected with CAR bacilli. Severe aggregation of lymphoid cells around the airways. CAR bacilli (Arrow) on the epithelium. BALB/*c-nu*/+ mouse.

production of gene-manipulated mice, in which groups of new genes were identified by studying their transcriptome profiles, were carried out. That is, we generated chimeric mice derived from embryonic stem (ES) cells, by manipulating three new genes (A, B, and C) using the aggregation method for ES cells and host embryos, a simplified and practical method, which does not require various complicated equipments. The percentages of chimeric mice were as follows: chimeras derived from A gene, 28.9% (71/264) ; B gene, 19.2% (14/73); C gene, 32.1% (17/53), respectively; and control, 72.1% (145/201). Chimeric mice were established four strains and one of these strains was confirmed to be a new gene-manipulated mouse lineage.

8)Regarding the collection of physiological data on laboratory animals, we are currently collecting basic anatomical data on four strains of mice bred in collaboration with the Laboratory Animal Development and Management Office and preparing for the release of data on one strain.

Major publications:

1) Hideyuki Mizuno*, Takehiro Tomitani, Mitsutaka Kanazawa, Atsushi Kitagawa, Jorg Pawelke*, Yasushi Iseki*, Eriko Urakabe, Mitsuru Suda, Akihiro Kawano, Riichirou Iritani, Satoru Matsushita, Taku Inaniwa, Teiji Nishio*, Shigeo Furukawa, Koichi Ando, Yuzuru Nakamura*, Tatsuaki Kanai: Washout measurement of radioisotope implanted by radioactive beams in the rabbit, *Physics in Medicine and Biology*, 48, 2269-2281, 2003
2) Riki Okeda*, Shinobu Okada*, Akihiro Kawano, Satoru Matsushita, Toshihiko Kuroiwa*: Neuropathology of Delayed Encephalopathy in Cats Induced by Heavy-ion Irradiation, *Journal of Radiation Research*, 44, 345-352, 2003
3) Hiromi Omoe, Katsuhiko Omoe*, Masahiro Sakaguchi*, Yousuke Kameoka*, Satoru Matsushita, Toshiki Inada*: Analysis of protein expression by mammalian cell lines stably expressing lactate dehydrogenase-elevating virus ORF 5 and ORF 6 proteins., *Comparative Immunology, Microbiology & Infectious Diseases,* 27, 81-92, 2004
4) Seiji Kito, Yoshiko Noguchi*, Yuki Oota, Tatsuya Ohhata*, Masumi Abe, Naoko Shiomi, Tadahiro Shiomi, et.al: Evaluation of developmental competence of vitrified-warmed early cleavage-stage embryos and their application for chimeric mouse production, *Experimental Animals*, 52, 179-183, 2003
5) Akihiko Koga*, Atsuo Iida*, Megumi Kamiya*, Ryoko Hayashi*, Hiroshi Hori*, Yuji Ishikawa, Akira Tachibana*: The medaka fish Tol2 transposable element can undergo excision in human and mouse cells., *Journal of Human Genetics*, 48(5), 231-235, 2003
6) Satoshi Tanaka*, Igunasya Tanaka*, Sumiko Sasagawa*, Kazuaki Ichinohe*, Takashi Takabatake*, Satoru Matsushita, Tsuneya Matsumoto*, Yuji Ohtsu*, Fumiaki Sato: No Lengthening of Life Span in Mice Continuously Exposed to Gamma Rays at Very Low Dose Rates, *Radiation Research*, 160, 376-379, 2003

3.10. Studies on Experimental Carcinogenesis Induced by Plutonium Compounds

Yutaka Yamada, D.V.M., Ph.D.,Team Leader

Outline of Research Career:

Dr. Yamada received a Ph.D. on Veterinary Medicine from the 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 proceeded to Institute for Environmental Sciences as a senior scientist from 1999 through 2001.

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Objectives:

The purpose of this research subject is to investigate the biological effects and cancer risks of internally deposited radionuclides, especialy 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) identifing target cells for the lung and bone tumors induced by inhalation and injecion of plutonium, 2) establishing primary cell cultures of the target cells and cell lines from the tumor tissues, 3) analysing radiosensitivity 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 which genes are targeted, and 5) determining variation in target cells for lung tumors relates to lung cancer susceptibility.

In the present study, cell lines were established from plutonium-induced lung and bone tumors , and the biological properties were characterized. In addition to the lung tumor cell line, tumorigenesities of immortalized and transformed epithelial cell lines from rat respiratory tract were examined in nude mouse transplantation assay. Primary culture cells from rat trachea and lung also were established for future study of radiation-induced transformation and tumorigenicity assay.

Progress of Research:

Establishment and characterization of tumor cell lines from Pu-exposed animals

Lung tumor (adenocarcinoma) of rat exposed to plutonium dioxides was cultivated in vitro in an attempt to establish cell line by utilizing explant and trypsinization techniques. The epithelial cell line (PuD2) exhibited multilayering and anchourage-independent growth in agarose medium. Positive reaction of surfactant apoprotein A in immunohistochemical staining indicated that the PuD2 cells were derived from TypeII alveolar epithelial cells. Chromosome analysis by Giemsa staining revealed trisomy of No.4 and a marker chromosome of No.11. Transplantation of the PuD2 cells into nude mouse (BalbC nu/nu) resulted in the formation of nodule with a diameter of 12 - 15 mm within two weeks.

An cell line (mOS) was also established from bone tumor (osteosarcoma) of plutonium citrate-injected mouse. The mOs cells were morphologically similar to spindle-shaped cells or polykaryocytes. Tartrate-resistant acid phosphatase (TRAP) staining indicated that the mOS cells partially originated from osteoclast. The mOS cells developed a nodule at the injection site of nude mouse by 8-9 weeks after implantation. Use of these cell lines will allow investigation of carcinigenenic mechanisms of plutonium compounds and alpha-irradiation.
(Chromosome analysis was supported by Dr. Minamihisamatsu and Dr. Kohno)

Tumorigenesis assay of respiratory tract epithelial cell lines

Several respiratory tract epithelial cell lines established from normal rats were also transplanted to compare tumorigenicity at different stages of

cancerous development. Although virus-immortalized SV40T2 cells and gamma ray-transformed RTiv3 cells could not be tumorigenic, chemical transformed benzo [a] pyrene-induced BP (*p53* wild type), BP(P)Tu, BP130 and BP270 (*p53* mutation) cells formed a nodule three weeks after the implantation in nude mouse. These BP cell lines were transplantable and resulted in a rapid growth within two weeks in the second implantation. The growth of PuD2 cells, p53 wild type, is extremely rapid in the nude mouse. These results indicate that the tumorigenicity of respiratory tract epithelial cell lines is dependent on their different stages of the carcinogenic processes from the initiation through promotion and leading to the progression. The *p53* mutation, however, does not seem to play an important role in the tumorigenesis of rat respiratory tract epithelial cells. Association with other genes and the genetic alterations is under investigation. (Table 1)

Establishment of primary cultures of rat tracheal and lung epithelial cells

The purpose of this study is to develop a method of isolating primary Type II cells and tracheal epithelial cells from rat. Pneumocytes were isolated from lung of Wister rats by enzyme digestion and separated on isotonic density gradients. Type II cells rich fraction was recovered from the density range around 1.06 g/ml of the gradient. The Type II cells were identified by immunohistochemistry utilizing epithelial cell- specific rat cytokeratin 17 antibody and by alkaline phosphatase staining, and the purity was approximately 40% in the staining. Tracheal epithelial cells were collected after enzyme digestion and infusion of buffered solution through trachea. The Type II and tracheal epithelial cells could be subcultured in serum-free medium including epidemal growth facters on Mylar bottom dishes for alpha irradiation. This primary epithelial cell culture system will be useful for analysis of radiation sensitivity among the defferent target cells and mechanistic studies of early changes in the rat lung carcinogenesis initiated by alpha irradiation.

Major publication:

1) Comparative Study on Tp53 Gene Mutations in Lung Tumors from Rats Exposed to 239Pu, 237Np and 222Rn, *Journal of Radiation Research,* 45, 69-76 (2004)

Table 1. Summary of Characteristics of the Cell Lines

Cell Line	Animal	Origin of Cell Line	Tumorigenicity*	Anchorage-Independent Growth* *	*p53* (Exon 5-8)	Chromosome Aberration	Originator
PuD2	Rat	Lung tumor, Pu-induced	Yes	Yes	Wild type	Trisomy No.4 Marker chromosome No.11	NIRS
mOS	Mouse	Bone tumor, Pu-induced	Yes	Yes	ω	ω	NIRS
SV40T2	Rat	Type II cell from neonatal rat lung, virus-immortalized	No	No	Wild type	ω	A. Clement, Univ. Paris
RTiv3	Rat	Primary tracheal cell, gamma ray-transformed	No	No	Wild type	ω	J. L. Poncy, CEA
BP	Rat	Fetal lung, *in utero* benzo [a] pyrene-induced	Yes	Yes	Wild type	ω	E. May, CEA
BP(P)Tu	Rat	Tumor in syngeneic rat inoculated with BP cell	Yes	Yes	Codon 130 AAG to AGG	ω	E. May, CEA
BP130	Rat	Cultured BP cell	Yes	ω	Codon 130 AAG to AGG	ω	E. May, CEA
BP270	Rat	Cultured BP cell	Yes	ω	Codon 270 GTT to TTT	ω	E. May, CEA

*Tumorigenicity assay in nude mouse

**Colony formation in agarose medium

ω : Not tested

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 for 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 is now an Internal Editorial Adviser of the Journal of Radiological Protection and an Advisory Editorial Board Member of Nuclear Technology & Radiation Protection.

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Objectives:

The statutory function of the Research Center for Radiation Emergency Medicine is the establishment of a solid system for dealing with a radiation emergency; the Research Center is assigned as a tertiary emergency medicine hospital within the nuclear disaster prevention plan in Japan. Required aims are as follows.

1.To accept exposed victims who require further expert diagnosis and treatment
2.To dispatch a radiation emergency medical team to the local emergency medical headquarters
3.To facilitate exchange of information, research activities, and human resources, by constructing networks in cooperation with outside expert organizations
4.To maintain and reinforce an efficient radiation emergency medicine system under normal conditions
5.To promote technical development and research on radiation emergency medicine

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

1.Pathologic physiology of high-dose exposure
2.Chelating agents for removing radionuclides
3.Development of systems for precise measurement and evaluation in emergencies
4.Mitigation of radiation injuries
5.Emergency response 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 the emergency preparedness for 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 our 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 as the tertiary radiation emergency hospital.

A. Network System

Strengthening its institutional system to prepare for radiation emergencies by establishing three nation-wide network committees, for medicine, chromosome analysis as bio-dosimetry, and physical dosimetry.

A-1. NIRS Radiation Emergency Medicine Network Council

This is a group of experts and medical organizations from which NIRS asks for their help 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.

A-2. Chromosome Network Council

This council forms a network among nationwide organizations having dose evaluation functions based on chromosome analysis under the leadership of NIRS. Through this network, NIRS can be prepared for radiation emergencies, and also help maintain and enhance the technical standards of organizations involved by providing support and advice.

A-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 in prompt and precise dose measurement systems. It is also responsible for accumulating dose evaluation technology, while fostering followers.

A-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, a specific collaboration system with NIRS is required to be set up, specifying the steps to be performed in the prompt transfer of patients from a site to a hospital, including radiation management and prevention at the hospital, and sending patients to other facilities when necessary.

B. Training

Conducting educational training in radiation emergency medicine for medical professionals and disaster prevention personnel such as doctors and nurses involved in nuclear disaster medical care, emergency crews, and nuclear establishment employees. IAEA/RCA training workshops were conducted at NIRS on radiation emergency for medical doctors in 2001 and 2004. The following training courses were held in Fiscal Year of 2003.

(1)Radiation emergency medicine course

The course was held three times in 2003 with 20 participants in each course. More than 200 participants were trained so far. Many of them are working actively in primary or secondary medical emergency hospitals.

(2)Emergency rescue training course

The course was held three times in 2003 with 30 participants in each course.

(3) Refresher seminar for emergency medicine

This was held in Sendai on August 22, 2003.

C. Emergency Exercises

Participation in nuclear disaster prevention training, seminars on exposure medicine, and other activities conducted by local governments so as to enlighten the people by disseminating radiation exposure medicine to the area.

D. Follow-up Studies

In addition to the activities required for the tertiary emergency hospital, Research Center for Radiation Emergency Medicine also conducts research work in a wide range of areas: medical care, radiation measurement and investigation, health physics, cytogenetics, and psychology. In addition, the center's researchers 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. NIRS carries on follow-up clinics for the victims of a thermonuclear explosion test on the Bikini Atoll, patients with thorotrastosis and a JCO accident victim who survives.

D-1. Follow-up examination of the victims of the Bikini nuclear tests

During the nuclear test on Bikini Atoll on March 1, 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 almost 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.

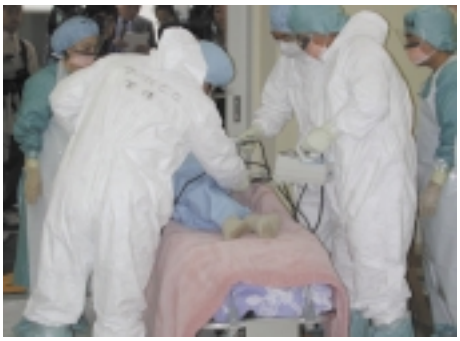
D-2. Follow-up examination of patients with thorotrastosis

Thorotrast is a radioactive contrast medium for angiography. The main constituent is thorium dioxide. A German company started sales 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 aims to estimate the amount of thorium deposit in surviving patients, investigate their clinical symptoms, analyze the relationship between the deposited amount and malignant carcinogenesis, and understand the effects of long-term internal radiation exposure on human bodies. Physical examinations of the patients were done in this year.

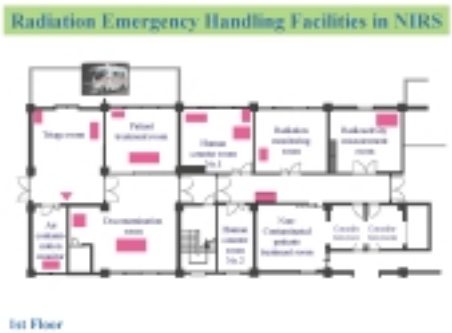
E. Database

A database contributing to exposure treatment and investigation of the victims 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 workers decide strategies to treat patients, and improve and establish 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 these accidents and exchanging information with countries that have developed radiation accident medicine. In 2003, 50 data sets for acute exposure patients were obtained from the Institute of Biophysics in Russia.

Radiation Emergency Exercise



Radiation Emergency Handling Facilities



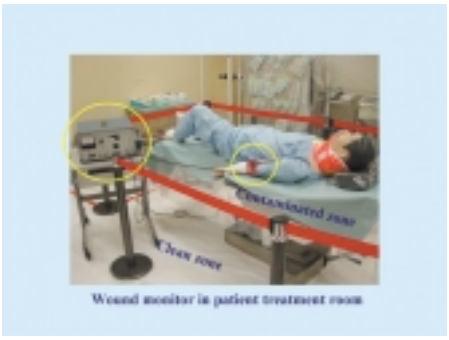


Fig.15.

4.1. The Study for Radiation Emergency Medical Preparedness

Makoto Akashi, MD, PhD
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Outline of Research:

Recently, uses of ionizing radiation and radioactive materials are increasing at hospitals, factories, universities/institutes and others. There are also many plans for new nuclear power plants. Thus, the risk of radiation accidents has been increasing, although they rarely occur. Therefore, preparedness of organizations for radiation emergency is demanded by society. In this project, fundamental research required for diagnosis and treatment for victims is performed in various fields, such as biology, biochemistry and molecular biology, medicine, zoology, nuclear engineering, mechanical engineering, physics, and radiology.

Objectives:

1) Study on pathologic physiology of high-dose exposure.

This study team aims to understand the effects of high-dose radiation exposure on intracellular signal transmission and the mechanisms of transducing the signals among cells, which need to be known for treatment of acute radiation injury. The team also aims to identify genes that are related to skin injury caused by high-dose radiation exposure, and 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 team is performing experiments using experimental animals to investigate the removal of radionuclides that have been incorporated by new agents and also their adverse effects. This team also aims to prepare manuals describing safe and effective treatments with these agents (DTPA, Prussian blue, etc.) for use in radionuclide-contamination accidents on the basis of the data from these experiments.

3) Development of systems for precise measurement and dose-assessment in emergencies

This research team aims to develop devices for measuring low-level radiation in easy-to-prepare specimens by fast and precise methods for evaluating the dose received.

4) Research on the mitigation of radiation injuries

This research team investigates pharmaceutical products (protectors) for mitigating the damage to patients exposed to radiation by conducting animal experiments. The team 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

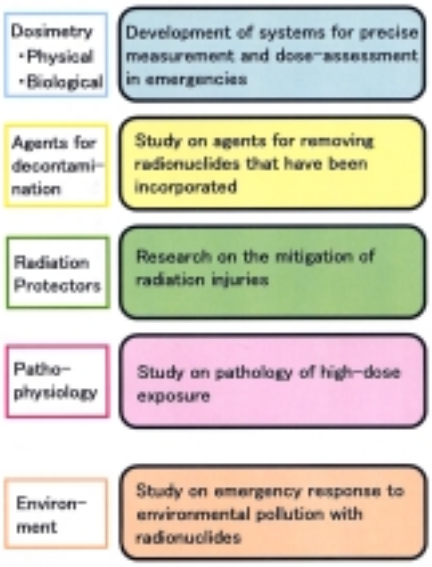


Fig.16.
The study for radiation emergency medical preparedness

pollution with radionuclides

Aims of this study are to prepare for environmental pollution emergencies due to accidents of nuclear facilities, mishandling of radioisotopes (RIs) 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 pathologic physiology of high-dose exposure.

Irradiation causes DNA damage and induces neoplastic transformation. In response to irradiation, cells induce genes or activate proteins that protect themselves from the external insult. Nuclear factor κB (NFκB) activates transcription of target genes and plays important roles in inflammation. We studied the mechanism(s) for activation of NFκB by irradiation in human monocytic cells THP-1. Gel mobility shift assays showed that irradiation stimulated the NFκB-DNA binding activity of nuclear extracts from these cells. Western blot analysis using polyclonal antibody against phosphorylated IκB protein showed that irradiation increased the levels of phosphorylated IκB. The production of tumor necrosis factor α (TNFα) was stimulated by irradiation in these cells. Treatment with exogenously-added TNFα also stimulated the NFκB binding activity with concomitant degradation of IκB. Further study found that the activation of NFκB by irradiation was inhibited by a neutralizing anti TNFα antibody. Macrophages from TNFα-deficient mice were also defective in the irradiation-induced activation of NFκB. These results indicate that endogenous production of TNF α in macrophages/monocytes is required for NFκB activation by irradiation. Our data also suggest that TNFα in monocytes/macrophages exposed to irradiation is involved in signal transduction network initiation.

Mitochondria have their own genome encoding subunits of the electron transport chain. The recent progressin studyies of mitochondria has allowed us to use mitochondria DNA(mtDNA)-depleted cells (ρ^0cells) and their control cells(ρ^+cells). Using ρ^0 cells), we studied the role of mtDNA in irradiation. Loss of mtDNA inhibited cell growth and reduced the level of reactive oxygen species (ROS) as compared to ρ^+ cells. ρ^+ cells were more resistant to irradiation than ρ^0 cells. Scavenging ROS with N-acetyl cysteine (NAC) reduced the ability of colony formation in irradiated ρ^+ cells but not in irradiated P0 cells. Upon irradiation, ρ^0 cells showed delayed G2 arrest and decreased ability of a cell to recover from the G2 checkpoint compared to γ^+ cells. Irradiation increased the generation of ROS even more in γ^+ cells. Irradiation markedly increased the levels of phosphorylated forms of ERK1/2 in γ^+ cells, whereas phosphorylated levels of the kinases were affected slightly in γ^0 cells. Furthermore, inhibition of the ERK pathway led to a delayed G2 arrest and a delayed recovery from the arrest in irradiated γ^+ cells, and treatment with NAC also induced dysfunction of the G2 checkpoint in irradiated γ^+ cells. These results suggest that the accumulation of ROS potentiated ERK1/2 kinases after irradiation in γ^+ cells, leading to less sensitivity to irradiation. Thus, mtDNA is important for the generation of ROS that act as second messenger.

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

The effects of three chelating agents, CBMIDA, 3, 4, 3-LIHOPO, and Ca-DTPA, for removing Pu-239 in rats were compared. Forty female Wistar rats, 2 months old, were pre-injected intraperitoneally with 37,000Bq/kg of plutonium nitrate and divided into four groups. Thereafter the rats of three groups were injected intraperitoneally with three chelating agents at a dose of 30mmol/kg, equivalent to a daily recommended human dose of Ca-DTPA, at intervals of 24hr for 3 days, beginning 30 min after plutonium injection on the first day of treatment. Urine and feces were collected every 24 hr. On day 4, the rats were sacrificed to obtain organs including the liver, kidney, and spleen, as well as the femur and serum. The amounts of excreted plutonium in urine of the CBMIDA and Ca-DTPA groups were increased significantly over that in the 3,4,3-LIHOPO and control groups, while those in the feces of the 3,4,3-LIHOPO group were increased significantly over the other groups on the first day. The total amount of excreted plutonium by 3 day-treatments was highest in the 3,4,3-LIHOPO group. The toxicity of each agent was discussed. It is concluded that at the same doses, the effect of 3, 4, 3-LIHOPO was superior to CBMIDA and Ca-DTPA for removing plutonium in rats.

3) Development of systems for precise measurement and dose-assessment in emergencies

We studied and developed a chromosome analysis for dose assessment on a partial body exposure

using hair root cells. Collection of hair root cells after wetting the skin had a high rate (hundreds of cells / hair root on the back of the hand). These cells were cultured and the optimal specimen was able to be made by the PCC induction and the air-dry method.

In another study, we found that the simultaneous measurement of a liquid scintillation detection machine and germanium-detection machine was effective for detection of alpha nuclides.

4) Research on the mitigation of radiation injuries

Green tea is a rich source of polyphenols, and (-)-epigallocatechin-3-gallate (EGCG) is a major constituent of green tea polyphenols. In the present study, we investigated the effect of EGCG on apoptosis induced by irradiation in the human keratinocytic cell line HaCaT. Irradiation by gamma-ray induced apoptosis with concomitant cleavage of caspase-3 and its *in vivo* substrate poly(ADP-ribose) polymerase. Treatment of cells with EGCG inhibited irradiation-induced apoptosis as detected by Hoechst staining and internucleosomal cleavage of DNA, and prevented the cleavage of these proteins by irradiation. We also found that the treatment of cells with EGCG alone suppressed cell growth and induced apoptosis in these cells. Our results suggest that EGCG inhibits irradiation-induced apoptosis by inactivating the caspase pathway in HaCaT cells. Our study also indicates that EGCG has a dual effect on the survival of these keratinocytes.

5) Study on emergency response to environmental pollution

A new system of a gamma-ray direction finder was established. The manual for detection of environmental pollution with radionuclides in radiation accidents has been completed and presented on the web site of NIRS.

Major publications:

1) Fukuda, S., Iida, H., Yan, X., Xie, Y., Burgda, R. and Bailly, T.: Efficacies of three chelating agents on removal of plutonium in rats: comparison of CBIDA, 3,4,3-LIHOPO and Ca-DTPA. *Journal of Health Physics.* 38:62-67, 2003.
2) Koike, M. and Koike, A.: Subcellular localization and molecular mechanisms of nuclear transport of multifunctional Ku70 and Ku80 proteins. *Recent Research Developments in Biophysics and Biochemistry.* 3:141- 158, 2003.
3) Kondo, H., Park, S., Watanabe, K., Yamamoto, Y. and Akashi, M.: Polyphenol(-)-epigallocatechin gallate inhibits apoptosis induced by irradiation in human HaCaT keratinocytes. *Biochem. Biophys. Res. Commun.* 316: 59-64, 2004.
4) Ishihara, H., Tanaka, I., Wan, H. and Cheeramakara, C.: Disappearance of Nuclear Binding Proteins Specifically Bound to the Upstream Region of the Interleukin-1 beta Gene Immediately after Irradiation of Mouse Macrophages. *Journal of Radiation Research.* 44: 117-123, 2003.
5) Hachiya, M., Takada, M., Sekikawa, K. and Akashi, M.: Endogenous Production of TNFa is required for Activation of NFkB by Irradiation in Human Monocytic Cells THP-1. *Cytokine.* 25: 147-154, 2004.
6) Tanosaki, S., Ikezoe, T., Heaney, A., Said, JW., Dan, K., Akashi, M. and Koeffler, HP.: Effect of ligands of nuclear hormone receptors on sodium/iodide symporter expression and activity in breast cancer cells. *Breast Cancer Research and Treatmen.* 79 (3): 335-345, 2003.
7) Hirama, T., Tanosaki, S., Kandatsu, S., Kuroiwa, N., Kamada, T., Tsuji, H., Yamada, S., Katou, H., Yamamoto, N., Tsujii, H., Suzuki, G. and Akashi M.: Initial medical management of patients severely irradiated in the Tokai-mura criticality accident. *British Journal of Radiology.* 76: 246-253, 2003.
8) Hirabayashi, Y., Yoshida, K., Aizawa, S., Kodama, J., Kurokawa, Y., Yoshimura, I. and Inoue, T.: Evaluation of nonthreshold leukemogenic response to methyl nitrosourea in p53-deficient C3H/He mice. *Toxicology and Applied Pharmacology.* 190: 251-261, 2003.

5. Research Center for Charged Particle Therapy

Hirohiko Tsujii, MD.
Supervisory Director

Outline of Research:

The Research Center for Charged Particle Therapy has been established for research on heavy particle beams using the HIMAC (Heavy Ion Medical Accelerator in Chiba) and for joint research as well as for efficient research and development of advanced diagnostic imaging techniques. It comprises eight departments and the following overview presents the results achieved by these departments in fiscal 2003.

1. Operations Office

The Operations Office is in charge of the administrative work required for the effective running of the Center's research and operational activities. It is responsible for the administrative procedures involved in charged particle therapy using the HIMAC and in the joint utilization thereof. A committee was created to design a new protocol for charged particle therapy. This is the "Phase I/II Protocol for Pre-operative Short-term Carbon Ion Beam Irradiation for Esophageal Squamous Cell Cancer." The Operations Office also took charge of the arrangements and preparations for the commemorative event held to celebrate the 10th Anniversary of the HIMAC (HIMAC 10) and created the organizational structure for accepting a research project on a commission basis: The First Phase Clinical Study, Pharmacodynamic Investigation of LY248686 Using PET -Investigation of LY248686 occupancy rate of the Serotonine Transporter Using (11C) DASB-.

2. Hospital

The hospital of the Research Center for Charged Particle Therapy is unique in its position as an exclusive research and teaching hospital even on a national scale, specializing in radiation therapy and diagnosis, as well as management of unexpected radiation exposures. It is also designated in Japan as the Third Medical Facility designed to function as a core medical institution to provide medical emergency services for unexpected radiation exposures and is actively engaged in establishing and maintaining a service outfit in readiness for radioactive exposure accidents, jointly with the Medical Center for Emergency Radioactive Exposure Therapy. To fulfill its role as a research hospital, it has not only outpatient and inpatient wards but also a full complement of pharmacies and clinical laboratories to well above normal standards. It is equipped with a range of state-of-the-art diagnostic imaging equipment (including CT, MRI, PET, ultra-sonography and endoscopy) on a scale and level well above a general hospital.

2-1 Ministerial Approval of Advanced, State-of-the-Art Medical Therapy

The Research Center for Charged Particle Therapy has mainly conducted clinical trials using the HIMAC to investigate the safety and effectiveness of charged particle therapy (using a carbon ion beam) for the treatment of cancers intractable with conventional therapies since June 1994. The Center's hospital has played a leading role in these trials that have been conducted from the beginning with the cooperation of a range of Committees consisting of internal and external experts. It has meanwhile been established that charged particle therapy is safe and effective for the treatment of a significant number of diseases. The results obtained through these clinical studies were officially recognized in fiscal 2003 when the Ministry of Welfare, Health and Labour gave its approval on November 11 for the advanced, state-of-the-art therapy called "Charged

5.1. Heavy Ion Clinical Trial

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

Outline of Research Career:

Dr. Kamada received a Ph.D. from Hokkaido University in 1996 for his study on radiotherapy of the bile duct cancer. He has had 25 years of experience in clinical reseach on radiation oncology, including 10 years experience of carbon ion radiotherapy at NIRS. Since 2003, he has been project leader of the Heavy Ion Clinical Trial.

Contact point (E-mail) : t_kamada@nirs.go.jp

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 August 2003, a total of 1,601 patients were enrolled into clinical trials using carbon ion beams generated by HIMAC. Carbon ion radiotherapy of these patients was carried out by the 40 different phase I/II or phase II protocols. Of them, twenty were already closed for patient registration. Twenty protocols are still on going. Six phase II protocols were activated for head and neck, lung, liver, prostate and bone and soft tissue tumors. Tumor sites and annual patient accrual are listed in Table 2. We treated almost 300 patients/ year in the last year. Lung, head and neck, prostate, liver and bone and soft tissue tumors are the leading 5 tumors in the trials. A total of 1,297 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 Tumor

Locally advanced tumors were treated in head and neck protocols. Two dose-escalating protocols were carried out and then a fixed 16 fractions over 4 weeks phase II study was conducted. Two-year local control rates in these studies were 80, 71 and 69 % respectively. Four-year survival rates were 47, 32 and 36 % respectively. In these studies, non-squamous cell cancers such as malignant melanoma, adenoid cystic carcinoma and adeno-carcinoma, those considered to be radio-resistant, showed better outcomes compared to squamous cell cancer.

2)Lung cancer

The type of lung cancer chosen for the study was the non-small cell lung cancer. Patients with medically inoperable stage I tumor were treated in several protocols. We started with a fixed 18 fractions over 6 weeks dose-escalating study, and then shortened the overall treatment time to 3 weeks in 3 protocols. Two-year local control rates in stage I lung cancer were 62 to 100 %, and 4-year survival rates of 60 to 78 % were achieved in these protocols. These results are better than those of conventional photon radiotherapy, and almost the same as those of surgical treatment. We have conducted a fixed 4 fractions over one week protocol for stage I non-small cell lung cancer since 2000. We could give a very high dose in a week without unacceptable side effects. A single fraction (one day) dose escalating study was started in 2003. It is too early to say something definite, however the results are quite promising.

3)Liver Cancer

For liver cancer, a 15 fixed fractions over 5 weeks dose- escalating protocol was carried out initially. Overall treatment time of 5 weeks then was shortened to 3, 2 and 1 week in the following protocol. The results of these protocols were quite promising. Two-year local control rates in 2 studies were 74 % and 85 % and 4-year survival rates were 46 %. A phase II study using 4 fractions in one week was ended in 2003. We have conducted a fixed 2 fractions (2 days) dose escalating protocol since 2003.

4) Prostate Cancer

A fixed 20 fractions over 5 weeks protocol was employed for all prostate cancer studies. At first, a dose-escalation study was carried out and the total dose of 66 GyE was found to be an optimal dose. In the prostate study, no local recurrence was observed for the 36-month follow up. Survival rates are so far very high. We also conducted a shorter 16 fractions over 4 weeks protocol since 2003.

5) Bone and Soft Tissue Tumors

Unresectable bone and soft tissue tumors were treated with fixed 16 fractions over 4-week phase I/II and II study. Bone and soft tissue tumors are one of the most radio-resistant tumors. Two-year local control rates in 2 studies were 77 % and 92 %. Four-year survival rate was 49 % in the phase I/II study. Carbon ion radiotherapy seems to be a safe and effective modality in the management of bone and soft tissue sarcomas not eligible for surgical resection, providing good local control and offering a survival advantage without unacceptable morbidity.

6) Morbidity

Incidence of high-grade reactions was very low throughout the study, however some severe complications were experienced at an early phase of the study. Analysis using DVHs of affected organs was rigorously performed to avoid high-grade complications. Incidence of severe complications has been lowred.

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. Carbon ion radiotherapy has been approved by the Ministry of Health, Labor and Welfare of Japan as the "Highly Advanced Medical Technology" since November 2003.

Major publications:

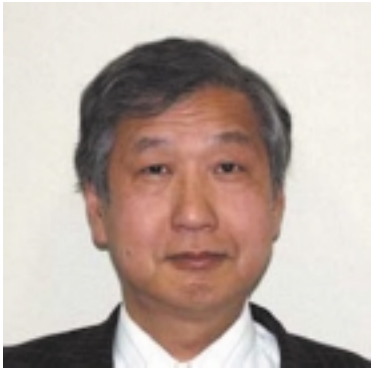
1) Miyamoto, T., Yamamoto*, N., Nishimura*, H., Koto*, M., Tsujii, H., Mizoe, J., Kamada, T., Katou, H., Yamada, S., Morita, S., Yoshikawa, K., Kandatsu, S., Fujisawa*, T.: Carbon ion radiotherapy for stage I non-small cell lung cancer, *Radiotherapy and Oncology,* 66, 127-140, 2003

Table 2. Patient Distribution of Carbon Ion Radiotherapy at NIRS (Treatment: June 1994 to August 2003)

Sites	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	Total	%
Head & Neck	9	10	19	31	22	38	29	39	40	15	252	15.7
Brain	6	8	10	6	9	7	15	10	6	1	78	4.9
Base of Skull	-	-	-	6	4	2	2	4	8	3	29	1.8
Lung	6	11	27	17	28	33	45	51	55	14	287	17.7
Liver	-	12	13	19	25	17	22	28	18	12	166	10.4
Prostate	-	9	18	10	30	30	31	44	47	30	249	15.6
Uterus	-	9	13	11	10	11	13	5	10	2	84	5.4
Bone & soft tissue	-	-	9	13	19	18	25	23	32	23	162	10.1
Esophagus	-	-	1	16	4	-	2	-	-		23	1.4
Pancreas (pre/op)	-	-	-	-	-	-	3	7	12	7	29	1.8
Rectum (p/o pelvic rec)	-	-	-	-	-	-	-	10	13	7	30	1.9
Eye melanoma (advanced)	-	-	-	-	-	-	-	8	16	9	33	2.1
Lacrimal gland	-	-	-	-	-	-	-	-	5	2	7	04
Miscellaneous	-	24	16	30	17	32	14	12	14	13	172	11.4
Total	**21**	**83**	**126**	**159**	**168**	**188**	**201**	**241**	**276**	**138**	**1601**	**100**

2) Sawajiri*, M., Mizoe, M.: Changes in bone volume after irradiation with carbon ions, *Radiation and Environmental Biophysics,* 42, 101-106, 2003
3) Sawajiri*, M., Mizoe, J., et al: Changes in osteoclasts after irradiation with carbon ion particles, *Radiation and Environmental Biophysics,* 42, 219-223, 2003
4) Yamamoto*, N., Miyamoto, T., Nishimura*, H., Koto*, M., Tsujii, H., Owada*, H., Fujisawa*, T.: Preoperative carbon ion radiotherapy foy non-small cell lung cancer with chest wall invasion-pathological findings concerning tumor response and radiation induced lung injury in the resected organs., *Lung Cancer,* 42, 87-95, 2003
5) Yamamoto, N., Mizoe, J., Hasegawa, A., Tsujii, H., et al: A case report of primary sebaceous carcinoma of the lacrimal gland treated by carbon ion radiotherapy., *International Journal of Clinical Oncology,* 8(6), 386-390, 2003

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



Masahiro Endo,Ph.D,
Director, Department of Medical Physics

Outline of Research Career:

Dr. Endo received his B.S. degree from the Deptertment of Pure and Applied Science, University of Tokyo in 1971 and completed the M.S. programs there in 1973, when he joined the National Institute of Radiological Sciences. He was engaged in development and application of new medical imaging system, such as X-ray CT, MRI, and PET. He was also engaged in development of patient treatment system at HIMAC. He is now the leader of this project and the director of the Department of Medical Physics. 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 advent of CT in 1973, dynamic imaging of moving organs in living human has been the ultimate dream in this field. This concept is simply called as 4D CT because it takes 3D image with 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 interventional therapy. The objectives of this project are developing a 4D CT and exploring its clinical potentials. The project goal is 1) developing a prototype of 4D CT-scanner that can continuously take volume images of 10 cm long and 50 cm diameter with 1 mm spatial resolution and 0.5 s temporal resolution in the end of the fiscal year 2004, and 2) making clinical studies in the fiscal year 2005. The detail specifications are listed in Table 1. Because volume data (3D data) can be acquired by cone-beam CT using a rotation of 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 of the 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 the fiscal year of 2001 and have been evaluating its performances since that time. We also developed the ultra-high-speed reconstructor in the fiscal year of 2002.

Progress of Research:

In the fiscal year of 2003 (the third year of a 5-year project), we achieved the followings.

1. Construction of the prototype

We completed the detailed design of the prototype CT-scanner (the second model) that satisfied the specifications listed in Table 1, and started its construction.

2. Development of the 4D viewer

We completed the development of the 4D viewer that was real-time viewing device for 4D imaging. This viewing device can process input data of 10 volumes/s, where the volume data consists of a 512 × 512 × 256 matrix. We connected the device to the ultra-high-speed reconstructor, and tested successfully a series of process from image reconstruction to real-time display.

3. Performance evaluation of the first model

We continued to evaluate the performances of the first model with phantoms, animals (pigs), normal volunteers and patients with liver cancer.

We evaluated physical performance of the first model with the phantom experiments, and compared it to that of commercially available 16-slice CT-scanner. As a result, we found that image noise, uniformity and high contrast detectability were independent of z-coordinate. A Feldkamp artifact was observed in distortion measurements. Full width at half maximum (FWHM) of slice sensitivity profiles (SSP) increased with z-coordinate. With regard to low contrast detectability, smaller objects were detected more clearly at the midplane (z=0 mm) than at z=40 mm, though circular-band like artifacts affected detection. The comparison between

Table 3. Specification of the first and second model

	First model	Second model
Scan mode	Cone-beam continuous rotation (4D)	Cone-beam continuous rotation (4D) Helical cone-beam (precise 3D) Physiological signal
Detector	912 × 256	The same as the first
Scan time	1 s/rot (14 s max)	0.5 s/rot (60 s max) Programmable
Reconstruction matrix	512 × 512 × 256	512 × 512 × 512
Contrast resolution	Less than 0.5 %	The same as the first
Reconstruction time	6 m for 512 × 512 × 256	Less than 1 s
End of construction	March 2002	January 2005

the 16-slice scanner and the first model showed better performance for the 16-slice scanner regarding the SSP, low contrast detectability and distortion. The inferiorities of the first model in other than distortion measurement (Feldkamp artifact) seemed to be partly caused by the prototype nature of the model and can be improved. The image noise, uniformity and high contrast detectability were almost identical for both CTs. The first model was superior to the 16-slice scanner regarding the PSF, though it was caused by the smaller transverse beam width of the model.

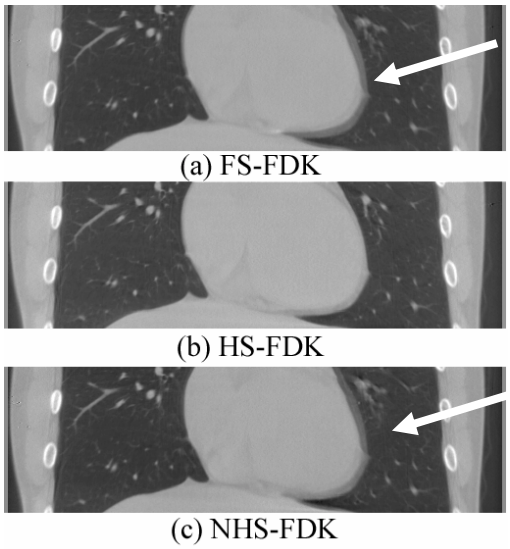

Fig.17.Coronal images of normal chest. Arrows show motion artifacts at the pericardial regions

With the animal experiments, we carried out the following studies: 1) Contrast study of heart and large vessels, 2) Cerebral blood flow analysis and 3) Observation of artifact caused by respiratory or heart motion and improvement of the artifacts.

With the human study, we carried out the following studies: 1) Contrast study of patients with liver cancer. 2) Knee movement of normal volunteers, and 3) Observation of artifact caused by respiratory or heart motion and improvement of the artifacts. Fig.17 shows coronal images of a normal chest. Motion artifacts appear at the pericardial regions for FS and NHS (arrows), while HS has fewer artifacts, where FS denotes full scan (temporal resolution of 1 s), HS and NHS denote half scan and new half scan, respectively. Though HS and NHS shows temporal resolution of 0.5 s, there time-response curves are different.

Major publication:

1) M. Endo, S. Mori, T. Tsunoo, S. Kandatsu, S. Tanada, and H. Aradate et al., "Development and performance evaluation of the first model of 4-D CT-scanner," *IEEE Trans. Nucl. Sci.,* vol. 50, pp. 1667-1671, 2003

5.2.2 Next Generation PET Project

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

Outline of Research Career:

Since the mid 1970s instrumentation research in nuclear medicine has been carried out and basic studies on systems of scintillation detectors for radioisotope imaging have been studied by the Imaging Physics Group. In the 1980s the group was dedicated to development of new detectors in order to construct PET scanners for head studies and whole body studies for humans and animals. In the 1990s, the group studied reconstruction methods and data correction techniques for SPECT and PET. Recently, members proposed a new concept for a depth-encoding detector in order to accomplish both high sensitivity and high spatial resolution in a PET scanner, and a new research group was established to achieve the next generation PET project.

Contact point (E-mail) : mur@nirs.go.jp

Objectives:

This group does basic studies of 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) are studied, and data processing techniques are also studied from the viewpoint of an increased signal component or reduction of the noise component. Simulation techniques for modeling the nuclear medicine imaging process have become an important and indispensable complement to experimental methods and clinical studies, and we are proceeding on more accurate simulation studies of the physics and instrumentation involved in the process. A next generation PET system with higher spatial resolution and higher sensitivity is under development through collaboration with both academic and industrial groups. 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) Performance of 256ch flat panel PS-PMT with small crystals for DOI PET detector (Fig.18)

To assess a 256ch flat panel position sensitive photomultiplier tube (256ch FP-PMT) for application to a DOI PET detector composed of small crystal elements, its basic performance was measured with Gd_2SiO_5 (GSO) crystals sized 1.42 mm x 1.42 mm x 4.5 mm. The 256ch FP-PMT is newly developed and has 52 mm x 52 mm opening area with a 89 % useful area. Its 256 anodes are placed with a 3.04 mm interval, about twice the crystal size. For

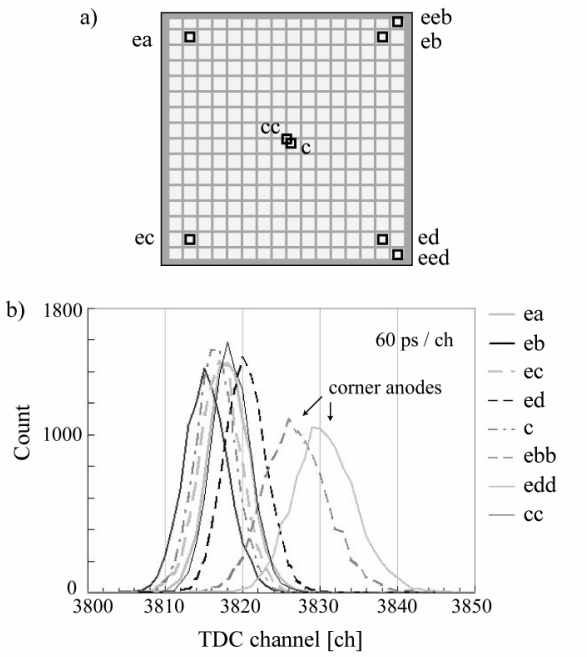

Fig.18. a) Top view of a LYSO crystal position on a 256ch FP-PMT photocathode. b) Time resolutions of the LYSO crystal. The TDC 1ch corresponded to 60.

the performance test, light spread functions of anodes at central and peripheral parts of the prototype 256ch FP-PMT were measured with the GSO crystal. It turned out that light spread functions of peripheral anodes were similar to the functions of center anodes and the functions measured with a 2.9 mm x 2.9 mm x 7.5 mm GSO crystal were almost the same size as the anode interval. Transit time fluctuation among the 256ch FP-PMT anodes was estimated by measuring time resolutions of a $LuYSiO_5$ (LYSO) crystal at some central and peripheral positions. The LYSO crystal had the same dimensions as the small GSO crystals. BaF_2 was used for reference. The obtained distributions had about the same time resolution between the central and peripheral positions and the full width at half maximum (FWHM) was (366 ± 15) ps. The transit time fluctuation was ± 106 ps. Positioning image maps of a 32 x 32 GSO crystal array and two layers of a 9 x 9 GSO crystal array were obtained by uniform gamma-ray irradiation. The 32 x 32 array covered all the useful area. The 9 x 9 x 2 array was coupled to the peripheral region. The resultant maps confirmed that the 256ch FP-PMT had enough capability to identify crystals in this size even on the periphery.

2) Three-dimensional array of scintillation crystals with proper reflector arrangement for a DOI detector (Fig.19)

A new method to acquire four-layer depth of interaction (DOI) information was proposed for the next generation positron emission tomography scanner (jPET-D4) that realizes high resolution and high sensitivity. The detector module of the jPET-D4 is a 16 x 16 x 4 Gd_2SiO_5: Ce (GSO) multicrystal array coupled with a 256ch flat panel position sensitive photomultiplier tube (256ch FP-PMT) having large opening area. The first task to encode DOI information was carried out with 8 x 8 array of units consisting of 2 x 2 x 4 crystal elements. The unit was previously developed for four-layer DOI encoding. Its crystal identification performance was evaluated by uniform gamma ray irradiation. The measured scintillation events were mapped on a two-dimensional (2D) position histogram according to the relative ratio of the multianode output of the FP-PMT. However, peaks corresponding to the crystal elements of one unit formed a colony in the resultant 2D position histogram and there was a large space between adjacent colonies. In the new method, the reflector arrangement which provides proper light sharing in the multicrystal array eliminated much wasted space. Consequently, peak-to-valley on the 2D position histogram was improved to 3.3:1 from 1.8:1. Energy performance was also enhanced by the new method.

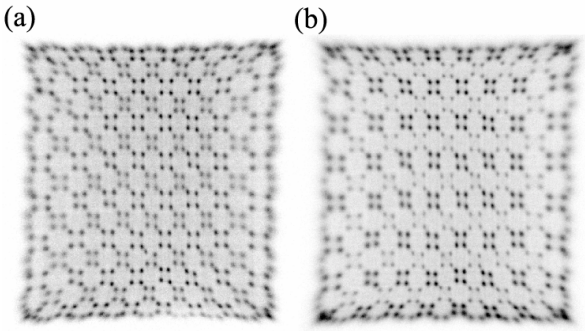

Fig.19. 2D position histograms with DOI detector module with concatenated unit. All detected events are plotted on these histograms. (a) corresponds to events detected in the first and third layers and (b), in the second and fourth layers.

3) Calibration procedure for a DOI detector

The DOI detector unit developed for the next generation PET scanner consists of 8x8 crystal blocks with 4 layers of 2x2 Gd_2SiO_5:Ce arrays coupled to a 52 mm square position sensitive photomultiplier tube (PS-PMT). Each scintillation event is mapped in a two-dimensional (2D) position histogram through the relative ratio of the output signals of the PS-PMT. To facilitate high spatial resolution imaging, accurate crystal identification is needed. A statistical model based on the approach of a Gaussian mixture model (GMM) is introduced for crystal identification. In the GMM, a cluster center and range attributed to individual peaks in the 2D position histogram are defined. The GMM can simultaneously estimate overlapping regions projected on each crystal element. After block separation of 8x8 on the 2D distribution, the crystal element regions are identified by the GMM in each block. The GMM method is applied two times, once for the cluster centers and once for determination of the range. These results are used to generate a Look-Up-Table (LUT). This method successfully identified all crystal elements in the clustering area. By Monte Carlo simulation, we also proved that the GMM method could choose LUT patterns with high resolution or high sensitivity with one parameter.

4) A four-layer DOI detector block for small animal PET

In order to meet the demands of higher sensitivity for small animal PET, we proposed a new DOI detector arrangement to obtain DOI information by using a four-layer detector with all the same crystal elements. In this DOI detector, we control the

behavior of scintillation photons by inserting the reflector between crystal elements so that the DOI information of four layers can be extracted from one two-dimensional (2-D) position histogram made by an Anger-type calculation.

As a preliminary experiment, we measured crystal identification performance of the DOI detector which consists of four layers of a 16 x 16 crystal array using Gd_2SiO_5 crystals with Ce concentration of 0.5 mol %; each crystal size was 1.42 mm x 1.42 mm x 4.5 mm. A crystal block was optically coupled to a 256-channel flat panel position sensitive photomultiplier tube whose opening area was 52.0 mm x 52.0 mm. We obtained sufficient positioning performance for this four-layer DOI detector on the 2-D position histogram and we judged it promising for realization of a small animal PET scanner with high sensitivity and high resolution.

Major publications:

1) Inadama, N., Murayama, H., Watanabe, M., Omura, T., Yamashita, T., Kawai, H., Umehara, T., Kasahara, T., Orita, N., and Tsuda, T. : Performance of a PET detector with a 256ch flat panel PS-PMT. *IEEE Trans. Nucl. Sci.*, 51, pp. 58-62, 2004.
2) Yamaya, T., Hagiwara, N., Obi, T., Yamaguchi, K., Kita, K, Ohyama, N., Kitamura, K., Hasegawa, T., Haneishi, H., and Murayama, H. : DOI-PET image reconstruction with accurate system model reducing redundancy of imaging system. *IEEE Trans. Nucl. Sci.*, 50, pp. 1404-1409, 2003.
3) Kasahara, T., Murayama, H., Omura, T., Yamashita, T., Ishibashi, H., Kawai, H., Inadama, N., Umehara, T., Orita, N., and Tsuda, T. : Improvement of the depth of interaction detector for PET on full energy pulse height uniformity. *IEEE Trans. Nucl. Sci.*, 50, pp.1439 -1444, 2003.
4) Shimizu, S., Sumiya, K., Ishibashi, H., Senguttvan, N., Redkin, BS., Ishii, M., Kobayashi, M., Susa, K., and Murayama, H. : Effect of Mg-, Zr-, and Ta-doping on scintillation properties of Gd2SiO5:Ce crystal. *IEEE Trans. Nucl.* Sci., 50, pp. 778-781, 2003.
5) Hasegawa, T., Murayama, H., Matsuura, H., Yamaya, T., and Tanada, S.: Shielding effects of body-shields for 3D PET. *Jpn. J. Med. Phys.,* 22, pp. 318-326, 2002.

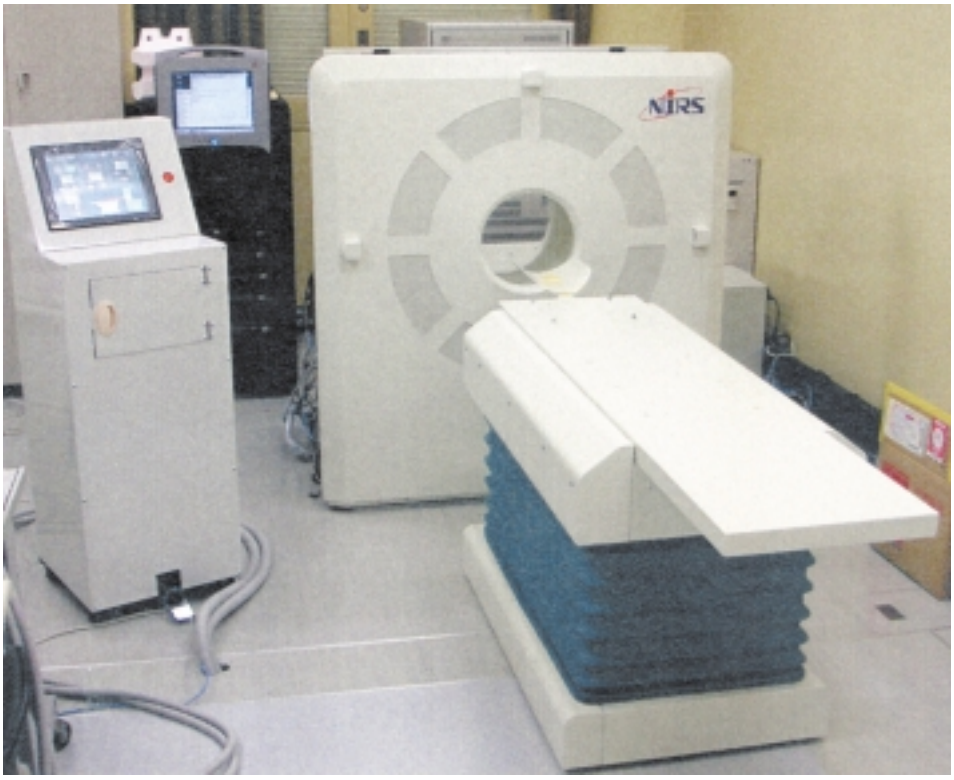

Fig.20 Photograph of the prototype four-layer DOI-PET scanner : jPET-D4

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

Satoru Yamada, Ph.D.
Director, Department of Accelerator Physics and Engineering

Outline of Research Career:

Dr. Yamada received his PhD in 1974 from Tokyo Institute of Technology. In 1976, he was appointed as a research assistant at Institute for Nuclear Study, University of Tokyo and joined the Design and R&D group of NUMATRON, a heavy ion synchrotron facility for nuclear physics. In 1987, he moved to NIRS and was appointed Head of the High Energy Beam Research Section, Department of Accelerator Physics and Engineering. He currently holds additional post of Director of the Department and is responsible for the operation and developmental studies of HIMAC, a heavy ion synchrotron for particle therapy.

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Objectives:

Excellent clinical results of carbon therapy have been obtained with high-energy carbon beams at HIMAC. The primary aim of our research is to design a compact accelerator facility for carbon therapy at a reasonable cost. As a secondary aim, the essential part of the R&D studies should be completed by the end of FY2005 to allow start the construction of the therapy accelerator in 2006 at a site outside NIRS.

Progress of Research:

In this fiscal year, major activities of our group were concentrated on three major subjects: R&D studies concerning beam handling techniques, design study of a compact carbon therapy accelerator, and R&D studies of the therapy accelerator. These studies are outlined here.

R&D Studies of Beam Handling Techniques

At HIMAC, the RF knockout slow-extraction technique has been developed with amplitude and frequency modulated knockout voltages. An advantage of this method is quick response of beam intensity extracted from a synchrotron ring; it takes less than 1 ms after input of a gate signal. This method was applied to daily operation in beam irradiation for cancer treatment gated with patient's respiration. It was shown through HIMAC experiments that time structure of the extracted beam was appreciably improved with properly optimized knockout voltages.

A spot scanning technique has been developed using ^{11}C radioactive beams at HIMAC. The ^{11}C beams are produced as a secondary beams by irradiating ^{12}C beams on a thin Be target. Preliminary tests showed an excellent 3D dose distribution was obtained with about 10,000 beam spots. It took about 5 min to paint whole region of interest.

Design Study of a Compact Carbon Therapy Accelerator

Based on 10 years experience with HIMAC, specifications of a compact carbon therapy accelerator were determined. They are summarized in Table 3. The maximum energy of carbon ions has been 400 MeV/u to realize a 25 cm range in water equivalent tissue. The maximum value of the carbon energy is enough to treat almost all therapeutical targets. Three treatment rooms are located on the same floor and equipped with a horizontal beam line, a vertical line and horizontal and vertical lines, respectively. More than 30% of the patients have been treated with the respiration gated beam extraction technique at HIMAC. The technique and the layer stacking irradiation method should be applied in order to suppress undesirable dose on normal cells. A spot scanning technique will not be adopted because of its disadvantage in treatments of organs moving with a patient's respiration.

A beam intensity of 2×10^9 pps will give an dose rate of 2/Gy/min, where field diameter, size of spread out Bragg peak (SOBP), and beam-utilization efficiency are assumed to be 20 cm, 10 cm, and 40%, respectively. The values for the field diameter and SOBP cover more than 80% of therapeutical targets at HIMAC. The whole facility size is designed to be within 60 m$\times$50 m as the goal. For this purpose, both the irradiation port length and the

Table 4
Specifications of a Compact Carbon Accelerator

Ion Species	^{12}C
Maximum Energy	400 MeV/u
Beam Intensity	2Δ10⁹ pps
Treatment Rooms	3 (H, V, H&V)
Max. Range in Water	25 cm
Max. Field Size	22 cm λ#
Field Uniformity	< ∂2%#
Typical Dose Rate	2 Gy/min

synchrotron radius should be limited to about half the size of HIMAC, which means 5.5 m and 10 m, respectively.

The proposed facility consists of two 10 GHz ECR ion sources with permanent magnets, an injector linac cascade (RFQ+IH) with an output energy of 4 MeV/u, a synchrotron ring with an extraction energy ranging from 140 to 400 MeV/u and beam delivery systems with a spiral wobbler method. A cut-away view of the proposed facility is shown in Fig.21.

The injector linac cascade is composed of a 4 vane type RFQ linac and an interdigital-H type (IH) linac. Input energy of the injector is designed to be 12 keV/u. With the RFQ linac, the C^{4+} beam is bunched and accelerated to 600 keV/u. For the IH linac, an alternating phase focusing structure, APF, is adopted so any external focusing elements are unnecessary. Between these two linacs, a triplet quadrupole magnet is placed to achieve transverse beam matching. After the IH linac, $C4^{+}$ ions are accelerated to 4 MeV/u and fully stripped by a thin carbon foil.

Fig.21 A cut-away view of the proposed facility.

Operating frequency is 200 MHz for both RFQ and IH linacs, and the diameter of these linacs is about 30 cm. Lengths are about 2 m and 3 m for the RFQ and IH, respectively.

The synchrotron is designed to accelerate a C^{6+} beam from 4 to 400 MeV/u at maximum. The FODO lattice structure is chosen, because this simple structure can increase the dipole-magnet filling factor while keeping a small beam size. The cell number is to be 6, considering the phase advance per cell and the third-order slow extraction. The extraction system should employ RF-KO extraction for the layer stacking method and respiration gated irradiation. Each cell in the lattice contains three dipole magnets having a rectangular shape and two quadrupole magnets (QF and QD). Ring circumference is 61.5 m, and the dipole-magnet filling factor of 43 % is achieved. (Qx/Qy) = (1.70/3.13) and (1.70/1.85) are candidate as working points considering the resonance lines and space charge effect. The horizontal and vertical acceptances are 240 and 30π mm mrad after the COD correction, respectively, while that of the injection beam is 10π mm mrad. An rf voltage of 2 kV is required under a ramping speed of 2.7 T/s and a dilution factor of 1.2, which gives a maximum bucket height of $\pm 0.4\%$ in $\triangle p/p$.

Assuming an output current of 200 eμA from the ion source and a gain of 20 by multiturn injection, delivered intensity is estimated to be 2×10^{9} pps at maximum. It is noted that the efficiencies in each process are taken into account in the estimation.

According to the design considerations, the beam delivery system should realize a residual range of 250 mm with a beam energy of 400 MeV/u and an irradiation-field radius of 220 mm at maximum. Length of the irradiation port is assumed to be 5.5 m. For the purpose, a spiral wobbler method has been proposed. In this method, the beam center at the isocenter moves along a spiral orbit by modulating the amplitude of the wobbler currents. This method can realize a uniform irradiation field even with a considerably smaller beam size than that in the conventional wobbler method. A relatively small beam size is obtained in a short drift space even with a thin scatterer resulting in a small energy loss. This method can be easily applied to respiration gated irradiation. Angular and AM frequencies of the spiral wobbler are 59 Hz and 23 Hz, respectively. Simulation predicts a lateral-dose uniformity of less than 3% in the irradiation field size of 220 mm with a residual range of 250 mm for the 400 MeV/u carbon beam.

The irradiation port consists of beam monitors,

wobbler magnets, a scatterer, ridge filter, range filter and collimator. Using the ridge filter, the SOBP size is changeable from 40 to 150 mm. The range shifter is installed to adjust the residual range in a patient. A multi leaf collimator, MLC, is used to define a irradiation field. A bolus can shape the distal field precisely. A secondary emission monitor as a main dose monitor is placed upstream from the wobbler magnets to measure the total dosage. As a sub dose monitor, a parallel-plate ionization chamber is used upstream from the MLC. A multi-segmented ionization chamber is used to check field size and dose uniformity.

R&D Studies of the Compact Therapy Accelerator

A compact ECR source has been developed to produce C^{4+} ions. A photograph of the source is shown in Fig.22. Permanent magnets of NdFeB are adopted to generate both sextupole and mirror fields. In order to perform fine-tuning of the source, a traveling wave amplifier with variable frequency from 9 to 18 GHz is used. Based on operation experience with a previous ECR source, an output current of C^{4+} ion was obtained at 500 eμA for the new ECR source with a microwave power of 300 W.

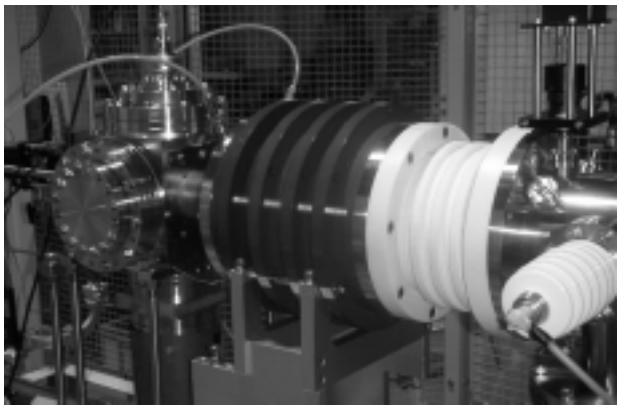

Fig.22.A compact ECR source with permanent magnets.

Design of the injector linac is now underway, and model measurements of the APF-IH linac will start in the near future. Systematic R&D studies for other parts of the compact therapy accelerator including beam delivery system and treatment planning system are scheduled in the next two years. Preparatory studies were started during the second half of FY2003.

Major publications:

1) Furukawa, T., Noda, K., Muramatsu, M., Uesugi, T., Shibuya, S., Kawai, H., Takada, T., Yamada, S.: New Approach toward Optimum Resonant Slow-Extraction; *Nucl. Instr. Meth.* A515 pp.861-869, 2003.
2) Komori, M., Kanai, T., Noda, K., Furukawa, T.: Irradiation System by means of Spiral Wobbler Method for Heavy-Ion Radiation Therapy; *Proc. 5th Symp. Accelerator and Related Technology for Application,* Oct. 2003, Tokyo, pp.35-36.
3) Muramatsu, M., Kitagawa, A., Sakamoto, Y., Sato, Y., Yamada, S., Ogawa, H., Drentje, A. G., Biri, S., Yoshida, Y.: Development of Compact ECR Ion Source with Permanent Magnets for Carbon Therapy; *Proc. 5th Symp. Accelerator and Related Technology for Application,* Oct. 2003, Tokyo, pp.73-76.
4) Noda, K., Furukawa, T., Shibuya, S., Uesugi,T., Muramatsu, M.: Slow beam extraction at the HIMAC synchrotron; *Proc. 14th Symp. on Accel. Sci. Tech.,* Tsukuba, Japan, Nov. 2003, pp.14-16.
5) Uesugi, T., Noda, K., Fujisawa, T., Uchiyama, H., Mori, Y., Machida, S., Hashimoto, Y., Syresin, E., Shibuya, S.: Study of beam instabilities with HIMAC synchrotron; *Proc. 14th Symp. on Accel. Sci. Tech.*, Tsukuba, Japan, Nov. 2003, pp.114-116.

5.4. Development of a precise irradiation system for heavy-ion therapy

Tatsuaki Kanai, Ph.D., Head of Biophysics of Heavy Ion Radiotherapy, Department of Medical Physics.

Outline of Research Career:

Dr. Kanai received his B.S. degree from the Deptertment of Science, Physics Course, Tokyo University of Education, in 1972 and completed the M.S. programs there in 1974. He took Ph.D degree in 1983 from The Tsukuba University. In 1972, he joined the National Institute of Radiological Sciences as a researcher at Physics division. He was engaged in development and application of proton irradiation system, using a scanning method. In construction of HIMAC facility, he was engaged in development of irradiation system and in establishment of clinical dose system. He is now the section head of therapy biophysic in the Department of Medical Physics.

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Objectives:

For efficient heavy-ion radiotherapy, it is necessary to expect the biological effects of heavy-ion beams, to determine the optimal heavy ion for radiotherapy, and to determine an optimal irradiation schedule. It is also necessary to precisely measure beam quality and dose. Further, it is very important to establish a national standard for the traceability of the dosimetry for medical treatments including photons, electrons, neutrons, protons, and heavy ions.

Progress of Research:

Beam-quality Measurements and Effective Method of Evaluating Biological Effects:

Systematic evaluations of the beam quality is required for optimized treatment using heavy ions. Depths-dose distributions, depths LET distributions, and a particle-kind distributions in water phantoms, were measured and summarized as a database for heavy ion radiotherapy.

Spatial distributions of beam quality are also important for the evaluation of treatment planning for heavy ion radiotherapy. A Delta-E and E counter telescope system, placed over 2m downstream of the water phantoms, was used to measure the angular distributions of fragmented particles.

Development of a Clinical Dose Detector:

In the treatment planning system for heavy-ion radiotherapy, a clinical dose is used for heavy-ion beams. The clinical dose is defined as a physical dose multiplied by RBE. We determined the RBE of the carbon beam in a semi-empirical way.

The survival curves of biological cell lines are described using the LQ model. The LET dependence of the coefficients α and β of the LQ model are experimentally determined for the mono-energetic carbon beam. The survival curves for SOBP beams are estimated using the dose-averaged values of coefficients α and β of the mono-energetic beams. SOBP are designed so that survival fractions are uniform in the SOBP, using the obtained coefficients of the LQ model. Based on this method of clinical dose, we can determine the clinical dose for only a beam that is broken down into mono-energetic components. We have had no means to calculate RBE or clinical dose from measurable physical quantities, the method for determining clinical dose used by the Germany GSI group is completely different from our method.

We have started to try to determine clinical dose using microdosimetric measurements. Using a ROSSI counter, z distributions were measured for SOBP beams of various widths. According to a dual radiation action theory including a saturation effect, we tentatively deduced the coefficients of α and β of the LQ model from the microdosimetric measurements. It became clear that inconsistency still existed in deducing clinical dose using this method. Further studies are necessary, to determine clinical dose using physical quantities.

Development of a Calorimeter:

Dosimetry for heavy-ion beams is usually performed using an ionization chamber. IAEA has tentatively recommended a dosimetry protocol for heavy-ion beams using an ionization chamber, but w-values, stopping-power ratios, and other quantities necessary to ionization chamber dosimetry, are not satisfactorily examined for heavy-ion beams. It is

necessary to have more direct dose measurements, in addition to the ionization chamber dosimetry. For this purpose, we have designed a calorimeter for the dosimetry of heavy-ion beams. A graphite calorimeter has been designed, and is now being built. The characteristics examination of various thermo sensitive registers has also been started.

Major publications:

1)N. Matsufuji, A. Fukumura, M. Komori, T. Kanai, T. Kohno: Influence of fragment reaction of relativistic heavy charged particles on heavy-ion radiotherapy, *Physics in Medicine and Biology,* 48, 2003, 1605-1623

2)Akifumi Fukumura, Takeshi Hiraoka, Tatsuaki Kanai: A new dosimetry protocol for external beam radiotherapy in Japan, AbsDos2003, Melbourne, August 2003

3)Masataka Komori, Akifumi Fukumura, Masaaki Hirai, Tatsuaki Kanai, Naruhiro Matsufuji, Eriko Shintani, Kengo Akiu, Yuuki Kase, Toshiyuki Kohno, Makoto Sakama: Study of the Fluence and LET Distribution of Projectile Fragments Produced from Heavy Ion Therapeutic Beams, World Congress on Medical Physics and Biomedical Engineering, Sidney, August 2003

4)Shinichi Minohara, Tatsuaki Kanai, Masahiro Endo, Hirotoshi Katou, Tadaaki Miyamoto: Analysis of organ movement during respiratory gated irradiation for particle radiotherapy, World Congress on Medical Physics and Biomedical Engineering 2003, Sidney, August 2003

5.5. Establishment of dosimetry and beam quality measurements of heavy-ion beams

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Outline of Research:

Irradiation system for eye melanoma using 140 MeV/n carbon beam is complete and already is applied to clinical trial. Conformal irradiation system for heavy-ion radiotherapy using a layer-stacking method is also almost complete. Various test are now performed. Simplified monitor calibration procedures are proposed and tested. Radiotherapy system using radioactive beam is complete and physical characteristics of the irradiation port are now measured.

Objectives:

Heavy-ion radiotherapy has been expected to achieve good clinical results because of its good dose localization to the target, and the high biological effectiveness of the beam. On the whole, the spatial and dose accuracy of irradiation using current heavy-ion treatments are believed to be 5mm and about 5 percent, respectively. To extend the treatment region on a patient's body, and to improve clinical results, such techniques as exact treatment planning, exact patient positioning, and exact irradiation, should be developed further. Research activities to improve the medical treatment accuracy of heavy-ion radiotherapy have been accomplished within the 5-year basic-research target.

Progress of Research:

Conformal Irradiation System for Heavy-ion Radiotherapy Using a Layer-stacking Method:

The conformal irradiation system of HIMAC has been upgraded for a clinical trial using a layer-stacking method. The system has been developed to localize irradiation dose to target volume more effectively than current irradiation doses. In the current passive irradiation method using a ridge filter, a scatterer, a pair of wobbler magnets, and a multileaf collimator, the width of a spread-out Bragg peak (SOBP) in the radiation field cannot be changed. More conformal radiotherapy can be achieved with dynamic control of the beam-modifying devices during irradiation. To safely perform treatments using this conformal therapy, moving devices should be monitored during irradiation, and synchronicity among the devices should be checked. The system must be adequately safe for patient irradiations, and so was constructed and tested for safety and the quality of dose localization.

To safely perform dynamic irradiations, the system should record the apparatus's movement during irradiation. The system to record this movement should be completely independent of the control device. A recording system was added to the current control system, and an overall examination test has been performed.

Development of Dose Estimation Method:

The dose calibration factor for the monitor unit is obtained by measuring the dose at the center of SOBP under the treatment conditions of each patient, without a compensator. To determine the monitor presets for treatment, it is more convenient to estimate them from a measurement of doses under standard conditions for all irradiation cases. For this, we have obtained a database of dose calibration factors under various irradiation conditions, and a dose estimation system was installed in the irradiation control system.

We found that dose calibration factors also depend on field size, because of the large angle deflection of fragmented particles. We have started to calculate this effect on the dose calibration procedure.

Development of Patient Positioning Technique:

Treatment is performed assuming that internal organs in a patient's body never deform or change. The position and shape of the organ and the target are the same as those when treatment was being planned. The position and shape of the organs, however, will change each day. To increase the accuracy of the treatment, we should understand how organs change, and how to manage for their movement in the particle treatment. A research subject was prepared in order to ascertain these. We start this research project by developing a method to analyze ultrasonic images for movement.

Development of Irradiation System Using Radioactive Beams:

Radioactive beams such as 11C or 10C are produced by bombarding Be or graphite with a high-

energy 12C beam. The radioactive beam produced is transported to the irradiation system for the treatment using the radioactive beam. The efficiency of the production of radioactive particles is very small, and so a scanning system is essential for radioactive beam therapy. The beam line for the scanning was complete. The three-dimensional dose distributions of the spot radioactive beam were measured, and reproducibility was examined. There has been an system examination of the spot scanning method, and the results have been summarized.

By detecting the stopped position of the radioactive particles in the patient's body using a positron camera, the irradiated region can be confirmed during or immediately after treatment. A pencil radioactive beam is injected into a head phantom, and the position of the stopped region is measured using the developed positron camera. The position was compared with the planned position by the treatment planning system, which uses CT values for the calculation of the path length of the beam in the phantom. Consequently, calculation from CT value proved to have produced a maximum of 1.6mm error.

Major publications:

1)Shinichi Minohara, Masahiro Endo, Tatsuaki Kanai, Hirotoshi Katou, Hirohiko Tsujii; Estimating Uncertainties of the Geometrical Range of particle Radiotherapy during Respiration, *International Journal of Radiation Oncology Biology Physics,* 56, 121-125, 2003

2)Youji Osanai, Norio Tagawa, Akihiro Minagawa, Tadashi Moriya, Shinichi Minohara; Automatic Tracking of Region of Interest in Sonograms Using Respiratory Information, *Japanese Journal of Applied Physics,* 42, 3281-3286, 2003

3)H. Mizuno, T. Tomitani, M. Kanazawa, A. Kitagawa, J. Pawelke, Y. Iseki, E. Urakabe, M. Suda, A. Kawano, R. Iritani, S. Matsushita, T. Inaniwa, T. Nishio, S. Furukawa, K. Ando, Y. K. Nakamura, T. Kanai and K. Ishii; Washout measurement of radioisotope implanted by radioactive beams in the rabbit, *Physics in Medicine and Biology* 48, 2269-2281, 2003

4)N. Kanematsu, N. Matsufuji, R. Kohno, S. Minohara, T. Kanai; A CT calibration method based on the polybinary tissue model for radiotherapy treatment planning, *Physics in Medicine and Biology*, 48, 1053-1064, 2003

5)Q. Li, T. Kanai, and A. Kitagawa; A model to evaluate the biological effect induced by the emitted particles from a beta-delayed particle decay beam. *Phys. Med. Biol*. 48, 2971-2986, 2003.

5.6. Studies necessary for promotion of particle radiotherapy

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Outline of Research:

QA guidelines for particle radiotherapy have been tentatively established, and a conceptual-design irradiation system for compact heavy-ion radiotherapy facility has begun.

Objectives:

In Japan, there are many particle therapy facilities within or next-door to hospitals. Good results are expected in clinical trials of particle therapy, which depend on the physical characteristics of particle beams, as well as on the quality assurance and control of the treatment procedure. Quality control of irradiation system is especially important. To expect good clinical results, and to promote particle therapy, it is necessary to establish standards or guidelines for the quality assurance and control of the irradiation system. It is also very important to train medical physicists who can work in particle radiotherapy facilities.

Progress of Research:

Establishment of QA Guidelines for Particle Radiotherapy:

Efforts have been made to standardize treatment equipment, systems, record data formats, and other aspects, for the promotion and the quality assurance and control of particle therapy. Discussions between medical physicists at various particle therapy facilities about QA/QC guidelines for particle radiotherapy gave been summarized and tentatively established. These guidelines are now being discussed by JASTRO's QA committee.

Conceptual Design for Compact Heavy-ion Radiotherapy Facilities:

A conceptual design has been advanced for a practical irradiation system for the prevalent types of heavy-ion radiotherapy facilities. In these facilities, there must be beam reproducibility with high accuracy in irradiation. Based on this good reproducibility, irradiation will be performed using the calculated results of dose distributions, instead of measurements for each patient's conditions.

Irradiation systems will be divided into closed essential parts, irradiation devices, patient positioning systems, dose measurement systems, treatment planning systems, and RIS/HIS. Each closed system should be as simple as possible.

Major publications:

1)M. End, Physics of particle therapy, 5th JASTRO summer seminar, 3-12, 2003
2)T. Kanai, N. Kanematsu, S. Minohara, K. Yusa, E. Urakabe, H. Mizuno, Y. Iseki, M. Kanazawa, A. Kitagawa, T. Tomitani, Physical and engineering aspect of carbon beam therapy, American Institute of Physics Conference Proceedings, Vol. 680, 2003, 1146-1149
3)T. Kanai, Promotion of heavy-ion radiotherapy. Seminar for application of compact accelerator, July 2003, KEK
4)N. Kanematsu, Quality assurance of CT for treatment planning in the particle radiotherapy. *Japanese Journal of Medical Physics 23,* 140-146, 2003

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. Ando has developed 35 years experience in research on high-LET radiation biology at NIRS. Between 1976 -1979 he was at M.D.Anderson Cancer Center (Texas, U.S.A.) as a post doctoral fellow to study radiation effects on tumor metastasis, and in 1984 at Massachusetts General Hospital (Boston, U.S.A) as a Visiting Lecturer. He served as Editor-in-Chief, Journal of Radiation Research between 2000 and 2003. Since 2001 he is Director at National Institute of Radiological Sciences, and Visiting Professor of Chiba University (Chiba, Japan)

Doctorate 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 will be spent to develop a method by which high-responder tumors that well respond to heavy ions could be distinguished from low-responder tumors. We will achieve our goal of the following 2 details by 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 the fiscal year of 2003 included the following 4 items. (1) Difference of radiosensitivity between human squamous cell carcinomas and malignant melanoma. We are comparing radiosensitivities of human squamous cell carcinomas between X rays and carbon ions. (2) Effects of carbon ions on normal tissues including gut, bone marrows and brain. (3) LET dependence of sublethal damages caused by heavy ions. (4) Biological effectiveness of therapeutic beams at domestic and overseas facilities.

Progress of Research:

The biological effectiveness of carbon ions relative to γ rays (RBE) was compared between the tumor growth delay and an early skin reaction of syngeneic mice. The RBE was larger for a tumor than skin when irradiated with large doses of high-LET (linear energy transfer) carbon ions. The intra-track damage (α term of a linear quadratic model) of a tumor and skin equally increased with an increase of the LET, while the inter-track damage (β term) of skin alone increased with the LET. These data provide evidence that high-LET radiotherapy could achieve therapeutic gains by minimizing the difference in response to fractionated irradiation between the tumor and normal tissue.

Survival curves were obtained for in vitro cultured cell lines of 10 human malignant melanoma (MM) and 11 human squamous cell carcinomas (SCC) after single irradiation with X-rays (200kVp) and carbon-ion beams (290MeV/u, center of the 6cm-SOBP, LET=50 keV/μm). All cell lines showed higher sensitivities for carbon-ion beams than for X rays. We calculated survival parameters such as α, β, D_{37}, D_{10}, D_0, D_q, SF_2 from obtained dose response curves. No differences in D_{37}, D_{10}, D_0, SF_2 were observed between MM and SCC cells. However, most MM lines showed smaller Dq values than SCC lines. Further interestingly observed was a difference in distribution pattern of α/β ratios such that SCC lines showed narrower distribution for carbon ions than X rays whereas MM lines showed a wider distribution for carbon ions than X rays. α/β ratios for 10 MM lines varied from 1.2 to 15.6 $Gy^{-1}$and from 3.0 to 34.3 Gy^{-1} after X-ray and carbon-ion beam irradiations, respectively, while those for 11 SCC lines ranged from 1.9 to 40.3 Gy^{-1} and from 1.7 to 9.7 Gy^{-1}, respectively. The largest α/β ratio after X-ray irradiation was obtained for a SCC line, while the largest α/β ratio after carbon-ion beams was for a MM line. These results well fit clinical observations that carbon-ion radiotherapy effectively controls malignant melanoma.

Major publications

1)C. Shao, C., Furusawa, Y., Kobayashi, Y. , Funayama T. and Wada, S. : Bystander effect induced by counted high-LET particles in confluent human fibroblasts: a mechanistic study. *FASEB* J 17: 1422-1427, 2003

2)Takahashi, Y., Teshima, T. , Kawaguchi, N. , Hamada, Y. , Mori, S. , Madachi, A. , Ikeda, S. , Mizuno, H. , Ogata, T. , Nojima, K. , Furusawa, Y. and Matsuura, N.: Heavy ion irradiation inhibits in vitro angiogenesis even at sublethal dose. *Cancer Res.* 63: 4253-4257, 2003

3)Monobe, M. , Arimoto-Kobayashi, S. and Ando, K.: β-Pseudouridine, a beer component, reduces radiation-induced chromosome aberrations in human lymphocytes. *Mutation Research* 538, 93-99, 2003

4)Koike, S., Ando, K., Oohira, C., Fukawa, T., Lee, R., Takai, N., Monobe, M., Furusawa, Y. , Aoki, M., Yamada, S., Shimizu, W., Nojima, K. and Majima, H.: Reltive biological effectiveness of 290 MeV/u carbon ions for the growth delay of a radioresistant murine fibrosarcoma. *J.Radiat.Res.* 42, 247-255, 2002

5)Ritter, S., Nasonova, E., Furusawa, Y. and Ando, K.: Relationship between aberration yield and mitotic delay in human lymphocytes exposed to 200 MeV/u Fe-ions or X-rays. *J.Radiat. Res.* 43 Suppl., S175-S179, 2002

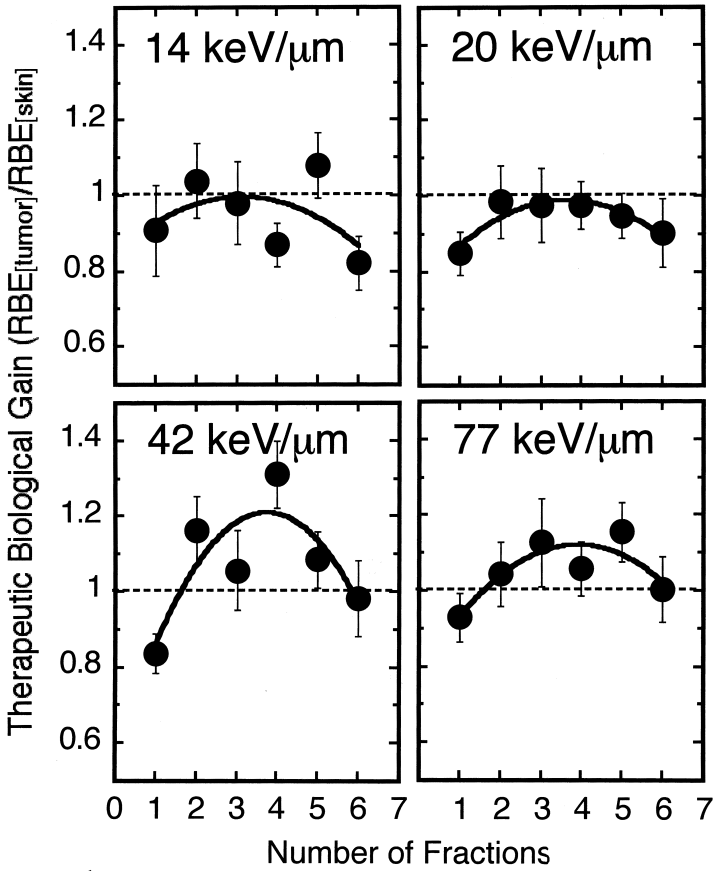

Fig.23.
Biological effectiveness of carbon ions relactive to γ rays. The therapeutic gain is the ratio of the tumor RBE to the normal tissue (skin) RBE, and means positive when the RBE ratio exceeds 1.0 (Fig.3B)

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

Hinako Toyama,Ph.D.
Director of Special Research on Information Management

Outline of Research Career:

Dr.Toyama graduated from Ochanomizu University in 1966. She entered the graduate school of Tokyo Institute of Technology in 1967, and received the Ph.D. in 1972. After graduation she joined the Tokyo Metropolitan Institute of Gerontology until March 1999 including three years as a lecturer at University of Tsukuba(1985-1988). Since April 1999, she has had the position of Special Researcher of NIRS, and concurrently Chief of Medical Information Processing Office, Research Center for Charged Particle Therapy. She specializes in medical information systems and nuclear medicine. She is now working in the Department of Health Service Management, International University of Health and Welfare. She is a member of the Japanese Society of Nuclear Medicine(councilor), the Japan Society of Medical Physics , the Japanese Society for Medical and Biological Engineering, and the Japan Association of Medical Informatics.

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Objectives:

By using image information, response and toxic effect, 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 to promote sharing the therapy results between groups.

Progress of Research:

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

We improved the coordination among several database systems (Hospital Information System, Therapy plan database, therapy schedule management system and PACS)(Fig.24). These systems are connected to each other and the data are transmitted to the destination systems. We could gather data directly from the information source. We prepared the Electronic Medical Record (EMR)(Fig.25) and developed the input method for the patient's findings, symptoms, tumor response, and toxic reactions that need to be evaluated by the physician during clinical interviews.

We improved the function of retrieval and input. We can automatically generate summary documents for the evaluation committee and network committee. We will examine use of the documents in future. We also developed the retrieval function for basic patient information, treatment method, tumor information, tumor response and toxic effects. The retrieval results can be transformed to a value separated value 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 making of fusion images among

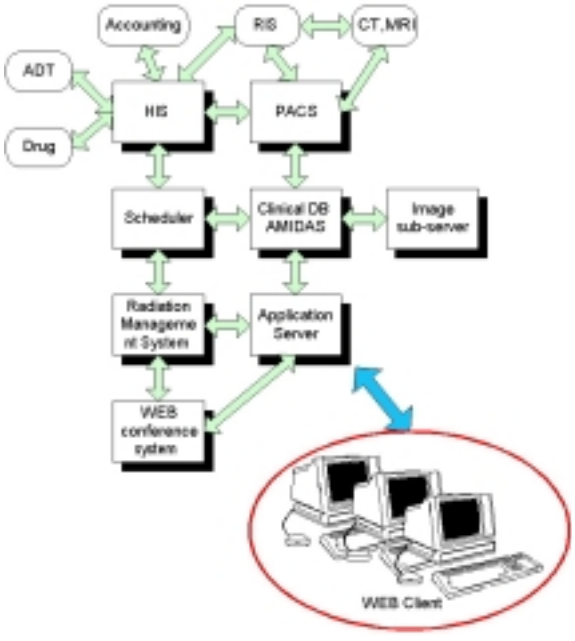

Fig.24. NIRS medical information network.

temporal series images. We evaluated the size of lung tumor in a series of PET and CT images of a patient with lung cancer. We read a paper at an academic meeting (Japan Society of Medical Physics and Japanese Society of Nuclear Medicine) concerning the results.

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

We continued to maintain standardization of the database, and the XML module for radiation therapy. We prepared to communicate clinical radiotherapy data to other hospitals and/or medical facilities.

Major publications:

1) Evaluation of image reconstruction methods for improving resolution in radial direction with PET
2) Functional correlation map in motor system during visuo-motor task using monkey PET

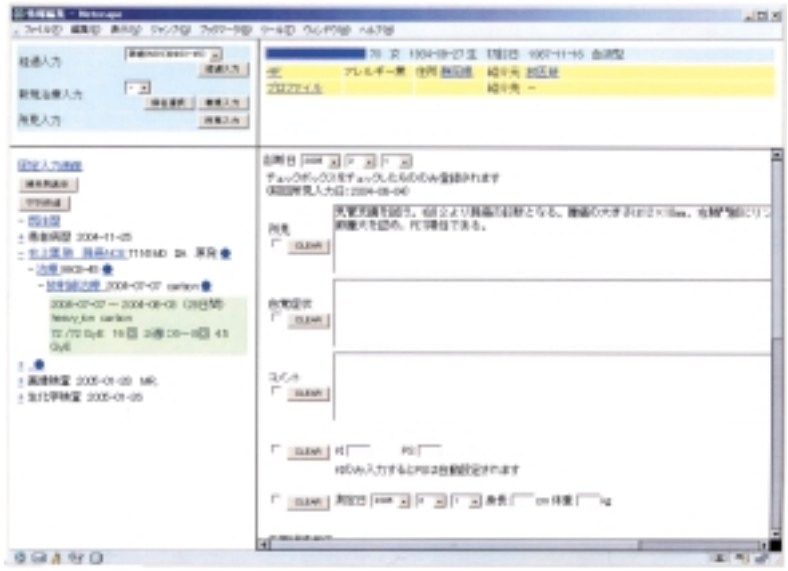

Fig.25. AMIDAS-EMR can provide the display and entry of clinical symptoms, tumor response and toxic reactions for physicians.

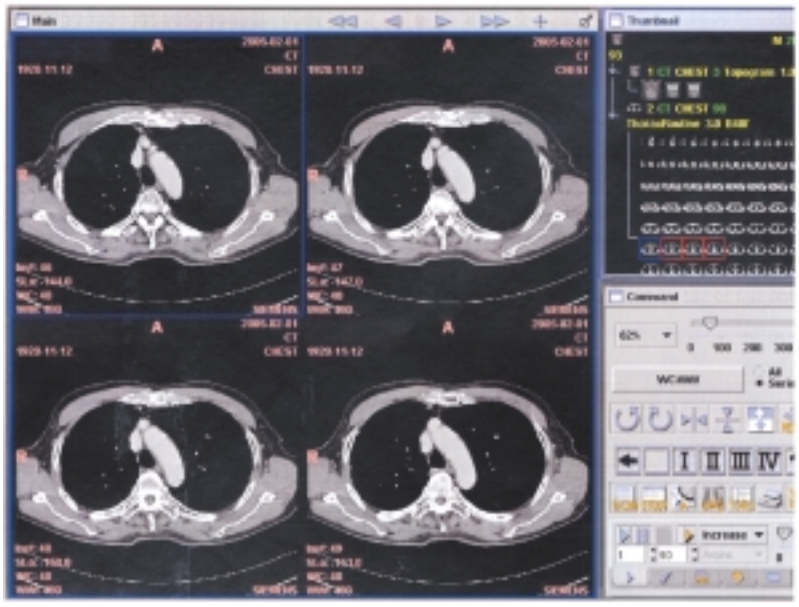

Fig.26. CT images are displayed by the Web DICOM viewer.

5.9. Medical Imaging Research and the Associated Mission

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

Outline of Research Career:

Dr.Shuji Tanada received a medical degree from Kyoto University in 1988 for his study on the role of positron emission tomography on the evaluation of cerebral perfusion and metabolism in various pathological conditions. He has had 27 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 instruments. He has participated in the IAEA/RCA projects on nuclear medicine since 1998.

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Summary of Research:

Medical imaging research and the associated mission 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 mission is to contribute to the promotion of cancer radiotherapy and biological functional imaging with respect to neuroscience, cardiovascular science and oncology.

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, the development of production and synthesis systems for various PET radiopharmaceuticals led to a multi-purpose automated synthetic module and a wide-use controller. Ultra-high specific activity was achieved for F-18 labeled compounds. As new PET radiopharmaceuticals, ligands for peripheral benzodiazepine (^{18}F-FEtDAA110), NMDA, AMPA receptors and hypoxic cancer cells have been developed. The enzyme activity of butyrylcholinesterase was measured in the brain of normal volunteers. 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. In clinical research, the enzyme activity of acetylcholinesterase was measured successfully in the brains of victims of the sarin subway attack. This may lead to the possible evaluation of the patho-physiological mechanism in post-traumatic stress disorder (PTSD). In collaboration with private companies, we promoted using contracts for extra funds from the companies. The clinical trial of Phase I with the incorporation of PET was conducted in collaboration with a pharmaceutical company, which was the first such work in Japan.

In the field of NMR, the research and development of fast data acquisition, micro-volumetric measurement and NMR spectroscopy have been continued for neuro-imaging and cancer imaging. The brand-new self-shielded 7Tesla magnet (bore : 40 cm) has been developed successfully. This was a achievement by the re-structured organization of NIRS, the Independent Administrative Institution.

Regarding support for the research conducted in the Medical Imaging Building and Cyclotron Facility, the production and quality assurance evaluation of short-lived PET radiopharmaceuticals have been continued both for clinical and animal experiment use. Two new PET radiopharmaceuticals ([^{11}C]verapamil and [^{18}F]FEtDAA1106) were released and approved by the Institutional Review Board in April 2003. Those have been applied to clinical research in addition to other 4 PET radiopharmaceuticals ([^{11}C]MP3B, [^{11}C]5R3B, [^{11}C]DAA1106 and [^{11}C]PE2I) which were approved in March 2002.

Progress of Research:

1. PET and SPECT related research.

1) Development of a multi-purpose synthetic module and a wide-use controller:

A multi-purpose automated synthetic module and a wide-use controller were developed, which enabled us to apply a wide variety of precursors such as ^{18}F-FEtBr, ^{18}F-FMeI, $^{18}F^-$, ^{11}C-CH_3I, etc. and to produce most of the radiopharmaceuticals used in PET. The performance of the automated apparatus was evaluated to approve the suitability for clinical applications by producing ^{18}F-FEtDAA1106 and ^{18}F-FetTy as model compounds.

2) ^{11}C-labeled compounds:

The production methods of ^{11}C-labeled EtI, PrI, etc. by the Grignard reaction were established with the multi-purpose automated apparatus which we manufactured ourselves last year. The [^{11}C] EtI and [^{11}C] PrI were automatically produced at yields of 3.7GBq (100mCi) and >3.7GBq (100mCi), respectively. Both compounds could be synthesized at the same time by selecting the reaction conditions.

3) ^{18}F-labeled compounds:

The technique of achieving high specific activity on ^{18}F-labeled compounds was developed to give 185GBq(5Ci)/μmol on [^{18}F]FEtDAA1106, high enough for receptor study in the brain. Further improvement of the specific activity of ^{18}F-labeled compounds might be possible by avoiding the isotopic dilution in purification and concentration of $^{18}F^-$.

4) Production of the PET/SPECT radionuclides:

The production method of ^{61}Cu-ATSM known as an imaging agent for hypoxic tissues or cells was established and used to evaluate usefulness for an animal PET study. A remote controlled production system of ^{76}Br was constructed and the yield of ^{76}Br by the ^{79}Br(p,4n)^{76}Kr$\rightarrow^{76}$Br reaction was evaluated. It was concluded that the nuclear reaction gives enough activity for animal experiments, but not for human study.

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

(1) In development of ^{18}F-labeled radiopharmaceuticals targeting acetylcholinesterase (AChE) in the brain, a new modification of the design and synthesis of candidates was attempted based on the previous results. Through the evaluation of labeled derivatives for enzymatic characteristics in vitro and in vivo dynamics in small animals, certain promising derivatives were found, which will be further evaluated in details by using monkey experiments.

(2) Concerning the development of PET radiopharmaceuticals to measure butyrylcholinesterase in the brain, we launched clinical research of two ^{11}C-labeled radiopharmaceuticals, whose potency and safety had been verified in a preclinical evaluation. Studies with healthy volunteers are in progress.

(3) We proposed that the expression of tenascin-C was a remarkable target for molecular imaging of tissue remodeling and we evaluated ^{111}In-labeled anti-tenascin-C Fab as the imaging probe. Using rat models of acute myocardial infarction, the bio-distribution of ^{111}In-labeled anti-tenascin-C Fab was examined. By autoradiography, high radioactivity was observed in the granulation tissue around the necrotic area of the infarcted myocardium. The SPECT imaging provided clinical ability to non-invasively assess the tissue remodeling after acute myocardial infarction.

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

(1) For establishment of quantitative image analysis we prepared software for kinetic analysis, which can provide a parametric image of AChE activity by using ^{11}C-MP4A/PET assay. The kinetic analysis in the software involves two methods, in which one needs arterial blood sampling, and the other does not.

(2) The applicability of two reference tissue-based analyses without arterial blood sampling was evaluated for the measurement of brain regional acetylcholinesterase (AChE) activity using N-[^{11}C]methylpiperidin-4-yl propionate ([^{11}C]MP4P) in 12 healthy subjects.

(3) Clinical studies have been continued for assessment of cholinergic alteration in the brain of demented patients and the therapeutic effect of acetylcholinesterase (AChE) inhibitor on Alzheimer's diseases by using ^{11}C-MP4A/PET, which can feasibly assay the AChE activity in the brain with PET. In such research the regional brain AChE activities were measured in five victims of the sarin attack in Tokyo subways. In comparisons with 17 normal controls the AChE activity in the temporal cortex was significantly reduced in the victims, suggesting that the long-term effects on the brain

may be related to remaining symptoms such as PTSD in the victims.

(4) As other clinical applications we started clinical research using ^{11}C-MP4P, which is suitable for quantitative assay of AChE activity in cerebellum and brain stems, in which the enzyme activity is higher than in the cerebral cortices. The study has mainly focused on the diseases of cerebellar degeneration. Utility of the method on assessment or differential diagnosis of these diseases is under investigation.

7) Others:

(1) Contracts for analysis of FDG solutions were made with three private companies. Under the contracts, 193 samples from 32 PET facilities in Japan were accepted for analysis.

(2) Contracts for permission to manufacture and sell the automated apparatus and the control system, as well as the clean heater, the radiation detector, 6-way valve and so on, using NIRS know-how were made with five private companies.

(3) Gefitinib (Iressa), widely used as an anticancer drug, was labeled with C-11 and its usefulness was evaluated as a PET probe with cancer-bearing rats. The bio-radiography technique was used for this in collaboration with the NIRS Hospital and the Heavy-ion Radiobiology Research Group.

2. NMR related research.

1) Early verification of the irradiated area in human liver using super-paramagnetic iron oxide (SPIO)-enhanced MR imaging.

It is difficult to confine the radiation field for a hepatic tumor due to its respiratory movement. Super-paramagnetic iron oxide (SPIO) enhanced MR imaging was applied to the early verification of the accuracy of the treatment planning for carbon ion radiotherapy (CIRT). Thirty patients with hepatocellular carcinoma (HCC) underwent both SPIO-enhanced MR imaging and dynamic X-ray CT (n=7), or dynamic X-ray CT alone (n=6) after CIRT. CIRT was carried out at a total dose of 52.8 Gy equivalent (GyE) in 4 fractions. The irradiated liver area showed a significantly higher signal intensity than the non-irradiated liver ($p<0.001$) in SPIO-enhanced MRI within 0 - 4 days after CIRT, and was visualized more clearly than in X-ray CT obtained at 4 - 12 days after CIRT. SPIO-enhanced MR imaging can detect the irradiated area immediately after CIRT for HCC, and thus may be useful for the early verification of the accuracy of the treatment planning for HCC.

2) Quantitative proton MR spectroscopy.

Single voxel proton MR spectroscopy was conducted to measure the absolute concentration of the metabolites in the human brain. One of the most difficult impediments to the accurate measurement was the signal contamination from CSF. If the voxel contains CSF, the apparent concentration of metabolites may decrease. There are two possible ways to separate tissue from CSF in the voxel. One method is to utilize 3D image data. However, it takes a long time to take the data so applying it to clinical routine practice is difficult. The alternative method is to separate them using T_2 values. There is a big difference in T_2 values between tissues (~80ms) and CSF (~500ms). This technique requires only a few more minutes of scan time. This method has proved to be influenced by eddy current effect strongly if the voxel size is larger than 8 cubic cm and gradient crushers in the scan sequence are strong. We made the crusher weaker and cut the ROI size to 3.375 cubic cm to avoid the problem. The volunteer study proved that CSF/tissue ratio is less than 10% when the voxel was selected carefully, which is almost the same accuracy as measured concentrations. We decided to use this segmentation method only to know whether the measured data are good enough for analysis. Another concern of research was the LC Model. The LC Model has a basic set of metabolites spectra and combines them linearly to fit the measured spectra. Metabolite concentrations are derived from the weighting factors of the fitting. But the basis is not orthogonal. We calculated the co-variance matrix of spectra and found that glutamine and glutamate are the most similar pair ($r=0.68$). We mixed the two signals by computer and analyzed it by LC Model, with the two bases, and without one base. We found that the lack of one base caused erroneous results if bases are quite similar in spectral features.

3) Development of RF volume coil for 7T.

We have been developing an RF antenna coil for the 7T animal MR system. Until the system became available in winter 2004, we studied the feasibility of a TEM type RF volume coil. We made an eight-element, quadrature transmit/receive volume coil for 4.7T. The inner and outer diameters were 18cm and 27cm,

respectively and the length was 34cm. Q value was 400 and 180 under unloaded and loaded conditions, respectively. We performed imaging experiments with the whole body 4.7T MR system (Varian) at the National Institute of Environment Research. Imaging was obtained using gradient echo, spin echo and EPI methods. Signal-to-noise ratio (SNR) of gradient echo images remained almost the same level as 1.5T and RF sensitivity profile was worse than expected. The drop of signal strength reached almost 20% at 7cm off the center in the azimuthal direction in the most severe case. We are now perusing the causes to make a new better TEM coil for 7T.

Major publications:

1) Zhang Ming-rong*, Jun Maeda*, Toshimitsu Fukumura, Yuichirou Yoshida*, Masanao Ogawa*, Tetsuya Suhara, Kazutoshi Suzuki: [^{18}F]FMDAA1106 and [^{18}F]FEDAA1106: Two positron emitter labeled ligands for peripheral benzodiazepine receptor(PBR)., *Bioorganic & Medicinal Chemistry Letters,* 13, 201-204, 2003.
2) Tsuyoshi Fuchigami, Terushi Haradahira, Takuya Arai, Takashi Okauchi, Jun Maeda, Kazutoshi Suzuki, Fumihiko Yamamoto*, Tetsuya Suhara, Shigeki Sasaki, Minoru Maeda: Synthesis and Brain Regional Distribution of [^{11}C]NPS 1506 in Mice and Rat: an N-Methyl-D-aspartate (NMDA) Receptor *Antagonist, Journal of Pharmaceutical Sciences,* 26, 1570-1573, 2004.
3) Hitoshi Shinotoh, Kiyoshi Fukushi, Shin-ichiro Nagatsuka, Noriko Tanaka, Akiyo Aotsuka, Tsuneyoshi Ota, Hiroki Namba, Shuji Tanada, Toshiaki Irie: The Amygdala and Alzheimer's Disease Positron Emission Tomographic Study of the Cholinergic System, The Amygdala in Brain Function : Basic and Clinical Approaches *Annals of the New York Academy of Sciences*: vol.985, 411-419, 2003.
4) Toshiaki Osuga*, Takayuki Obata, Hiroo Ikehira: Proton magnetic resonance imaging of flow motion of heavy water injected into a hollow fiber dialyzer filled with saline, *Magnetic Resonance Imaging*, 22, 413-416, 2004.
5) Takayuki Obata, Thomas T. Liu*, Miller Karla*, Wen-Ming Luh*, Eric C. Wong*, Lawrence R. Frank*, Richard B. Buxton*: Discrepancies Between BOLD and Flow Dynamics in Primary and Supplementary Motor Areas: Application of the Balloon Model to the Interpretation of BOLD Transients, *NeuroImage*, 21, 144-153, 2004.

5.10 Electron Density Measurement with Dual-Energy X-ray Computed Tomography

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

Outline of Research Career:

Dr. Torikoshi received a Ph.D. from Tohoku University in 1983 for his study on pion spectroscopy with pion photoproduction reaction in carbon. He has had 11 years experience at NIRS in research and development on the high-energy beam transport system and irradiation system of HIMAC and research on medical application of synchrotron radiation.

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Objectives:

Electron density distribution of a body is indispensable for treatment planning of proton and heavier ion radiotherapy for cancer. More accurate electron density is required to make the treatment planning more precise. One method for directly measuring the electron density of an examinee is dual-energy x-ray CT imaging. Feasibility study of the dual-energy x-ray CT in which two different energy x-rays are independently used was started to establish a practical way to measure the electron density quantitatively. It was experimentally proved that the electron densities of phantom materials were measured at about 1 % accuracy in the dual-energy x-ray CT. In the study of 2003, the CT system with a two-dimensional detector was developed. In the experiments, biological samples of rats and porcine organs were mainly used. In the experiments, a two-dimensional (2D) x-ray detector was used for the CT scanning in a short time. It was proved experimentally that it was possible to make quantitative measurement with the 2D x-ray detector. The electron densities of water and solvents of chemical compound were measured with accuracy more than 99 %. The images of the electron density and an effective atomic number are reconstructed from the dual-energy x-ray CT. It was found that these two images showed characteristics of a material separately, that were "compactness" and "weight". The typical case was a lung as shown in pictures. It should be proved experimentally that the two images provide the information that is useful for medical diagnoses.

Progress of Research:

While electron density has not played an important role in medical diagnosis, it is an essential factor in treatment planning for heavier ion radiotherapy. At present, the electron density is derived from CT number obtained in conventional CT with an assumption of one-to-one correspondence between the electron density and the CT number. It was reported that there was about 2 % uncertainty in the electron density due to ambiguity of the model as well as the beam hardening effect. We proposed dual-energy x-ray CT (DXCT) using monochromatic x-rays for a direct measurement of the electron density to eliminate the uncertainty as much as possible. We experimentally proved accuracy to be 1 % in the DXCT with a one-dimensional CT system in 2002. The accuracy of 1 % was our first goal of this study. In the study of 2003, images based not only on the electron density but also on the quantity of effective atomic number as a by-product in the DXCT were found to have potential as a new modality of medical diagnosis.

Experiments were carried out at the beamline BL20B2 of SPring8/JASRI. The CT system consisted of a rotation table mounted on a table movable in two directions and a two-dimensional scintillator array detector. The detector consisted of 256 × 96 elements made of a $Gd_2O_2S(Pr)$ scintillator. Each element was 1.028 mm (vertical) × 0.894 mm (horizontal) including a dead area. The signals induced from scintillation light emitted in the element were converted to 16-bit digital signals with an ADC device. Since the detector system could take one projection image in about 11 ms excluding exposure time, about a hundred frames could be taken per one second at the

maximum. The overall dynamic range of the detector with respect to the x-ray beam intensity was experimentally proved to be order of about 2.5.

For biological samples, Donryu rats (6 weeks old, female) and several porcine organs: brain, heart, liver, kidney, pancreas and spleen were used. Each of the porcine organs was extracted right after slaughtering and immersed in 1 % agarose-physical saline gel in a polyethylene vessel to be immobilized. Sodium-azide was added in the agarose solution for antisepsis. Every organ sample contained a water sample in the vessel to monitor the accuracy of measurement. A rat sample was contained in a bottle made of polyethylene terephthalete with the water sample. The rat was euthanised by administering an over dose of barbiturate. Water and chemical compound: solutions of di-potassium hydrophosphate with concentrations of 1 %, 2 %, 3 %, 4 % and 5 % and ethanol were also used for verifying the accuracy of this method.

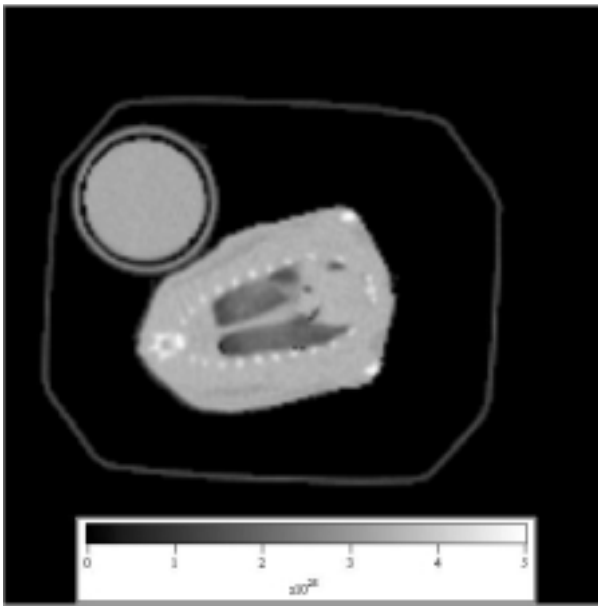

Figure 27.
Rat thorax image based on electron density

Figure 28.
Rat thorax image based on effective atomic number

The results for water and the chemical compound solutions proved that the accuracy of the DXCT with the two-dimensional detector system was also within 1 %. Rat thorax images of the DXCT were typical for the electron density (Fig.27) and effective atomic number (Fig.28). The former image clearly separates the lungs from surrounding tissues, while in the latter it is difficult to distinguish the lungs from the surrounding tissues. Since the lungs consist of numerous alveoli with diameter of 0.006 - 0.02 mm, which contain air in the cells, the lungs seem low density in comparison with other tissues. There is about a 40 % difference in the electron density between them. The effective atomic number indicates "weight" of constituents of an object. The fact that there is less contrast between the lungs and the surrounding tissue means the constituents of the lungs and the surrounding tissue must be similar. This result is very reasonable because the constituents of each cell of both the tissues should be very similar. The difference between images is well explainable. Comparison of the images based on the electron density and effective atomic number might provide different contrast with each other according to characteristics of the object. There is a potential for detecting abnormalities in tissue.

Major publications:

1) Torikoshi, M., Tsunoo, T., Endo, M., Noda, K., Kumada, M., Yamada, S., Soga, F. and Hyodo, K.: *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.: *Phys. Med. Biol.* 48, 673-685, 2003.
3) Tsunoo, T., Torikoshi, M., Sasaki, M., Yagi, N. and Uesugi, K.: *IEEE Trans. on Nucl. Sci.,* 50, 1678-1682, 2003

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

Outline of Research Career:

Dr. Nishizawa received a Ph.D. from Kyorin University in 1985 for her study on dose estimation of patients in X-ray examination. She has had 28 years of experience in research and development on dose estimation in medical exposure and occupational exposure on medical staff at Kyorin University and NIRS. At 1996, she was at the Radiation Protection Institute of Sweden as a visiting scientist where she studied dose measurement at mammography and CT examination.

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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 are to estimate the doses of patients from medical exposure in investigating the optimized dose range, and to reduce the doses of medical staff. In FY2003, we estimated the doses of patients from multi-row CT examinations. We studied the method of dose estimation for patients and medical staff in interventional radiology beginning in FY2002.

Continuing national surveys of the frequency and tendency of medical radiation usage were also done as the basic studies for estimation of population doses. The population doses would be used for comparison with radiation exposures from other radiation sources or of the exposure situation between states. Also, it would be used for estimating detriments. The target of the national survey each year is selected from X-ray diagnoses, X-ray mass screening, nuclear medicine, radiation therapy or dental radiological diagnosis.

Progress of Research:

1) Dose estimation and protection towards medical radiation

For patient dose evaluation in an examination with a multi-row detector CT (16- row detector), an anthropomorphic phantom composed of tissue equivalent material and two kinds of thermo-luminescence dosimeters (TLDs) encapsulated in glass and glass dosimeters were used. Because of variation of detector row combinations, the doses of the patients are changed. The examination conditions like detector row combinations, mAs, pitch factor, etc. should be selected by balancing of clinical needs and image quality.

The measurement range should widen because the exposure area is wider when increasing the number of detector rows on the CT, so that a longer PMMA phantom and ion chamber are needed for evaluating the CT dose index easily. To establish the simple exposure dose index with reference to the effective dose, the effective length of the ion chamber and measurement ranges of the phantom, which can be applied as the dose index for multi-row CT, were tested.

Using a Japanese male voxel phantom, organ doses in X-ray CT examinations were estimated by computer simulations. For chest and abdomen X-ray CT examinations, absorbed energy of each organ was calculated for each slice, and the relationship between exposure area and organ dose was studied.

The doses of patients and medical staff in interventional radiology (IVR) were monitored using glass dosimeters. Examination data of head or pelvis area were mainly collected. There were many differences among patients. IVR is one method with

the possibility of causing severe skin injuries to patients because of its high dose exposures, so that quick and accurate dose estimation is required. We started a system which can be not only feedback data to doctors, but also construct a database.

2) Survey of medical exposures

This year, we performed a national survey on diagnoses and therapies in nuclear medicine using written questionnaires. The terms were sex, age, target region, radiopharmaceutical and medication method to the patients. All 1225 nuclear medicine facilities and 55 PET facilities were targeted by the survey. The response rates were 55% for general nuclear medicine facilities, and 58% for PET facilities.

3) Results

The doses of patients and medical staff for 30 pelvis IVR examinations are shown in Table 4. For the measurements of surface doses of patients, 15 sets of 3 glass dosimeters were located on the X-ray entrance surface of their bodies. As the examinations were performed almost symmetrically, the catheter entrance side was kept clean, and dosimeters were set on the other side. To measure the doses of medical staff, 16 sets of 3 TLD and 3 glass dosimeters were attached on 16 points of their whole bodies, and cumulative doses were measured during examinations. The organ or tissue doses of patients were obtained by anthropomorphic phantom measurements using the mean conditions of 30 clinical cases.

Table 4 also shows the mean conditions of 30 clinical cases as mentioned above. The mean values of 15 measured points of surface varied from 2.3 to 416.3 mGy. The highest dose was 1.65 Gy for a case with 33.5 min fluoroscopy and 11 Dose Subtraction Angiographs (DSAs). As major depth organ doses, 9.5 mGy and 11.4 mGy were measured for ovaries and uterus respectively as mean conditions of 30 cases. The estimated mean effective dose was 3.26 mSv. For medical staff, mean surface dose was 0.046mGy near the crystalline lens, and the highest mean dose was 0.105mGy on the left arm.

In IVR, fluoroscopy time and numbers of DSAs varied with examinations and cases, and doses were quite different for each case. For the maximum dose of 1.65Gy, the ovaries and uterus doses were proportionally estimated as 43mGy and 52mGy, respectively. In ICRP Publication 85, it is recommended that the examinations should be recorded when over 1Gy exposure, and patients should be made known of the fact when the dose would be over 3Gy. The progress after exposure should also be recorded. The dose should be accurately estimated including specification of maximum exposure area of the patients' bodies.

Table 5. Mean conditions and doses of 30 IVR examinations.

	Mean	
Time of fluoroscopy (min)	27.9	10.6
Mean tube voltage of fluoroscopy (kV)	74.9	6.6.4
Sum of fluoroscopy (mAs)	2369	1272
DSA photographs	8.66	2.55
Surface dose of patients (mGy)		
Maximum dose of 15 points	364.	339.
Minimum dose of 15 points	5.31	6.95
Estimated effective dose (mSv)	3.26	3.05
Surface dose of medical staff (mGy)		
Left arm	0.105	0.146
Back of the left hand	0.068	0.120

Major publications:

1) Iwai, K., Mase, N., Honda, K., Kashima, M., Shinoda, K., Nishizawa, K., Maruyama T., Estimation of population doses and stochastic risks in dental radiographic examination in Japan, 1994. *Dental radiology,* 43:65-69, 2003

2) Nishizawa, K., Moritake, T., Matsumaru, Y., Tsuboi, K., Iwai. K.: The dose measurement of patients and physicians using a glass dosimeter during endovascular treatment for brain disease. *Radiat. Prot. Dosimetry.,* 107:247-252, 2003.

3) Nishizawa, K., Matsumoto, M., Iwai, K. Maruyama. T.: Survey of CT Practice in Japan and Collective Effective Dose Estimation., *Nippon Act. Radiol.,* 64:151-158, 2004.

6. Brain Imaging Project

Tetsuya Suhara, MD, Ph.D.
Director of Special Research,
Brain Imaging Project

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 work at NIRS from 1989. In 1992-1993 he studied at PET group of Department of Clinical Neuroscience, Karolinska Hospital, Sweden. He has researched on brain functional imaging for a long period. He serve as visiting professor, Department of Neuropsychiatry of Nippon Medical School from 2004.

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Objectives:

Our research group has been focusing on mental disorders and brain functional imaging using PET (Positron emission tomography), fMRI (functional Magnetic Resonance Imaging) and MRI.

The mechanism of mental disorders

Abnormal neurotransmission in the brain was suggested to be related to mental disorders such as schizophrenia and mood disorder. We have been investigating neurotransmitters such as dopamine and serotonin using PET with [^{11}C]FLB 457 and [^{11}C]DASB.

Psychopharmacological research

Some drugs for treatment of mental disorders work on the receptor or transporter in the brain. Using PET, the receptor occupancy can be measured. We have been investigating the receptor occupancy by antipsychotics and antidepressants.

Neuroscience research

We have been aiming for a systematic understanding of cortical dopamine functions, and we are performing PET studies to compare neuronal networks between healthy controls and patients with mental disorders, and between humans and animals.

Radioligand development

We have been developing new radioligands for NMDA receptors and peripheral benzodiazepine receptors.

Software development

We have made some software for the compartment analysis of PET data, and for placing the ROI automatically.

Progress of Research:

Development of new radioligands

We recently developed novel radioligands for peripheral benzodiazepine receptor(PBR), [^{11}C]DAA1106 and [^{18}F]FEt-DAA1106. Using PET data acquired from normal healthy volunteers, we investigated the model analysis and simulated the property and accuracy of several models. We finally established the method to quantify [^{11}C]DAA1106.

Clinical application of [^{11}C]DAA1106

We measured PBR in patients with dementia Alzheimer type and mild cognitive dysfunction with [^{11}C]DAA1106. We found a significant difference between the patients and normal controls. It is known that the damage to the neurons induces the change of PBR binding on glia cells. Therefore, it seems to be very significant to quantify the PBR for the diagnosis and estimation of dementia and other neurodegenerative disorders.

Serotonin transporter

[^{11}C]DASB is a new radioligand for serotonin transporter and it shows higher affinity and selectivity than [^{11}C](+)McN5652. In cooperation with NIH, we developed a method of quantitative analyses of [^{11}C]DASB without arterial blood samplings. We have also been investigating clinical and drug trials using [^{11}C]DASB.

Presynaptic dopaminergic activity

The dopamine hyperactivity hypothesis of schizophrenia remains one of the most influential theories on the pathophysiology of illness. The efficacy of antipsychotic medications is based on their antagonistic action on dopamine D2 receptor

which is believed to restore the function of hyperactive doperminergic neurons. But there has been no study to investigate the direct influence of antipsychotic medication on dopaminergic neurons of the patients in vivo. To investigate presynaptic dopaminergic function, uptake of DOPA in the brain is a good index because dopamine is generated from DOPA. Therefore, as a preliminary study, we measured [^{11}C]DOPA uptake in the brain of one neuroleptic-naive schizophrenia patient with PET. We measured the uptake of [^{11}C]DOPA several times to investigate the time course of the change of presynaptic dopaminergic activity. We calculated Ki index by using the Patlak method and compared the Ki value with the baseline. High Ki value means increased DOPA uptake, in other words, a hyperactive state of dopaminergic neurons. As a result, region of interest analysis showed transient decrease of Ki one day after initiating medication in the striatum and anterior cingulated cortex and increased Ki value in these regions afterwards compared with baseline. In the thalamus and amygdale, the Ki value increased shortly after initiating medication and remained at a high level one month and 3 months after initiating medication. These results imply antipsychotic medication directly affects the patient's presynaptic dopamine function, but we need further investigation to determine how these results can be combined with psychotic symptoms or cognitive functions.

Activation study in monkey

We can control distant tools effectively by manipulating other object as controllers in various remote-operated ways, even when the two mechanics are altered. To master the remote operation, we may rely on internal representation to organize individual moves of the controller and tool into a set of sequences by mapping the motor space among hand, controller and tool as a continuum. The present study confirmed that monkeys could also organize a sequence by mapping such a motor space or reorganize it by remapping even after alteration. In addition, to investigate the neural substrates underlying such mapping/remapping, we measured the regional cerebral blood flow of two monkeys during joystick-controlled operation with altered function of mechanics using PET $H_2{}^{15}O$. The monkeys were scanned during three different tasks produced by altering the differential gains of the x or y axis of the joystick - the two mechanics were congruent (standard task) and not congruent (reversed in the X or Y axis, X reverse or Y reverse task, respectively). Compared with random movement of the joystick as a control task, increased activities were detected in the prefrontal cortex, higher -ordered motor cortex, posterior parietal cortex and cerebellum during the standard task. Common brain areas during performance of the X reverse and Y reverse task were identified as showing almost the same pattern as during the standard task. These shared areas may not simply be associated with organization of individual motor imagery, but also with context-dependent processing of reorganization based on the current function by means of internal reorientation.

Assessment of Parkinson's disease model in monkeys using PET

Although the MPTP-treated monkey has been used commonly as a Parkinson's disease model, the process of MPTP-induced degeneration of nigrostriatal dopamine neurons had not been examined in detail. We examined the degeneration process of nigrostriatal dopamine neurons with PET using two unanesthetized MPTP-treated cynomolgus monkeys. The tracers used were [^{11}C]PE2I, [^{11}C]DOPA, and [^{11}C]raclopride for monitoring dopamine transporter (DAT) densities, dopamine (DA) turnover, dopamine D2-receptor (D2R) densities and behavior referring to the criteria of the PD symptoms, respectively. During the period when no major symptom was clearly observed, PET scans detected that DAT densities and DA turnover had already decreased greatly, but D2R densities had not changed. These findings suggest that PET imaging could detect the dopaminergic dysfunction in vivo in an early stage of Parkinson's disease.

In vivo PET measurements with [^{11}C]PE2I to evaluate fetal mesencephalic transplantations to unilateral 6-OHDA

We performed repeated PET scans with [^{11}C]PE2I, a tracer of the dopamine transporter, to evaluate the alteration of the expression of dopamine (DA) transmission component after a fetal mesencephalic transplantation. The fetal mesencephalic cells were transplanted into the striatum of unilateral 6-OHDA-lesioned rats. PET scans with [^{11}C]PE2I were performed to evaluate the DA transporter before, and 2 and 4 weeks after the transplantation. Rotation behavior tests, in vitro autoradiography, measurements of DA contents in the striatum by high-performance liquid chromatography (HPLC), and tyrosine hydroxylase (TH) immunohistological examinations were performed at the same time points and examined for their relationship to changes in the DA transporter. The number of ipsilateral rotations induced by methamphetamine injections decreased. DA contents in the striatum

measured by HPLC significantly increased. In the PET study, the binding potential of [^{11}C]PE2I increased at 4 weeks. The results of the *in vitro* autoradiography study corresponded with those of the PET study. The degrees of the change in the binding potentials correlated with those of the numbers of rotations in the behavioral study and the DA contents in the striatum. In the histological examination, TH-positive cells with axons were observed at 2 and 4 weeks after the transplantation. As the DA transporter was present only in the axon terminal of DA neurons, these results suggested that PET measurements of [^{11}C]PE2I binding indicated not only survival, but maturity and functioning of the transplanted cells. Repeated PET measurements of DA transporters are a useful tool in assessing the effectiveness of neural transplantations.

Assessment of new peripheral benzodiazepine receptor ligand [^{11}C]DAA1106 for PET

We investigated in vivo properties of [^{11}C]DAA1106 in rat and monkey brain. Higher uptakes and specific binding of [^{11}C]DAA1106 were observed in the monkey cortex compared to [^{11}C]PK11195.

Assessment of a ligand for P-glycoprotein, [^{11}C]verapamil for PET

We are using PET to confirm that the efflux systems of [^{11}C]verapamil at the monky brain are dependent on P-glycoprotein. Additionally, we are establishing quantitative imaging of [^{11}C]verapamil.

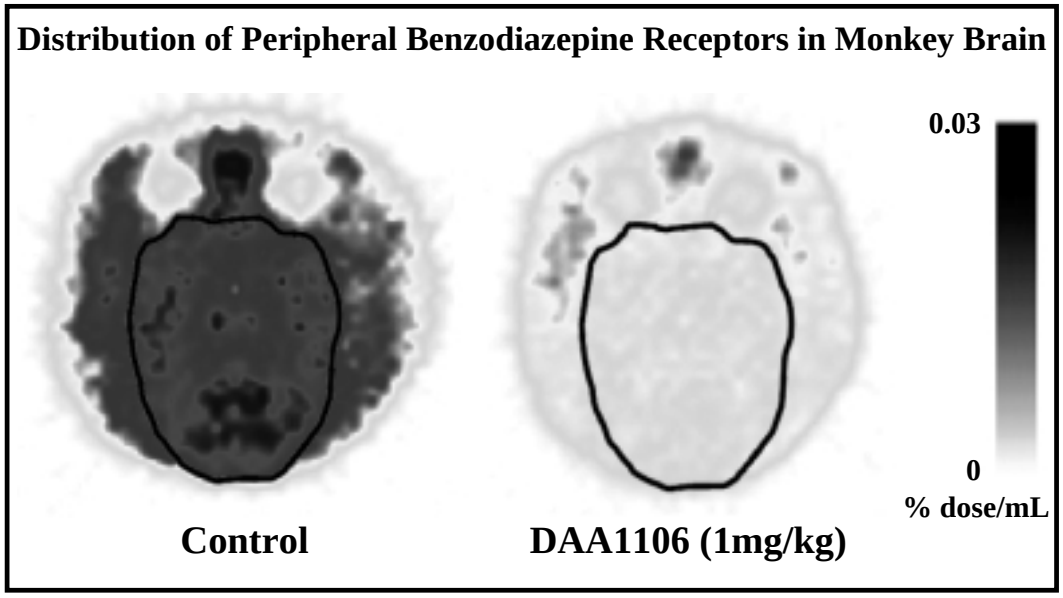

Fig.29.
Summed PET images (30-90min after injection) of [11C]DAA1106 (left) and with DAA1106 pretreatment (right) in the identical subject. The closed line represents the outline of the monkey brain. The application of [^{11}C]DAA1106 may provide useful information in the diagnosis of neurodegenerative disorders in future.

7. Frontier Research Center
RadGenomics Project

Hajime Murata, MD, Ph.D.
Supervisory Director

Outline of Research Career:

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 be the Head of 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 National Institute of Radiological Sciences as the Director of the Research Center of Charged Particle Therapy in 1997 and served 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 a new strategy for cancer treatment by radiotherapy using a heavy ion beam.

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Takashi Imai, Ph.D.
Director

Outline of Research Career:

Dr. Imai received a Ph.D. from the University of Tsukuba in 1986. Following a fellowship from the Japan Society (for the Promotion of Science for Japanese Junior Scientists) at the Institute of Applied Biochemistry, University of Tsukuba, he joined the Institute of Physical and Chemical Research's facility (RIKEN) at the Tsukuba Life Science Center. From 1988 to 1989, he worked at 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.

Contact point (E-mail): imait@nirs.go.jp

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 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.

Overview - For Personalized Radiotherapy -

The human genome contains approximately 3 billion base pairs, and the sequence differs at more than three million sites among the human population. It has been ascertained that this difference (genetic polymorphism) in base sequences determines human diversity - not only apparent diversity such as appearance and height but also internal diversity including responsiveness to alcohol, pollen allergen, or susceptibility to disease. Individual variance in susceptibility to radiation is believed to be closely associated with genetic variance.

The outcome of this research will allow us to identify any correlations between an individual DNA sequence and their 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

Our strategy is a candidate gene approach selected through the experiments using in vitro cultured human cell lines and animal models. SNPs on the selected genes have been typed using the DNA from white blood cells of cancer patients with clinical information. The scheme of our strategy is illustrated in Fig. 30.

1) Patients

The 1,071 patients in this study were 489 breast cancer patients, 149 ovarian cancer patients, 126 prostate cancer patients, and 133 head and neck cancer patients. They were registered between 2001 and 2004. Normal tissue reactions until the 3rd month after completion of the treatment were graded according to the National Cancer Institute-Common Toxicity Criteria (NCI/CTC). Late effects on normal tissues were graded according to the Radiation Therapy Oncology Group/ the European Organization for Research and Treatment of Cancer (RTOG/EORTC) scoring system and the Late Effects of Normal Tissues-Subjective, Objective, Management and Analytic (LENT-SOMA) scoring system. Patients were divided into two groups (radiosensitive and radioresistant) according to the grades determined by the above scoring systems.

2) Candidate gene selection

We have defined the following three criteria to select candidate genes. (1) Genes whose expression profile showed statistically significant association with cellular radiation sensitivity. (2) Genes whose expression were induced or reduced after ionizing radiation treatment. (3) Genes whose involvement in the radiation sensitivity had been evaluated in the literature. We have measured radiosensitivity of 32 different cultured human cancer cell lines and analyzed their gene expression profile by the microarray technique. In addition, we have analyzed *in vivo* gene expression profiles of mouse strains with different radiation sensitivity.

3) SNPs typing of the candidate genes and statistical analysis

The information about SNPs on the candidate genes was obtained from JSNP database (http://snp.ims.u-tokyo.ac.jp/) and dbSNP database (http://www. ncbi.nlm.nih.gov/SNP/). Typing of the SNPs was performed by the allele-specific termination of primer extension method using a MALDI-TOF mass spectrometer. Statistical analysis of association between the SNP types and radiosensitivity of patients was done using SNPalyze software.

As a total we have selected 108 candidate genes that met at least one of the above criteria. Six hundred and forty three SNPs were typed for the 108 candidate genes of 346 individuals (218 breast cancer, 57 ovarian cancer and 71 prostate cancer patients). So far, we found more than 12 genes that showed statistically significant association.

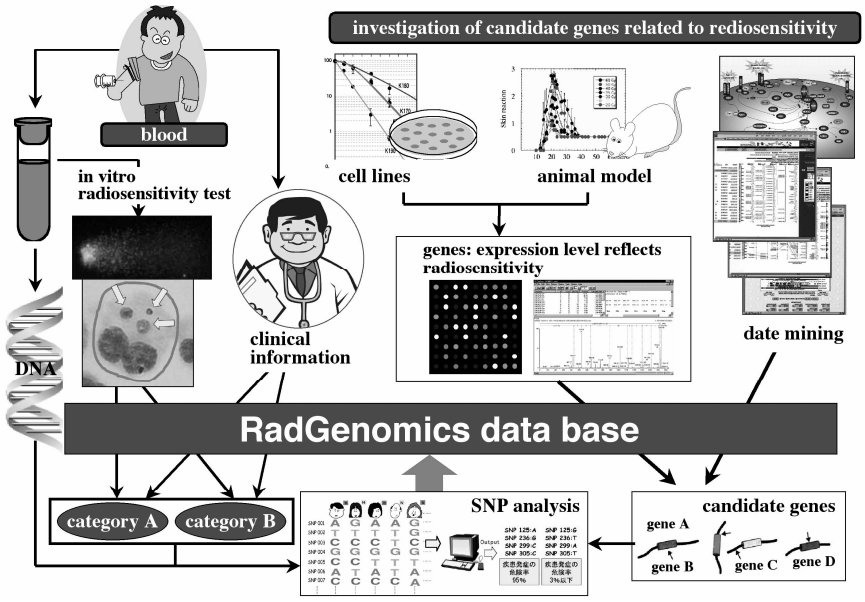


Fig. 30. Research strategy for detecting polymorphisms, associated with radiation-induced adverse effects on cancer patients.

Conclusion

This study implies that analysis of multiple SNPs on adequately selected candidate genes might be specifically suitable for identification of genetic constraints of radiation sensitivity. At present our findings are still preliminary and require assignment of functional influence of the SNPs to the expression of gene activity that relate to the radiation sensitivity. Our study should encourage a further comprehensive search for genetic polymorphisms that associate with radiation-induced normal tissue injury on cancer patients.

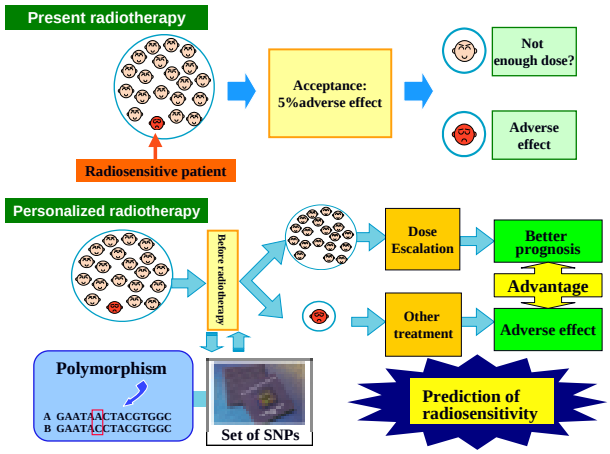


Fig.31.

Major publications:

1) Iwakawa, M., Noda, S., Ohta, T., Oohira, C., Tanaka, H., Tsuji, A., Ishikawa, A., and Imai, T. : Strain Dependent Differences in a Histological Study of CD44 and Collagen Fibers with Expression Analysis of Inflammatory Response Related Genes in Irradiated Murine Lung. *Journal of Radiation Research,* 45(3): 423-433, 2004

2) Gao, G., Bracken, A., Burkard, K., Pasini, D., Classon, M., Sagara, M., Imai, T., Helin, K., Zhao, J. : NPAT expression is regulated by E2F and is essential for cell cycle progression. *Molecular and Cellular Biology,* 23: 2821-2833, 2003.

3) Iwakawa, M., Noda, S., Oota, T., Kitazawa, C., Lee, R., Gotou, M., Wakabayashi, M., Matsui, Y., Harada, Y., Imai, T. : Different radiation susceptibility among five strains of mouse detected by skin reaction. *Journal of Radiation Research,* 44: 7-13, 2003.

4) Bonassi, S., Neri, M., Lando, C., Ceppi, M., Lin, Y. P., Chang, P., Holland, N., Volders, M.K., Zeiger, E., Fenech, M., Ban, S. : Effect of smoking habit on the frequency of micronuclei in human lymphocytes: results from the Human MicroNucleus project, *Mutation Research,* 543: 155-166, 2003.

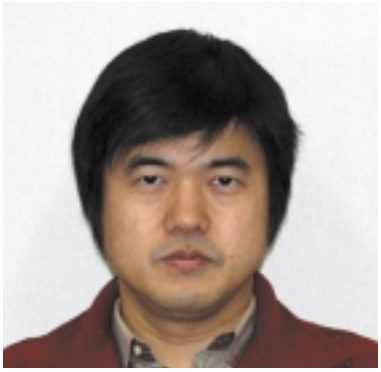
5) Sun, X.Z., Harada, Y., Zhang, R., Cui, C., Takahashi, S., Fukui, Y. : A genetic mouse model carrying the nonfunctional xeroderma pigmentosum group G gene., *Congenital Anomalies,* 43: 133-139, 2003.

8. Transcriptome Research Center Gene Expression Profiling Project

Sentaro Takahashi, Ph.D.
Supervisory Director

Outline of Research Career:

Dr. S. Takahashi graduated from Kyoto University in 1974, and after completing master course, started to work as a research scientist at the Division of Radiation Hazard, NIRS. He was at MRC Radiobiology Unit, UK as a visiting researcher between 1985 and 1986, and at Department of Radiation Oncology, University of Texas Medical Branch at Galveston, Texas as a visiting professor between 1996 and 1997. He is now the Supervisory Director, Research Center for Radiation Safety (from 2002) and the Supervisory Director, Advanced Transcriptome Research Center (from 2003, dual position) in NIRS.
Contact point (Email): sentaro@nirs.go.jp



Masumi Abe, Ph.D.
Director

Outline of Research Career:

MS Molecular Biology, Hiroshima Univ, 1983. PhD Molecular Biology, Hokkaido Univ Faculty of Science, 1993
Masumi Abe first joined the Radiation Effect Research Foundation in Nagasaki, Japan and studied the mechanism of VDJ recombination. He worked on isolating the gene responsible for SCID mutant mice, which features aberrant VDJ recombination. After moving to NIRS, in 1996, he became a Team Leader in 1998. His group identified DNA-PKcs as the responsible gene by detecting a mutation in its ORF, which is over 14 kb. Five years ago, the group changed to a genome-wide approach. They developed a new technique for gene expression profiling called HiCEP (High Coverage Gene Expression Profiling) and in Nov 2003 started the Transcriptome Research Center, where Dr. Abe is presently Project Leader.
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Objectives:

The Transcriptome Research Center was established on November, 1, 2003 to carry out systematic and collaborative research work in the field of tanscriptome analysis (gene expression and transcription) by using the newly developed transcriptome analytical method, HiCEP (High Coverage Gene Expression Profiling). Now that a significant number of species have been completely sequenced, post-genome projects including transcriptome and proteome projects are being carried out all over the world. Until now approaches using mutants have been standard, but there are some organisms and some biological phenomena for which these are poorly suited or inapplicable. A transcriptome analysis technique covering almost all expressed transcripts would be a powerful tool, especially for organisms that are difficult to analyze using mutants, like humans. The hybridization-based microarray method is the standard technique for gene expression profiling, but it has serious problems with coverage, sensitivity and reproducibility. The newly developed method, HiCEP, is designed to overcome these limitations. The objectives of this Center are further improvement of HiCEP and application of this unique method to a variety of fields including life science and medicine.

Overview:

In FY 2003, although only 4 months were available after the Center was established, much progress was achieved especially in hiring staff, setting up the research laboratory, and introducing administrative systems. At present, the Center contains a projective research group and a promotion office (including administrative activity), and is supervised by the Supervisory Director, Dr. S. Takahashi. The projective research group directed by Dr. M. Abe consists of three research teams. Masumi Abe leads the first and third teams, and Toshiyuki Saitoh leads the second team. The first team focuses on developing and improving HiCEP

technology, the second on bioinformatic analysis of mouse and human transcriptomes using the results of HiCEP analysis, and the third on case studies to identify genes of interest, such as radiation-induced genes and master genes for cell differentiation. At the start, there were only a few workers, but there are more than 15 stuffs at the end of this financial year. The installation of the laboratory equipment was rapidly carried out. Approximately 2.1 million yen was budgeted for this Center and was used mainly to purchase laboratory equipment and materials. The space for the Center, especially for the laboratory, was much expanded during this financial year. However, the shortage of the office space is still a problem and requests are being made to the administrative division of NIRS.

Objectives of Research Project:

This research program is supported by RR2002 (Japanese Ministry of Education, Culture, Sports, Science and Technology) and its objectives are as follows.

1. Developing next-generation high performance gene expression profiling technology
2. Achieving high throughput
3. Reducing the minimum sample size
4. Making application studies including ionizing radiation-induced genes, genome-reprogramming factors and clock genes
5. Creating a public gene expression profiling database and registration system

1, 2 and 3 were the main objectives during 2003.

Progress of Research:

The following is our progress for objectives 1, 2 and 3 above.

1. Developing next-generation high performance gene expression profiling technology

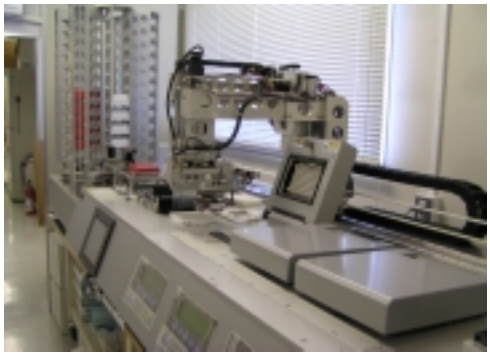
We developed a new method based on a different principle from that of microarray technology. The advantage of the method is that it can detect unknown genes and non-coding transcripts as well as known genes, because it does not require sequence information for its analysis. It detects over 70% of expressed genes and discriminates even 1.2-fold changes in gene expression. Its false positive rate is under 5%. The method can be applied to all eukaryotes, even those for which there is no genome sequence information.

2. Achieving high throughput

This is being done in collaboration with the transcriptome profiling group (Research Center for Radiation Safety). See the transcriptome profiling group report.

3. Reducing the minimum sample size

We have reduced the minimum sample size from 10,000,000 cells to 10,000, or 0.1 microgram of total RNA of mice or human. We achieved this by using magnetic beads for DNA handling throughout template preparation. Our goal is to be able to do HiCEP analysis using a single cell.



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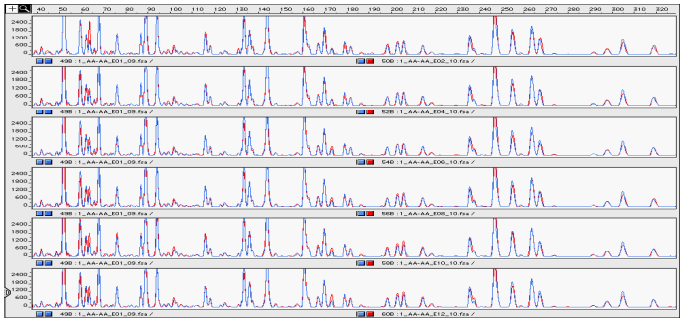

Fig.32

9. Development of Single Particle Irradiation System to Cell (SPICE) at NIRS

Masae Yukawa, Ph.D.
Director, Division of Technical Support and Development

Outline of Research Career:

Dr. Yukawa received Ph.D. from Rikkyo University in 1990 on studies on the distribution of trace elements in human body. She has had 35 years of experience in research and development on analysis of radionuclides and the stable isotopes in environmental and biological samples. She has been applying PIXE method to determination of trace elements in biological samples to investigate balance shift of essential elements in organisms induced by environmental stresses. She has participated in several academic societies, such as International Committee of Nuclear Analytical Method in Life Science, The Japanese Society for Hygiene, The Japan Radiation Research Society and The Japan Society for PIXE Research as a councilor or a secretary.

Contact point (E-mail) :m_yukaw@nirs.go.jp

Objectives:

Recent evidence on bystander effect by application of a particle microbeam to biological experiments has had a strong impact on radiation research at a low dose and low dose rate, with respect to mechanisms of radiation actions and to risk estimation for radiation protection. Selective irradiation with an ionizing particle to a targeted cell organelle may disclose such mechanisms as signal transaction among cell organelles and cell-to-cell communication in the processes toward an observed endpoint. Installation of the particle microbeam irradiation system to cell in NIRS was planned to investigate the bystander effect.

Progress of Research:

Feasibility of using the microbeam for radiation biology has been studied in NIRS since 1998. Survey of radiation biologists in NIRS suggested two types of motivation for future research using the microbeam irradiation system to cell. Those are (1) microscopic and real time observation of single cell throughout, during and after, irradiation of a single particle to the cell nucleus, and (2) assay requires quite a large number of cells for good statistics after irradiation of a single particle to the cell nucleus. The key element of the possible facility was understood to be more precise and faster irradiation with the microbeam. In 2002, the budget for construction of the facility (Single Particle Irradiation System to Cell: SPICE) was approved and its construction has started with a newly formed project team.

The accelerator, a Tandetron (High Voltage Engineering Europe Ltd.) was installed in 1997 in the Electrostatic Accelerator Building and provides beams of 3.4 MeV H^+ or 5.1 MeV He^{2+}. From the accelerator three beam ports have already been in operation for PIXE study. The microbeam facility named SPICE has been under construction as an additional beam port of the accelerator. The beam is driven by a 90-degree bending magnet from one of the horizontal beam ports as a branch, because cells must be irradiated by a vertical beam. Along the beam line, an electrostatic beam deflector at the entrance of the bending magnet and a triplet Q-magnetic lens (Oxford Microbeam Ltd.) at the upper top end, are most important. The former regulates the number of particles and the latter focuses the

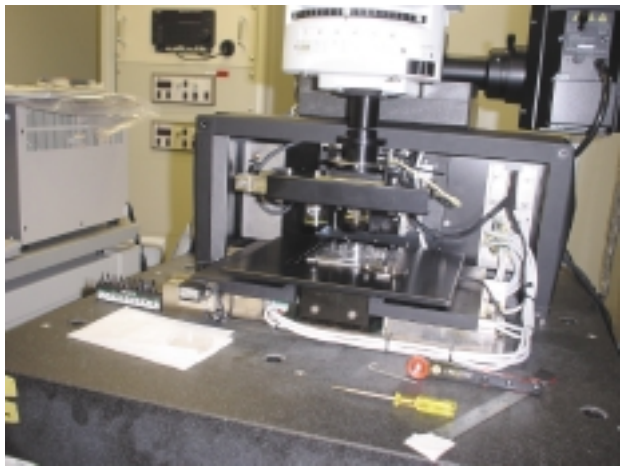

Fig.33. Cell irradiation stage of SPICE

Cells on the thin film placed at the hole of a plastic dish are irradiated from the bottom. The cell irradiation stage is moved fast and precisely by a Voice Coil motor in 40 nanometers resolution.

Beam and cell positions are observed with a thin scintillator placed on the position of a cell dish, and high sensitive CCD and ultra-violet light source attached to the revolver of the microscope.

particle beam down to μm size for irradiation of the cell nucleus. The SPICE beam port is designed with a special care against harmful environmental vibration by using an ingenious cradle system between two frames. The inner frame holds the beam port very tightly forming a solid structure and the outer frame holds the inner frame in soft contact by 4 legs of air suspension (Fig.34).

The focused particle exits from the window of the beam port into air and passes through the bottom of a cell dish. Two methods of targeting cell nucleus are possible: (1) with a fixed focused beam through movement of a stage on which the cell dish is held; and (2) with a fixed stage through scanning of the focused beam, cell-by-cell. The latter is our proposal for the requirement of "precise and fast" irradiation of many cells. Since this method will become available some time later after we get some experiences, for the time being, the less difficult method (1) is due to be used first. The Voice Coil motor is a device to improve speed of irradiation for method (1).

Fig.34. Single Particle Irradiation System to Cell (SPICE) at NIRS.

Three frames hold SPICE. The largest frame supports the irradiation cabin. Two frames inside form the cradle system: the outer frame holds the inner frame with 4 legs of suspension (seen as the upper black legs). The SPICE beam line is tightly fixed in the inner frame as a solid body including the microscope system of the upper end. The beam is supplied by the accelerator to the horizontal port from the right hand side and is driven to the vertical beam port by a 90 degree bending magnet of the triplet Q magnet.

A light source device, a mercury vapor ultraviolet epi-fluorescence module is installed to illuminate the target of a cell observed by a channel plate, an image intensifier and a CCD camera. After all coordinates of targets are registered, the position of the focused beam on the cell dish is registered with an optical device of very high sensitivity.

The required number of particles to irradiate is controlled by the particle detector and a beam shutter (the electrostatic ion deflector). The detector is a thin scintillation counter, embedded in the revolver of the microscope.

Position resolution to be gotten by SPICE is less than 2 micrometer after overcoming the uncertainties such as, coordinate acquisition of the target, precise positioning of the x-y stage to the beam focussing spot, and beam scanning operation. Effort has been made to reduce irradiation time as short as possible from data acquisition to repeated irradiation. So far our estimation as to the best performance by SPICE with the present conditions is around 2000 cells/hr.

We have concentrated on identification of the position of the beam spot at the cell dish. Two optical devices of different sensitivity in light intensity are necessary, for "rough or fine" adjustment. The rough adjustment focuses the beam with a size from a few hundred micrometers down to a few micrometers using an optical device of low sensitivity because of the relatively high rate of incident particles. It is followed by fine adjustment that focuses the beam down to 2 micrometers finally with the optical system of high sensitivity; this is the same conditions as actual irradiation at a very low particle rate.

In mid 2003, the fabrication of all parts was complete and 3 months later the first proton microbeam of 18 μm size was observed.

Major publications:

1) Yamaguchi, H., Yukawa, M., Soga, F.: Feasibility study of a microbeam at the National Institute of Radiological Sciences, *Radiat. Res.* Vol. 153, 237-238, 2000.

2) Yamaguchi, H., Sato, Y., Imaseki, H., Yasuda, N., Hamano, T., Y.Furusawa, Suzuki, M., Ishikawa, T., Mori, T., Matsumoto, K., Konishi, T., Yukawa, M., Soga, F.: Single particle irradiation system to cell (SPICE) at NIRS, *Nucl. Instr. Meth. Phys. Res.* B210, 292-295, 2003.

10. List of Original Papers

This list includes main publications by the staff members issued during the period from April 1, 2003 to March 31, 2004

**** Co-researcher outside the institute***

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

Low Dose Radiation Effects Research Project

1. Kyoko Yasumura*, Isamu Sugimura*, Kazuei Igarashi*, Shizuko Kakinuma, Mayumi Nishimura, Masahiro Doi, Yoshiya Shimada: Altered expression of Tfg and Dap3 in Ikaros-defective T cell lymphomas induced by X-irradiation in B6C3F1 mice, *British Journal of Haematology,* 124(2), 179-185, 2004
2. Hideo Tsuji, Hiroko Ishii, Hideki Ukai, Takanori Katsube, Toshiaki Ogiu: Radiation-induced deletions in the 5' end region of Notch1 lead to the formation of truncated proteins and are involved in the development of mouse thymic lymphomas, *Carcinogenesis,* 24, 1257-1268, 2003
3. Ryouka Kawahara*, Manabu Matsuda*, Tatsuhiko Imaoka, Takao Mori*: Up-regulation of thymosin beta4 gene expression in experimentally induced uterine adenomyosis in mice, *In Vivo,* 17(6), 561-566, 2003
4. Yoshiya Shimada, Mayumi Nishimura, Shizuko Kakinuma, Toshiaki Ogiu, Hirokazu Fujimoto*, Ayumi Kubo, Junya Nagai, Keizou Tano*, Shinji Yoshinaga: Genetic susceptibility to thymic lymphomas and K-ras gene mutation in mice after exposure to X-rays and N-ethyl-N-nitrosourea, *International Journal of Radiation Biology,* 79, 423-430, 2003
5. Yasushi Ohmachi, Yuka Ishida, Takeshi Hiraoka, Tsuyoshi Hamano, Shinji Fushiki, Toshiaki Ogiu: Postnatal Changes in Mice Exposed In Utero to Fast Neutrons, *Jornal of Toxicologic Pathology,* 17(1), 63-68, 2004
6. Mayumi Nishimura, Shizuko Kakinuma, Daisuke Yamamoto*, Yoshiro Kobayashi*, Gen Suzuki*, Toshihiko Sado, Yoshiya Shimada: Elevated Interleukin-9 Receptor Expression and Response to Interleukins-9 and -7 in Thymocytes during Radiation-Induced T-Cell Lymphomagenesis in B6C3F1 Mice, *Journal of Cellular Physiology,* 198(1), 82-90, 2004
7. Hideki Ukai, Hiroko Ishii, Maki Ukai-tadenuma*, Toshiaki Ogiu, Hideo Tsuji: Formation of an Active Form of the Interleukin-2/15 Receptor beta-Chain by Insertion of the Intracisternal A Particle in a Radiation-Induced Mouse Thymic Lymphoma and Its Role in Tumorigenesis, *Molecular Carcinogenesis,* 37, 110-119, 2003
8. Kazuei Mita*, Mitsuoki Morimyo, Kazuhiro Okano*, Yoshiko Koike*, Junko Nohata*, Toru Shimada*, et.al: The construction of an EST database for Bombyx mori and its application, Proceedings of the National Academy of Sciences of the United States of America, 100, 14121-14126, 2003
9. Ikuko Furuno-Fukushi, Ken Ichi Masumura*, Takeshi Furuse, Yuko Noda, Masahiko Takahagi, Toshiyuki Saito, Yuko Fujimori, Hiroshi Suzuki*, Anthony Wynshaw-boris*, Takehiko Nohmi*, Kouichi Tatsumi: Effect of Atm disruption on spontaneously arising and radiation-induced deletion mutations in mouse liver, *Radiation Research*, 160(5), 549-558, 2003
10. Fumiaki Watanabe*, Ken-ichi Shinohara*, Hirobumi Teraoka*, Kenshi Komatsu*, Kouichi Tatsumi, Fumio Suzuki*, Takashi Imai, Masashi Sagara, Hideo Tsuji, Toshiaki Ogiu: Involvement of DNA-dependent protein kinase in down-regulation of cell cycle progression., *The International Journal of Biochemistry & Cell Biology,* 35, 432-440, 2003

Project of "Physical and Biological protection of Man from Space Radiation"

(***International Space Radiation Laboratory***)

1. Chikako Kinoshita*, Takeshi Yaoi*, Kumie Nojima, Shinji Fushiki*: The Effects of heavy ion particles on the developing murine cerebellum, with special reference to cell death, *Acta Histochemica et Cytochemica,* 36, 145-151, 2003
2. Yukio Uchihori, Eric Benton*, James Moeller*, G Bendrick*: Radiation measurements aboard NASA ER-2 high altitude aircraft with the Liulin-4J portable spectrometer, *Advances in Space Research,* 32(1), 41-46, 2003
3. Masahiro Takeda*, Naoto Sakaki*, Ken Honda*, Michiyuki Chikawa*, Masaki Fukushima*, Naoaki Hayashida*, Naoya Inoue*, Kenji Kadota*, Fumio Kakimoto*, Kouichi Kamata*, Setsuo Kawaguchi*, Saburo Kawakami*, Yoshiya Kawasaki*, Norio Kawasumi*, A Mahrous*, Keiichi Mase*, Tomoko Mizobuchi*, Yuichirou Morizane*, Motohiko Nagano*, Hideyuki Ohoka*,

Satoko Osone*, Makoto Sasaki*, Masahiko Sasano*, Hirohiko Shimizu*, Kenji Shinozaki*, Masahiro Teshima*, Reiko Torii*, Itsurou Tsushima*, Yukio Uchihori, Tokonatsu Yamamoto*, Shigeru Yoshida*, Hisashi Yoshii*: Energy determination in the Akeno Giant Air Shower Array experiment, *Astroparticle Physics,* 19, 447-462, 2003

4. Masao Suzuki, Chizuru Tsuruoka, Tatsuaki Kanai, Takeshi Kato*, Fumio Yatagai*, Masami Watanabe*: Qualitative and quantitative difference in mutation induction between carbon- and neon-ion beams in normal human cells, *Biol. Sci. Space,* 17(4), 302-306, 2004
5. Satoshi Fukuda, Satoru Tsuchikura*, Haruzo Iida: Age-related Changes in Blood Pressure, Hematological Values, Concentrations of Serum Biochemical Constituents and Weights of Orfans in the SHR/lzm,SHRSP/lzm and WKY/lzm, *Experimental Animals,* 53(1), 67-72, 2004
6. Hiroshi Yasuda, Tatsuyo Ishidoya*: Time-resolved Photoluminescence from a phosphate glass (GD-300) irradiated with heavy ions and gamma rays, *Health Physics,* 84, 373-375, 2003
7. Ryuichi Okayasu, Kaoru Takakura*, S Poole*, Joel S. Bedford*: Radiosensitization of Normal Human Cells by LY294002: Cell Killing and the Rejoining of DNA and Interphase Chromosome Breaks, *Journal of Radiation Research,* 44(4), 329-333, 2003
8. Hiroshi Yamaguchi, Yukio Satou, Hitoshi Imaseki, Nakahiro Yasuda, Tsuyoshi Hamano, Yoshiya Furusawa, Masao Suzuki, Takahiro Ishikawa, Teiji Mori, Kenichi Matsumoto, Teruaki Konishi, Masae Yukawa, Fuminori Soga: Single particle irradiation system to cell(SPICE) at NIRS, *Nuclear Instruments & Methods in Physics Research Section B,* 210, 292-295, 2003
9. Hitoshi Takahashi*, Nakahiro Yasuda, et.al: Observation of double hypernuclei and lambda lambda interation, *Nuclear Physics A,* A721, 951-954, 2003

Establishment of radiation protection system against radioactive materials released into the environment

(*Environmental Radiation Protection Research Group*)

1. Alice Sigurdson*, Michele Doody*, Sowmya Rao*, Michal Freedman*, Bruce Alexander*, Michael Hauptmann*, Aparna Mohan*, Shinji Yoshinaga, Deirdre Hill*, Robert Tarone*, Kiyohiko Mabuchi*, Elaine Ron*, Martha Linet*: Cancer Incidence in the U.S. Radiologic Technologists Health Study, 1983-1998, *Cancer,* 97, 3080-3089, 2003
2. Sahoo Sarata Kumar, Kunio Shiraishi, Akimasa Masuda*: Environmental Studies of Geochemical Behaviours of Artificially Produced Uranium Isotopes, *Geochimica et Cosmochimica Acta,* 67, A407, 2003
3. V.n. Korzun*, I P Los*, P V Zamostyan*, Kunio Shiraishi, et.al: Ecological and hygienic problems of alimentation of population in the northern regions of Ukraine, *Gigiena N M,* 42, 442-448, 2003
4. Satoshi Murao*, Kouichirou Sera*, V.B Maglambayan*, E. Daisa*, Masae Yukawa, Shino Hara, Hitoshi Imaseki: The Role of PIXE in Environmental Monitoring and Education of Small-Scale Miners of Gold, *International Journal of PIXE,* 12, 175-180, 2002
5. Yoshiko Kawabata, Masayoshi Yamamoto*, Kunio Shiraishi, Susumu Kou, Yasuo Katayama*: Uranium Pollution in the Republic of Uzubekistan, *Journal Arid Land Studies,* 14(4), 227-233, 2003
6. Perveen Akhter*, M.K. Rahman*, Kunio Shiraishi, Hisao Kawamura*, N. Ahmad*: Uranium Concentration in Typical Pakistani Diet, *Journal of Radiation Research,* 44(3), 289-293, 2003
7. Yoshikazu Nishimura, Hee sun Kim*, Nobuo Ikota, Hiromi Arima*, Hee Seung Bom*, Young-ho Kim*, Yoshito Watanabe, Masae Yukawa, Toshihiko Ozawa: Radioprotective effect of chitosan in sub-lethally X-ray irradiation mice, *Journal of Radiation Research,* 44, 53-58, 2003
8. Masatoshi Yamada, Tatsuo Aono: Vertical profiles of $^{239+240}$Pu in seawater from the East China Sea, *Journal of Radioanalytical and Nuclear Chemistry,* 256(3), 399-402, 2003
9. Masae Yukawa, Hitoshi Imaseki: Micro-beam scanning PIXE analysis system at the National Institute of Radiological Sciences (NIRS), *Journal of Radioanalytical and Nuclear Chemistry,* 259(2), 281-285, 2004
10. Shino Homma-Takeda, Yoshikazu Nishimura, Yoshito Watanabe, Hitoshi Imaseki, Masae Yukawa: Elemental imaging of rat epididymis by micro-PIXE analysis, *Nuclear Instruments & Methods in Physics Research Section B,* 210, 368-372, 2003
11. Hitoshi Imaseki, Masae Yukawa, Takahiro Ishikawa, Hiroyuki Iso*, Tsuyoshi Hamano, Kenichi Matsumoto, Nakahiro Yasuda, et.al: The scanning microbeam PIXE analysis facility at NIRS, *Nuclear Instruments & Methods in Physics Research Section B,* 210, 42-47, 2003
12. Masaaki Ebara*, Hiroyuki Fukuda*, Masaharu Yoshikawa*, Nobuyuki Sugiura*, Masae Yukawa, et.al: Metal Contents in the Liver of Patients with

Chronic Liver Disease Caused by Hepatitis C Virus, *Oncology,* 65(4), 323-330, 2003

13. Eric Ansoborlo*, Philippe Berard*, Mike Bailey*, Keith Eckerman*, Vladimir Berkovski*, Alan Birchall*, Frances Fry*, Ray Guilmette*, Guthrie Miller*, Nobuhito Ishigure, Joyce Lipsztein*, Ditmer Nosske*: Review of methods and computer codes for bioassay data interpretation, *Radiation Protection Dosimetry,* 105(4), 341-346, 2003
14. Yoshikazu Nishimura, Sahoo Sarata Kumar, Hee sun Kim*, Shino Homma-Takeda, Yoshito Watanabe, Jiro Inaba*: Biokinetics of radiotellurium in rats, *Radiation Protection Dosimetry,* 105, 285-290, 2003
15. Nobuhito Ishigure, Takashi Nakano, Masaki Matsumoto, Hiroko Enomoto: Database of Calculated Values of Retention and Excretion for Members of the Public Following Acute Intake of Radionuclides, *Radiation Protection Dosimetry,* 105, 311-316, 2003
16. Shinzo Kimura, Masaaki Kurasaki*, Takeshi Saito*, Keizo Ito*, Toshiyuki Hosokawa*, Masashi Okabe*, Kunio Shiraishi, Tadashi Niioka*: Synthetic Dopamine-melanins, a Model for Neuromelanin, Show Superoxide Dismutase like Activity, *Trace Elements and Electrolytes,* 21, 55-59, 2004

Environmental and Toxicological Sciences Research Group

1. Matsui Kazuaki*, Nobuyoshi Ishii, Zenichiro Kawabata*: Release of Extracellular Transformable Plasmid DNA from Escherichia coli Cocultivated with Algae, *Applied and Environmental Microbiology,* 69, 2399-2404, 2003
2. Ryuichi Okayasu, Sentaro Takahashi, Hiroshi Sato, Yoshihisa Kubota, Staci Scolavino*, Joel S. Bedford*: Induction of DNA double strand breaks by arsenite: comparative studies with DNA breaks induced by X-rays, *DNA Repair,* 2, 309-314, 2003
3. Seigo Amachi, Mizuyo Kasahara, Satoshi Hanada*, Yoichi Kamagata*, Hirofumi Shinoyama*, Takaaki Fujii*, Yasuyuki Muramatsu: Microbial participation in iodine volatalization from soils, *Environmental Science & Technology,* 37, 3885-3890, 2003
4. Matsui Kazuaki*, Nobuyoshi Ishii, Zenichiro Kawabata*: Microbial interactions affecting the natural transformation of Bacillus subtilis in a model aquatic ecosystem, *FEMS Microbiology Ecology,* 45(3), 211-218, 2003
5. Udo Fehn*, G. Snyder*, Ryou Matsumoto*, Yasuyuki Muramatsu, Hitoshi Tomaru*: Iodine dating of pore waters associated with gas hydrates in the Nankai Area, Japan, *Geology,* 31, 521-524, 2003
6. Zofia Pietrzak-flis*, Pawel Krajewski*, Irena Radwan*, Yasuyuki Muramatsu: Retrospective evaluation of ^{131}I deposition density and thyroid dose in Poland after the Chelnobyl accident, *Health Physics,* 84, 698-708, 2003
7. Mahfuza Sharifa Sultana*, Yasuyuki Muramatsu, Satoshi Yoshida: Levels of lanthanides and natural radionuclides in the uncultivated soils near industial area of Bangladesh, *International Journal of Environmental Analytical Chemistry,* 83, 375-387, 2003
8. Tadaaki Ban-nai, Yasuyuki Muramatsu: Transfer Factors of Radioiodine from Voilcanic-ash Soil (Andosol) to Crops, *Journal of Radiation Research,* 44, 23-30, 2003
9. Yasuyuki Muramatsu, Satoshi Yoshida, Atsushi Tanaka*: Determination of Pu concentration and its isotope ratio in Japanese soils by HR-ICP-MS, *Journal of Radioanalytical and Nuclear Chemistry,* 255, 477-480, 2003
10. Shoichi Fuma, Nobuyoshi Ishii, Nobuyuki Tanaka, Hiroshi Takeda, Kiriko Miyamoto, Kei Yanagisawa, Masahiro Saitou*, Yusuke Ichimasa*: Comparative evaluation of effects of gamma-rays and heavy metals on mobility of the water flea Daphnia magna, *Radioisotopes,* 52, 319-326, 2003
11. Hiroshi Takeda, Shoichi Fuma, Kiriko Miyamoto, Noriko Kuroda, Jiro Inaba*: Transfer of carbon-14 to prenatal and neonatal rats from their mothers exposed to ^{14}C-compounds by ingestion, *Radiation Protection Dosimetry,* 105, 291-296, 2003
12. Dan Galeriu*, Hiroshi Takeda, Anca Melintescu*: Towards a model for the dynamic transfer of tritium and carbon in mammals, *Radiation Protection Dosimetry,* 105, 387-390, 2003

Studies on environmental radon and its biological effects

（***Radon Research Group***）

1. Hirokazu Ichitsubo, Yuji Yamada, Michikuni Shimo, Akira Koizumi: Development of a radon-aerosol chamber at NIRS - general design and aerosol performance, *Journal of Aerosol Science,* 35, 217-232, 2004
2. Kumiko Fukutsu, Yuji Yamada, Shinji Tokonami, Takao Iida*: A new graded screen array for radon progeny size measurements and its numerical verification, *Journal of Atmospheric Electricity,* 23(2), 49-56, 2003
3. Hidenori Yonehara: Safe Management of Spent Radiation Source (3) Current Status of Spent

Radiation Source Management in Japan, *Jpn. J. Health Phys,* 38(2), 161-163, 2003
4. Michikuni Shimo, Masato Sugino, Harumi Hatano*: Measurements of Radon Concentration in Water of Campus, Dormitory and Student Home in South Area of Gifu Prefecture and Northwest Area of Aichi Prefecturere, *Jpn. J. Health Phys,* 38(3), 261-266, 2003
5. Kainan Sun*, Qiuju Guo*, Weihai Zhuo: Feasibility for mapping radon exhalation rate from soil in China, *Journal of Nuclear Science and Technology,* 41(1), 86-90, 2004
6. Shinji Tokonami, Takao Matsuzawa*, Tetsuo Ishikawa, Takeshi Iimoto, Hidenori Yonehara, Yuji Yamada: Changes of indoor aerosol characteristics and their associated variation on the dose conversion factor due to radon progeny inhalation, *Radioisotopes,* 52, 285-292, 2003
7. Yumi Yasuoka*, Tadashi Ishii*, Yasuhide Kataoka*, Tsuyoshi Kubo*, Hirofumi Suda*, Shinji Tokonami, Tetsuo Ishikawa, Masaki Shinogi*: Determination of Radon Concentration in Water Using Liquid Scintillation Counter, *Radioisotopes,* 53(3), 123-131, 2004
8. Tetsuo Ishikawa, Yumi Yasuoka*, Yukinori Narazaki*, Shinji Tokonami, Tadashi Ishii*, Hirofumi Suda*, Yuji Yamada: Comparison of instruments for measuring radon in groundwater, *Radioisotopes,* 53(3), 133-140, 2004
9. Tetsuo Ishikawa, Yuji Yamada, Kumiko Fukutsu, Shinji Tokonami: Deposition and clearance for radon progeny in the human respiratory tract, *Radiation Protection Dosimetry,* 105, 143-148, 2003
10. Tetsuo Ishikawa, Yukinori Narazaki, Yumi Yasuoka, Shinji Tokonami, Yuji Yamada: Bio-kinetics of radon ingested from drinking water, *Radiation Protection Dosimetry,* 105, 65-70, 2003
11. Shinji Tokonami, Masahide Furukawa, Yuji Yamada, et.al: Characteristics of radon and its progeny concentrations in air-conditioned office buildings in Tokyo, *Radiation Protection Dosimetry,* 106(1), 71-75, 2003
12. Kumiko Fukutsu, Yuji Yamada, Shinji Tokonami, Takao Iida*: Newly designed graded screen array for particle size measurements of unatached radon decay products, *Review of Scientific Instruments,* 75(3), 783-787, 2004

Research on redox regulation against radiation
(*Redox Regulation Research Group*)

1. Kazunori Anzai, Tetsuya Aikawa*, Yoshiko Furukawa*, Yoshikazu Matsushima*, Shiro Urano*, Toshihiko Ozawa: ESR measurement of rapid penetration of DMPO and DEPMPO spin traps through lipid bilayer membranes, *Archives of Biochemistry and Biophysics,* 415, 251-256, 2003
2. Takashi Moritake, Koji Tsuboi*, Kazunori Anzai, Toshihiko Ozawa, Tadao Nose*: Reduction of nitroxides and radioprotective ability in glioblastoma cells, *Brain Tumor Pathology,* 20, 1-5, 2003
3. Akira Hanaki, Nobuo Ikota, Junichi Ueda, Akira Odani*, Toshihiko Ozawa: Transport of the Cu(II) Bound with Histidine-Containing tripeptides to Cysteine. Coordination Mode and Exchangeability of Cu(II) in the Complexes, *Bulletin of the Chemical Society of Japan,* 76, 2143-2150, 2003
4. Akira Hanaki, Toshihiko Ozawa, Yasuhiro Funahashi*, Akira Odani*: Comparative Studies on the Kinetic Stabilities of the Chelate-ring Structure in the Cu(II) Complexes Constructed by (N-(Glycyl)), (N-(beta-Alanyl)), and (N-(2-aminoethyl)) Moiety, *Bulletin of the Chemical Society of Japan,* 77(4), 699-707, 2004
5. Hidehiko Nakagawa, Mitsuko Takusagawa, Hiromi Arima*, Kumiko Furukawa*, Takeshi Kinoshita*, Toshihiko Ozawa, Nobuo Ikota, Selective scavenging property of the indole moiety for the nitrating intermediate of peroxynitrite, *Chemical & Pharmaceutical Bulletin,* 52(1), 146-149, 2004
6. Ikuo Nakanishi, Kei Ohkubo*, Kentaro Miyazaki*, Wataru Hakamata*, Shiro Urano*, Toshihiko Ozawa, Haruhiro Okuda*, Shunichi Fukuzumi*, Nobuo Ikota, Kiyoshi Fukuhara*: A planar Catechin analogue having a more negative oxidation potential than (+)-Catechin as an Electron-Transfer Antioxidant against a Peroxyl Radical, *Chemical Research in Toxicology,* 17(1), 26-31, 2004
7. Keita Saito, Keizo Takeshita, Kazunori Anzai, Toshihiko Ozawa: Pharmacokinetic Study of acyl-protected hydroxylamine probe, 1-Acetoxy-3-carbamoyl-2,2,5,5-tetramethylpyrrolidine, for in vivo measurements of reactive oxygen species, *Free Radical Biology and Medicine,* 36(4), 517-525, 2004
8. Chiho Nishizawa, Keizo Takeshita, Junichi Ueda, Michiko Mizuno, Kazuo T. Suzuki, Toshihiko Ozawa: Hydroxyl radical generation caused by the reaction of singlet oxyen with a spin trap, DMPO, increases significantly in the presence of biological reductants, *Free Radical Research,* 38(4), 385-392, 2004
9. Hiroshi Ishihara, Izumi Tanaka, Hong Wan*, Kumie Nojima, Kazuko Yoshida: Retrotransposition of limited deletion type intracisternal A-particle elements in the myeloid leukemia cells of C3H/He mice., *Journal of Radiation Research,* 45(1), 25-32, 2004

10. Masaichi-chang-il Lee*, Hirofumi Shoji*, Hiroyuki Miyazaki*, Kazunori Anzai, Toshihiko Ozawa, et.al: Measurement of oxidative stress in the rodent brain using computerized electron spin resonance tomography, *Magnetic Resonance in Medical Sciences,* 2, 79-84, 2003
11. Ikuo Nakanishi, Kentaro Miyazaki*, Tomokazu Shimada*, Yuko Iizuka*, Keiko Inami*, Masataka Mochizuki*, Shiro Urano*, Haruhiro Okuda*, Toshihiko Ozawa, Shunichi Fukuzumi*, Nobuo Ikota, Kiyoshi Fukuhara*: Kinetic Study of the Electron-Transfer Oxidation of the phenolate anion of a vitamin E model by molecular oxygen generating superoxide anion in an aprotic medium, *Organic & Biomolecular Chemistry,* 1(22), 4085-4088, 2003
12. Ikuo Nakanishi, Yoshihiro Uto*, Kei Ohkubo*, Kentaro Miyazaki*, Haruko Yakumaru, Shiro Urano*, Haruhiro Okuda*, Junichi Ueda, Toshihiko Ozawa, Kiyoshi Fukuhara*, Shunichi Fukuzumi*, Hideko Nagasawa*, Hitoshi Hori*, Nobuo Ikota: Efficient Radical Scavenging Ability of Artepillin C, a Major Component of Brazilian Propolis, and the Mechanism, *Organic & Biomolecular Chemistry,* 1(9), 1452-1454, 2003
13. Junichi Ueda, Keizo Takeshita, Shigenobu Matsumoto*, Kinya Yazaki*, Mitsuru Kawaguchi*, Toshihiko Ozawa: Singlet oxygen-mediated hydroxyl radical production in the presence of phenols: Whether DMPO-OH formation really indicates production of .OH・, *Photochemistry and Photobiology,* 77, 165-170, 2003
14. Takashi Moritake, Koji Tsuboi*, Kazunori Anzai, Toshihiko Ozawa, Koichi Ando, Tadao Nose*: ESR Spin Trapping of Hydroxyl Radicals in Aqueous Solution Irradiated with High-LET Carbon-Ion Beams, *Radiation Research,* 159, 670-675, 2003

Basic study of radiation hazards

（*Radiation Hazards Research Group*）

1. Shuichi Yamaguchi, Maki Hasegawa, Takako Suzuki*, Hidetoshi Ikeda*, Shirou Aizawa, Katsuiku Hirokawa*, Masanobu Kitagawa: In vivo distribution of receptor for ecotropic murine leukemia virus and binding of envelope protein of Friend leukemia virus, *Archives of virology,* 148, 1175-1184, 2003
2. Zhang Wei*, Isamu Hayata: Preferential reduction of dicentrics in reciprocal exchanges due to the combination of the size of broken chromosome segments by radiation, *Journal of Human Genetics,* 48, 531-534, 2003
3. Hiromi Itsukaichi, Masahiko Mori, Atsuko Nakamura, Koki Sato*: Identification of a new G-to-A transition mutation at nucleotide position 129 of the Xrcc4 gene in ionizing radiation-hypersensitive mutant LX830 Cells., *Journal of Radiation Research,* 44, 353-358, 2004
4. Tomohisa Hirobe, Kazumasa Wakamatsu*, Shosuke Ito*: Changes in the proliferation and differentiation of neonatal mouse Pink-Eyed dilution melanocytes in the presence of excess tyrosine, *Pigment Cell Research,* 16(6), 619-628, 2003
5. Tomohisa Hirobe, Masatake Osawa*, Shin-ichi Nishikawa*: Steel factor controls the Proliferation and Differentiation of neonatal mouse epidermal melanocytes in culture, *Pigment Cell Research,* 16(6), 644-655, 2003
6. Tomohisa Hirobe, Masatake Osawa*, Shin-ichi Nishikawa*: Hepatocyte growth factor controls the proliferation of cultured epidermal melanoblasts and melanocytes from newborn mice, *Pigment Cell Research,* 17(1), 51-61, 2004
7. Wang Bing, Harumi Ohyama, Yi Shang, Kaoru Tanaka, Shirou Aizawa, Osami Yukawa, Isamu Hayata: Adaptive response in embryogenesis: V. existence of two efficient dose-rate ranges for 0.3Gy of priming irradiation to adapt mouse fetures., *Radiation Research,* 161, 264-272, 2004
8. Wang Bing, Harumi Ohyama, Yi Shang, Kazuko Fujita, Kaoru Tanaka, Tetsuo Nakajima, Shirou Aizawa, Osami Yukawa, Isamu Hayata: Adaptive response in embryogenesis: IV. Protective and detrimental bystander effects induced by X radiation in cultured limb bud cells of fetal Mice., *Radiation Research,* 161, 9-16, 2004
9. Kazuhiro Daino, Sachiko Ichimura, Mitsui Nenoi :Comprehensive search for X-ray-responsive elements and the binding factors in the regulatory region of the GADD45 gene. *Journal of Radiation Research,* 44, 311-318, 2003.
10. Manabu Koike, Aki Koike: Subcellular localization and molecular mechanisms of nuclear transport of multifunctional Ku70 and Ku80 proteins, *Recent Research Developments in Biophysics and Biochemistry,* 3, 141-158, 2003
11. Satoko Matsumura, Tatsushi Matsumura*, Shuuji Ozeki, Shoko Fukushima*, Hideya Yamazaki, Takehiko Inoue*, Toshihiko Inoue*, Yoshiya Furusawa, Kiyomi Eguchi-Kasai: Comparative analysis of G2 arrest after irradation with 75 keV carbon-ion beams and 137Cs gamma-rays in a human lymphoblastoid cell line., *Cancer Detection and Prevention,* 27, 222-228, 2003

Analysis of gene networks in response to ionizing

radiation

（***Transcriptome Profiling Research Group***）

1. Hirokazu Takahashi, Nanae Umeda*, Yoko Tsutsumi*, Ryuutarou Fukumura, Hajime Ookaze*, Mitsugu Sujino, Gijsbertus Van Der Horst*, Akira Fujimori, Tatsuya Ohhata*, Ryoko Araki, Masumi Abe, et.al: Mouse dexamethasone-induced RAS protein 1 gene is expressed in a circadian rhythmic manner in the suprachiasmatic nucleus., *Brain Research Molecular Brain Research,* 110, 1-6, 2003
2. Toshiyuki Saito, Shinji Sato*: Structual Diversity of mRNAs Generated by Variable Splicing, *Cell Technology,* 22(9), 982-989, 2003
3. Yuko Fujimori, Ryoko Araki, Tatsuya Ohhata*, Ryuutarou Fukumura, Miki Nakamura, Hirokazu Takahashi, Yuko Noda, Seiji Kito, Masumi Abe, et.al: Growth retardation and skin abnormalities of the Recql4-deficient mouse, *Human Molecular Genetics,* 12(18), 2293-2299, 2003
4. Ryoko Araki, Hirokazu Takahashi*, Ryuutarou Fukumura, Fuen Son, Nanae Umeda*, Mitsugu Sujino*, Shin Ichi Inouye*, Toshiyuki Saito, Masumi Abe: Restricted expression and photic induction of a novel mouse regulatory factor X 4 transcript in the suprachiasmatic *Nucleus, Journal of Biological Chemistry,* 2004
5. Masahiro Muto, et.al: TCR delta gene rearrangements revealed by fine structure of the recombination junction in mice., *Microbiology and Immunology,* 47(11), 883-94, 2003
6. Ryuutarou Fukumura, Hirokazu Takahashi, Toshiyuki Saito, Yoko Tsutsumi*, Akira Fujimori, Shinji Sato*, Kouichi Tatsumi, Ryoko Araki, Masumi Abe: A sensitive transcriptome analysis method that can detect unknown transcripts, *Nucleic Acids Research,* 31(16), e94, 2003

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

（***Laboratory Animal Research Group***）

1. Hiromi Omoe, Katsuhiko Omoe*, Satoru Matsushita, Hideki Kobayashi*, Koushi Yamamoto*: Polymerase chain reaction with a primer pair in the 16S-23S rRNA spacer region for detection of Mycoplasma pulmonis in clinical isolates, Comparative Immunology, *Microbiology & Infectious Diseases,* 27(2), 117-128, 2004
2. Hiromi Omoe, Katsuhiko Omoe*, Masahiro Sakaguchi*, Yousuke Kameoka*, Satoru Matsushita, Toshiki Inada*: Analysis of protein expression by mammalian cell lines stably expressing lactate dehydrogenase-elevating virus ORF 5 and ORF 6 proteins., Comparative Immunology, *Microbiology & Infectious Diseases,* 27(2), 81-92, 2004
3. Seiji Kito, Yoshiko Noguchi*, Yuki Oota, Tatsuya Ohhata*, Masumi Abe, Naoko Shiomi, Tadahiro Shiomi, et.al: Evaluation of developmental competence of vitrified-warmed early cleavage-stage embryos and their application for chimeric mouse production, *Experimental Animals,* 52, 179-183, 2003
4. Akihiko Koga*, Atsuo Iida*, Megumi Kamiya*, Ryoko Hayashi*, Hiroshi Hori*, Yuuji Ishikawa, Akira Tachibana*: The medaka fish Tol2 transposable element can undergo excision in human and mouse cells., *Journal of Human Genetics,* 48(5), 231-235, 2003
5. Satoshi Tanaka*, Igunasya Tanaka*, Sumiko Sasagawa*, Kazuaki Ichinohe*, Takashi Takabatake*, Satoru Matsushita, Tsuneya Matsumoto*, Yuji Ohtsu*, Fumiaki Sato: No Lengthening of Life Span in Mice Continuously Exposed to Gamma Rays at Very Low Dose Rates, *Radiation Research,* 160, 376-379, 2003

Studies on Experimental Carcinogenesis Induced by Plutonium Compounds

（***Internal Radiation Effects Research Group***）

1. Yoichi Oghiso, Yutaka Yamada: Pre-B-cell lymphomas in mice following injection of 239Pu citrate: Comparison with MNU-induced T-lymphoblastic lymphomas, *Journal of Toxicologic Pathology,* 16, 93-102, 2003
2. Yoichi Oghiso, Yutaka Yamada: The specific induction of osteosarcomas in different mouse strains after injections of 239Pu citrate, *Journal of Radiation Research,* 44, 125-132, 2003
3. Yoichi Oghiso, Yutaka Yamada: Comparisons of pulmonary carcinogenesis in rats following inhalation exposure to pultonium dioxide or X-ray Irradiation, *Journal of Radiation Research,* 44, 261-270, 2003
4. Yutaka Yamada, Yoichi Oghiso, Jean Paul Morlier*, Kristel Guillet*, Paul Fritsch*, Nicolas Dudoignon*, Georges Monchaux*: Comparative Study on Tp53 gene mutations in lung tumors from rats exposed to 239Pu, 237Np and 222Rn, *Journal of Radiation Research,* 45(1), 69-76, 2004

○***Research Center for Radiation Emergency Medicine***

The study for radiation emergency medical

1. Hisayoshi Kondo, Sang-hee Park, Keiko Watanabe, Yasuhiro Yamamoto, Makoto Akashi: Polyphenol (-)-epigallocatechin gallate inhibits apoptosis induced by irradiation in human HaCaT keratinocytes, *Biochemical and Biophysical Research Communications,* 316, 59-64, 2004

2. Sakae Tanosaki*, Makoto Akashi, et.al: Effect of ligands of nuclear hormone receptors on sodium/iodide symporter expression and activity in breast cancer cells., *Breast Cancer Research and Treatmen,* 79(3), 335-345, 2003
3. Toshiyasu Hirama, Sakae Tanosaki*, Susumu Kandatsu, Norikazu Kuroiwa, Tadashi Kamada, Hiroshi Tsuji, Shigeru Yamada, Hirotoshi Katou, Naoyoshi Yamamoto, Hirohiko Tsujii, Gen Suzuki*, Makoto Akashi: Initial medical management of patients severely irradiated in the Tokai-mura criticality accident, *British Journal of Radiology,* 76, 246-253, 2003
4. Satoshi Fukuda, Haruzo Iida, Xueming Yan*, Yuyuan Xie*, Roman Burgda*, Theodorine Bailly*: Efficacies of three chelating agents on removal of plutonium in rats: comparison of CBIDA, 3,4,3-LIHOPO and Ca-DTPA, *Hoken Butsuri,* 38, 62-67, 2003
5. Hiroshi Ishihara, Izumi Tanaka, Hong Wan*, Cheerarattana Cheeramakara*: Disappearance of Nuclear Binding Proteins Specifically Bound to the Upstream Region of the Interleukin-1 beta Gene Immediately after Irradiation of Mouse Macrophages, *Journal of Radiation Research,* 44(2), 117-123, 2003
6. Manabu Koike, Aki Koike: Subcellular localization and molecular mechanisms of nuclear transport of multifunctional Ku70 and Ku80 proteins, *Recent Research Developments in Biophysics and Biochemistry,* 3, 141-158, 2003
7. Yoko Hirabayashi, Kazuko Yoshida, Shin-ichi Aizawa*, Yukio Kodama*, Jun Kanno*, Yuji Kurokawa*, Isao Yoshimura*, Tohoru Inoue*: Evaluation of nonthreshold leukemogenic response to methyl nitrosourea in p53-deficient C3H/He mice, *Toxicology and Applied Pharmacology,* 190, 251-261, 2003
8. Eric Ansoborlo*, Philippe Berard*, Mike Bailey*, Keith Eckerman*, Vladimir Berkovski*, Alan Birchall*, Frances Fry*, Ray Guilmette*, Guthrie Miller*, Nobuhito Ishigure, Joyce Lipsztein*, Ditmer Nosske*: Review of methods and computer codes for bioassay data interpretation, *Radiation Protection Dosimetry,* 105(4), 341-346, 2003
9. Nobuhito Ishigure, Takashi Nakano, Masaki Matsumoto, Hiroko Enomoto: Database of Calculated Values of Retention and Excretion for Members of the Public Following Acute Intake of Radionuclides, *Radiation Protection Dosimetry,* 105, 311-316, 2003
10. Misao Hachiya, Masuhiro Takada*, Kenji Sekikawa*, Makoto Akashi: Endogenous production of TNFa is a potent trigger of NFkB activation by irradiation in Human monocytic cells THP-1, *Cytokine,* 25(4), 147-154, 2004
11. Shinzo Kimura, Makoto Akashi, Sahoo Sarata Kumar, Kunio Shiraishi, Kenzo Fujimoto: Thorium Determination in Thorotrast Patient Organs Using Inductively Coupled Plasma Mass Spectrometry and Imaging Plate Autoradiography, ISMAS Silver Jubilee Symposium on Mass Spectrometry, 1,2, 561-564, 2003

○*Research Center for Charged Particle Therapy*

Heavy Ion Clinical Trial
(*Hospital*)

1. Syohei Koyama*, Hirohiko Tsujii: Proton Beam Therapy with High-Dose Irradiation for Superficial and Advanced Esophageal Carcinomas, *Clinical Cancer Research,* 9, 3571-3577, 2003
2. Nobuharu Yamamoto, Junetsu Mizoe, Azusa Hasegawa, Hirohiko Tsujii, et.al: A case report of primary sebaceous carcinoma of the lacrimal gland treated by carbon ion radiotherapy., *International Journal of Clinical Oncology,* 8(6), 386-390, 2003
3. Naoyoshi Yamamoto*, Tadaaki Miyamoto, Hideki Nishimura*, Masashi Koto, Hirohiko Tsujii, Hidemi Owada*, Takehiko Fujisawa*: Preoperative carbon ion radiotherapy foy non-small cell lung cancer with chest wall invasion-pathological findings concerning tumor response and radiation induced lung injury in the resected organs., *Lung Cancer,* 42, 87-95, 2003
4. Masahiko Sawajiri*, Junetsu Mizoe: Changes in bone volume after irradiation with carbon ions, *Radiation and Environmental Biophysics,* 42, 101-106, 2003
5. Masahiko Sawajiri*, Junetsu Mizoe, et.al: Changes in osteoclasts after irradiation with carbon ion particles, *Radiation and Environmental Biophysics,* 42, 219-223, 2003
6. Tadaaki Miyamoto, Naoyoshi Yamamoto*, Hideki Nishimura*, Masashi Koto, Hirohiko Tsujii, Junetsu Mizoe, Tadashi Kamada, Hirotoshi Katou, Shigeru Yamada, Shinroku Morita, Kyosan Yoshikawa, Susumu Kandatsu, Takehiko Fujisawa*: Carbon ion radiotherapy for stage I non-small cell lung cancer, *Radiotherapy and Oncology,* 66, 127-140, 2003
7. Kouichirou Akakura*, Hirohiko Tsujii, Shinroku Morita, Hiroshi Tsuji, Tsuguo Yagishita*, Shigeo Isaka*, Haruo Itou*, Hideyuki Akaza*, Makoto Hata*, Shin Fujime*, Masaoki Harada*, Jun Shimazaki*: Phase I/II Clinical Trials of Carbon Ion Therapy for Prostate Cancer, *The Prostate,* 58, 252-258, 2004

8. Akira Iyoda*, Masato Suzuki*, Masako Chiyo*, Seiri Yoshida*, Yasuo Sekine*, Kiyosi Shibuya*, Toshihiko Iizasa*, Yukio Saitoh*, Kennzou Hiroshima*, Masayuki Baba, Takehiko Fujisawa*: A new thin-type bronchoscope improves diagnostic accuracy of peripheral pulmonary carcinoma, 10, 387-389, 2003

Development of four-dimensional CT (4D CT)
（***Department of Medical Physics***）

1. Masahiro Endo, Shinichiro Mori, Takanori Tsunoo, Susumu Kandatsu, Shuji Tanada, Hiroshi Aradate*, Yasuo Saito*, Hiroaki Miyazaki*, Kazumasa Sato*, Satoshi Matsushita*, Masahiro Kusakabe*: Development and performance evaluation of the first model of 4D CT-scanner, *IEEE Transactions on Nuclear Science,* 50(5), 1667-1671, 2003

Next generation PET project
（***Department of Medical Physics***）

1. Shigenori Shimizu, Keiji Sumiya*, Hiroyuki Ishibashi*, N Senguttvan*, Redkin BS*, Mitsuru Ishii, Masaaki Kobayashi, Kenzo Susa*, Hideo Murayama: Effect of Mg, Zr, Ta- doping on scintillation properties of Gd2SiO5:Ce crystal., *IEEE Transactions on Nuclear Science,* 50(4), 778-781, 2003
2. Taiga Yamaya, Takashi Obi, Naoki Hagiwara*, Masahiro Yamaguchi*, Koichi Kita*, Nagaaki Oyama*, Keishi Kitamura, Tomoyuki Hasegawa, Hideaki Haneishi, Hideo Murayama: DOI-PET image reconstruction with accurate system model reducing redundancy of imaging system., *IEEE Transactions on Nuclear Science,* 50(5), 1404-1409, 2003
3. Takehiro Kasahara, Hideo Murayama, Tomohide Omura*, Takaji Yamashita*, Hiroyuki Ishibashi*, Hideyuki Kawai, Naoko Inadama, Takaya Umehara, Narimichi Orita, Tomoaki Tsuda: Improvement of the depth of interaction detector for PET on full energy pulse height uniformity., *IEEE Transactions on Nuclear Science,* 50(5), 1439-1444, 2003

R&D Studies of a Compact Accelerator for Carbon Therapy
（***Department of Accelerator Physics and Engineering***）

1. Takuji Furukawa*, Kouji Noda, Eriko Urakabe, Masayuki Muramatsu, Mitsutaka Kanazawa: Characteristics of fast beam switching for spot scanning, *Nuclear Instruments & Methods in Physics Research Section A,* 503, 485-495, 2003
2. Tetsumi Tanabe*, Kouji Noda, et.al: Resonant Neutral-Particle Emission in Collisions of Electrons with Peptide Ions in a Storage Ring, *Physical Review Letters,* 90(19), 193201-1-193201-4, 2003

Development of a precise irradiation system for heavy-ion therapy
（***Department of Medical Physics***）

1. Shinichi Minohara, Masahiro Endo, Tatsuaki Kanai, Hirotoshi Katou, Hirohiko Tsujii: Estimating Uncertainties of the Geometrical Range of particle Radiotherapy during Respiration, *International Journal of Radiation Oncology Biology Physics,* 56, 121-125, 2003
2. Youji Osanai*, Norio Tagawa*, Akihiro Minagawa*, Tadashi Moriya*, Shinichi Minohara: Automatic Tracking of Region of Interest in Sonograms Using Respiratory Information, *Japanese Journal of Applied Physics,* 42, 3281-3286, 2003
3. Ryosuke Kohno, Yoshihisa Takada*, Takeji Sakae*, Toshiyuki Terunuma*, Keiji Matsumoto*, Akihiro Nohtomi*, Hiroyuki Matsuda*: Verification of Water-Equivalent model for Calculation of Multiple Scattering Effects in Simplified Monte Carlo Dose Calculation, *Japanese Journal of Applied Physics,* 42, 3728-3729, 2003
4. Nobuyuki Kanematsu, Naruhiro Matsufuji, Ryosuke Kohno, Shinichi Minohara, Tatsuaki Kanai: A CT calibration method based on the polybinary tissue model for radiotherapy treatment planning, *Physics in Medicine and Biology,* 48(8), 1053-1064, 2003
5. Ryosuke Kohno, Yoshihisa Takada*, Takeji Sakae*, Toshiyuki Terunuma*, Keiji Matsumoto*, Akihiro Nohtomi*, Hiroyuki Matsuda*: Experimental evaluation of validity of simplified Monte Carlo method in proton dose calculations, *Physics in Medicine and Biology,* 48, 1277-1288, 2003
6. Naruhiro Matsufuji, Akifumi Fukumura, Masataka Komori, Tatsuaki Kanai, Toshiyuki Kohno*: Influence of fragment reaction of relativistic heavy charged particles on heavy-ion radiotherapy, *Physics in Medicine and Biology,* 48, 1605-1623, 2003

Establishment of dosimetry and beam quality measurements of heavy-ion beams
（***Department of Accelerator Physics and Engineering*** , ***Department of Medical Physics***）

1. Akifumi Fukumura, Tatsuaki Kanai, Nobuyuki Kanematsu, Ken Yusa, Akira Maruhashi*, Akihiro Nohtomi*, Teiji Nishio, Munefumi Shinbo, Takashi Akagi, Toshihiro Yanou*, Shigekazu

Fukuda*: Proton beam dosimetry/Protocol and intercomparison in Japan, Standards and Codes of Practice in Medical Radiation Dosimetry (IAEA Proceedings Series), 2, 321-326, 2003

Biological Effectiveness of Charged particle Radiotherapy

（***Heavy-Ion Radiobiology Research Group***）

1. Honglu Wu*, Yoshiya Furusawa, Kerry George*, Tetsuya Kawata*, Francesca A Cucinotta*: M-Fish analysis of chromosome aberrations in human fibroblasts exposed to energetic iron ions *in vitro, Advances in Space Research,* 31(6), 1537-1542, 2003
2. Satoko Matsumura, Tatsushi Matsumura*, Shuuji Ozeki, Shoko Fukushima*, Hideya Yamazaki, Takehiro Inoue*, Toshihiko Inoue*, Yoshiya Furusawa, Kiyomi Eguchi-Kasai: Comparative analysis of G2 arrest after irradiation with 75 keV carbon-ion beams and 137Cs gamma-rays in a human lymphoblastoid cell line., *Cancer Detection and Prevention,* 27, 222-228, 2003
3. Yutaka Takahashi, Teruki Tashima, Naomasa Kawaguchi*, Yoshinosuke Hamada*, Seiji Mori*, Ayako Madachi*, Satoko Ikeda*, Hirokazu Mizuno*, Toshiyuki Ogata, Kumie Nojima, Yoshiya Furusawa, Nariaki Matsuura*: Heavy Ion Irradiation Inhibits in Vitro Angiogenesis Even at Sublethal Dose, *Cancer Research,* 63, 4253-4257, 2003
4. Manami Monobe, Sakae Arimoto-kobayashi*, Koichi Ando: -Pseudouridine, a beer component, reduces radiation-induced chromosome aberrations in human lymphocytes, Genetic Toxicology and Environmental Mutagenesis : *A Section of Mutation Research,* 538, 93-99, 2003
5. Akihisa Takahashi*, I Ota*, Tetsurou Tamamoto*, Isao Asakawa*, Y Nagata*, H Nakagawa*, N Kondo*, Ken Ohnishi*, Yoshiya Furusawa, Hideki Matsumoto*, Takeo Oonishi*: p53-dependent hyperthermic enhancement of tumor growth inhibition by X-ray or carbon-ion beam irradiation, *International Journal of Hyperthermia,* 19, 145-153, 2003
6. Manami Monobe, Sachiko Koike, Akiko Uzawa, Koichi Ando: Effects of Beer Administration in Mice on Acte Toxicities Induced by X Rays and Carbon Ions, *Journal of Radiation Research,* 44, 75-80, 2003
7. Chunlin Shao, Yoshiya Furusawa, Mizuho Aoki: Sper/NO-induced reversible proliferation inhibition and cycle arrests associated with a micronucleus induction in HSG cells., Nitric oxide : *Biology and Chemistry,* 8, 83-88, 2003
8. Tatsuya Shimazaki*, Makoto Ihara*, Yoshiya Furusawa, Yutaka Okumura*: Induction of DNA double strand breaks in scid cells by carbon ions, *Radiation Protection Dosimetry,* 99, 155-157, 2002
9. Honglu Wu*, Marco Durante*, Yoshiya Furusawa, Kerry George*, Tetsuya Kawata*, Francesca A Cucinotta*: Truly incomplete and complex exchanges in prematurely condensed chromosomes of human fibroblasts exposed *in vitro* to energetic heavy ions, *Radiation Research,* 160(4), 418-424, 2003

Medical Imaging Research and Associated Mission

（***Department of Medical Imaging***）

1. Osamu Inoue*, Rie Hosoi*, Soutarou Momosaki*, Kaoru Kobayashi*, Takayo Kida*, Kazutoshi Suzuki, Antony Gee*: Ionic interaction of [11C]-N,a-dimethylbenzylamine (CMBA) in roden brain, *Annals of Nuclear Medicine,* 17(6), 467-473, 2003
2. Tsuyoshi Fuchigami, Terushi Haradahira, Takuya Arai, Takashi Okauchi, Jun Maeda, Kazutoshi Suzuki, Fumihiko Yamamoto*, Tetsuya Suhara, Shigeki Sasaki, Minoru Maeda*: Synthesis and brain regional distribution of [11C]NPS 1506 in mice and rat: an N-Methyl-D-aspartate (NMDA) receptor Antagonist, *Biological and Pharmaceutical Bulletin,* 26(11), 1570-1573, 2003
3. Zhang Ming-Rong*, Jun Maeda*, Kenji Furutsuka*, Yuichirou Yoshida*, Masanao Ogawa*, Tetsuya Suhara, Kazutoshi Suzuki: [18F]FMDAA1106 and [18F]FEDAA1106: Two positron emitter labeled ligands for peripheral benzodiazepine receptor(PBR)., *Bioorganic & Medicinal Chemistry Letters,* 13, 201-204, 2003
4. Tsuyoshi Fuchigami, Terushi Haradahira, Takuya Arai, Takashi Okauchi, Jun Maeda, Kazutoshi Suzuki, Fumihiko Yamamoto*, Tetsuya Suhara, Shigeki Sasaki, Minoru Maeda: Synthesis and Brain Reginal Distribution of [11C]NPS 1506 in Mice and Rat:an N-Methyl-D-asparate (NMDA) Receptor Antagonist, *Journal of Pharmaceutical Sciences,* 26(11), 1570-1573, 2004
5. Takayo Kida*, Junko Noguchi*, Zhang Ming-rong, Tetsuya Suhara, Kazutoshi Suzuki: Metabolite analysis of [11C]Ro15-4513 in mice, rats, monkeys and humans, *Nuclear Medicine and Biology,* 30, 779-784, 2003
6. Toshimitsu Fukumura, Masatoshi Yamaguchi*, Kazutoshi Suzuki: Radiolysis of an aqueous [11C]iomazenil solution, *Radiochimica Acta,* 92(2), 119-123, 2004
7. Toshimitsu Fukumura, Kazuhiro Okada*, Szelecsenyi Ferenc, Zoltan Kovacs, Kazutoshi Suzuki: Practical production of 61Cu using nattural Co target and its simple purification with a chelating resin for 61Cu-ATSM, *Radiochimica*

Acta, 92, 209-214, 2004
8. Terushi Haradahira, Takashi Okauchi, Jun Maeda, Zhang Ming-rong, Touru Nishikawa*, Kazutoshi Suzuki, Tetsuya Suhara: Effects of Endogenous Agonists, Glycine and D-Serine, on In Vivo Specific Binding of [11C]L-703,717, a PET Radioligand for the Glycine-Binding Site of NMDA ReceptorsPET, *Synapse,* 50, 130-136, 2003
9. Hitoshi Shinotoh, Kiyoshi Fukushi, Shin-ichiro Nagatsuka, Noriko Tanaka, Akiyo Aotsuka, Tsuneyoshi Ota, Hiroki Namba, Shuji Tanada, Toshiaki Irie: The Amygdala and Alzheimer's Disease Positron Emission Tomographic Study of the Cholinergic System, The Amygdala in Brain Function : Basic and Clinical Approaches(Annals of the New York Academy of Sciences ; v.985), 411-419, 2003
10. Kazuyuki Saito, Kouichi Ito, et.al: Numerical simulation for interstitial heating of actual neck tumor based on MRI tomograms by using a coaxial-slot antenna, IEICE Transactions on Electronics, E86-C(12), 2482-2487, 2003
11. Mitsuhiro Ono, et.al: Detection of electron paramagnetic resonance absorption using frequency modulation, *Journal of Magnetic Resonance,* 164, 233-241, 2003
12. Kouichi Ito, Kazuyuki Saito: Improvement on electrical performances of coaxial-slot antenna by use of computer simulations, *Journal of Microwave Surgery,* 21, 49-52, 2003
13. Toshiaki Osuga*, Takayuki Obata, Hiroo Ikehira: Proton magnetic resonance imaging of flow motion of heavy water injected into a hollow fiber dialyzer filled with saline, *Magnetic Resonance Imaging,* 22(3), 413-416, 2004
14. Toshiaki Osuga*, Takayuki Obata, Hiroo Ikehira: Detection of Small Degree of Nonuniformity in Dialysate Flow in Hollow-Fiber Dialyzer Using Proton Magnetic Resonace Imaging, *Magnetic Resonance Imaging,* 22(3), 417-420, 2004
15. Toshiaki Osuga*, et.al: Proton MRI of Diffusion of High- and Low- Molecular - Weight Contrast Agents in Opaque Porous Media Saturated with Water, *Magnetic Resonance Imaging,* 22, 1039-1042, 2004
16. Takayuki Obata, Thomas T. Liu*, Miller Karla*, Wen-Ming Luh*, Eric C. Wong*, Lawrence R. Frank*, Richard B. Buxton*: Discrepancies Between BOLD and Flow Dynamics in Primary and Supplementary Motor Areas: Application of the Balloon Model to the Interpretation of BOLD Transients, *NeuroImage,* 21(1), 144-153, 2004
17. Junichi Takanashi, Hiroko Suzuki, et.al: Contralateral rhinorrhea as a feature of infantile Horner's syndrome, *Neurology,* 61, 1309-1310, 2003
18. Junichi Takanashi, Hiroko Suzuki, et.al: Widening spectrum of congenital hemiplegia:Periventricular venous infarction in term neonates, *Neurology,* 61, 531-533, 2003
19. Junichi Takanashi, Hiroko Suzuki, et.al: Medullary steaks: Dilated medullary vessels in chronic ischemia in children, *Neurology,* 61, 583-584, 2003
20. Hiroko Suzuki, Junichi Takanashi, et.al: Temporal Parenteral Nutrition in Children Causing T1 Shortening in the Anterior Pituitary Gland and Globus Pallidus, *Neuropediatrics,* 34, 200-204, 2003

Electron Density Measurement with Dual-Energy X-ray Computed Tomography

(***Department of Accelerator Physics and Engineering***)

1. Takanori Tsunoo, Masami Torikoshi, Makoto Sasaki, Masahiro Endo, Naoto Yagi*, Kentaro Uesugi*: Distribution of Electron Density Using Dual-Energy X-Ray CT, *IEEE Transactions on Nuclear Science,* 50(5), 1678-1682, 2003

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

(***Department of Medical Physics***)

1. Kanae Nishizawa, Masaki Matsumoto, Kazuo Iwai*, Takashi Maruyama: Survey of CT Practice in Japan and Collective Effective Doses Estimation, *Nippon Acta Radiological,* 64(3), 151-158, 2004
2. Kanae Nishizawa, Takashi Moritake*, Yuji Matsumaru*, Koji Tsuboi*, Kazuo Iwai*: The dose measurement of patients and physicians using a glass dosemeter during endovascular treatment for brain disease, *Radiation Protection Dosimetry,* 107(4), 247-252, 2003

Bain Imaging Project

1. Tetsuya Suhara, Akihiro Takano, Yasuhiko Sudo*, Tetsuya Ichimiya, Makoto Inoue, Yoshiro Okubo, Fumihiko Yasuno, Youko Ikoma: High levels of serotonin transporter occupancy with low dose clomipramine in comparative occupancy study with fluvoxamine using positron emission tomography., *Archives of general psychiatry,* 60, 386-391, 2003
2. Kenji Oda*, Yoshiro Okubo, Ryuji Ishida*, Yuji Murata*, Katsuya Ohta*, Tetsuya Matsuda*, Eisuke Matsushima*, Tetsuya Ichimiya, Tetsuya Suhara, Hitoshi Shibuya*, Touru Nishikawa*: Regional cerebral blood flow in depressed patients

with white matter magnetic resonance hyperintensity/, *Biological Psychiatry,* 53, 150-156, 2003

3. Fumihiko Yasuno, Tetsuya Suhara, Tetsuya Ichimiya, Akihiro Takano, Tomomichi Ando, Yoshiro Okubo: Decreased 5-TH1A receptor binding in amygdale of schizophrenia, *Biological Psychiatry,* 55, 439-444, 2004
4. Sun Xue Zhi, Yoshinobu Harada, Rui Zhang*, Chun Cui*, Sentaro Takahashi, Yoshihiro Fukui*: A genetic mouse model carrying the nonfunctional xeroderma pigmentosum group G gene., *Congenital Anomalies,* 43, 133-139, 2003
5. Shigeru Obayashi, Tetsuya Suhara, Yuji Nagai, Takashi Okauchi, Jun Maeda, Atsushi Iriki*: Monkey brain areas underlying remote-controlled operation., European *Journal of Neuroscience,* 19, 1394-1407, 2004
6. M Ichise*, Js Loiw*, Jq Lu*, Akihiro Takano, K Modell*, Hiroshi Toyama*, Tetsuya Suhara, Rb Innis*, Re Carson*: Linearized reference tissue parametric imaging methods: application to [11C]DASB PET studies of serotonin transporter in human brain, *Journal of Cerebral Blood Flow and Metabolism,* 23, 1096-1112, 2003
7. Kazunori Anzai, Keita Saito, Keizo Takeshita, Sentaro Takahashi, Hiroyuki Miyazaki*, Hirofumi Shoji*, Masaichi-chang-il Lee*, Tosiki Masumizu*, Toshihiko Ozawa: Assessment of ESR-CT imaging by comparison with autoradiography for the distribution of a blood-brain-barrier permeble spin probe, MC-PROXYL, to rodent brain, Magnetic Resonance *Imaging,* 21, 765-772, 2003
8. Akihiro Takano, Tetsuya Suhara, Jun Maeda, Kiyoshi Andou, Takashi Okauchi, Shigeru Obayashi, Takashi Nakayama, S Kapur*: Relationship between cortical dopamine D2 receptor occupancy and suppression of conditioned avoidance response in non-human primate., *Psychiatry and Clinical Neurosciencis,* 330-332, 2004
9. Junichi Senba, Maki Wakuta*, Jun Maeda, Tetsuya Suhara: Nicotine withdrawal induces subsensitivity of hypothalamic-pituitary-adrenal axis to stress in rats: ons for precipitation of depression during smoking cessation., *Psychoneuroendocrinology,* 29, 215-226, 2004
10. Jun Maeda, Tetsuya Suhara, Koichi Kawabe*, Takashi Okauchi, Shigeru Obayashi, Junko Hojo*, Kazutoshi Suzuki: Visualization of a5 subunit of GABAA/benzodiazepine receptor in vivo by [11C]Ro15-4513 using emission tomography., *Synapse,* 47, 200-208, 2003
11. Kunihiko Shioe*, Tetsuya Ichimiya, Tetsuya Suhara, Akihiro Takano, Yasuhiko Sudo*, Fumihiko Yasuno, Masami Hirano*, Manabu Shinohara*, Masato Kagami*, Yoshiro Okubo, Masahiro Nankai*, Shigenobu Kamba*: No association between genotype of the promotor region of serotonin transporter gene and serotonin transporter binding in human brain measured by PET., *Synapse,* 48, 184-188, 2003
12. Jun Maeda, Tetsuya Suhara, Zhang Ming-rong, Takashi Okauchi, Tetsuya Ichimiya, Motoki Inaji, Shigeru Obayashi, Kazutoshi Suzuki: Novel Peripheral Benzodiazepine receptor ligand [11C]DAA1106 for PET: an Imaging tool for glial cells in the brain, *Synapse,* 283-291, 2004
13. Fumihiko Yasuno, Tetsuya Suhara, Takashi Nakayama, Tetsuya Ichimiya, Akihiro Takano, Tomomichi Ando, Makoto Inoue, Jun Maeda, Kazutoshi Suzuki: Inhibitory effect of hippocampal 5-HT1A receptors on human explicit memory., *The American journal of psychiatry,* 160, 334-340, 2003
14. Akihiro Takano, Tetsuya Suhara, Youko Ikoma, Fumihiko Yasuno, Tetsuya Ichimiya, Yoshiro Okubo*, Makoto Inoue, Yasuhiko Sudo*: Estimation of the time course of dopamine D2 receptor occupancy in living human brain from the plasma pharmacokinetics of anticpsychotics, *The International Journal of Neuropsychopharmacology,* 7, 19-26, 2004
15. Sun Xue Zhi, Rui Zhang*, Chun Cui*, Sentaro Takahashi, Yoshihisa Kubota, Kazuhiko Sawada*, Yoshihiro Fukui*: Expression of neural cell adhesion molecule L1 in the brain of rats exposed to X-irradiation in utero., *The Journal of Medical Investigation* : JMI, 50, 187-191, 2003
16. Masato Kinoshita*, Masatake Yamauchi, Motoe Sasanuma*, Yuuji Ishikawa, Takashi Osada*, Kouji Inoue*, Yuuko Wakamatsu*, Kenjirou Ozato*, et.al: A Transgene and Its Expression Profile are Stably Transmitted to Offspring in Transgenic Medaka Generated by the Particle Gun Method, *Zoological Science,* 20, 869-875, 2003

○*Frontier Research Center*

RadGenomics Project

1. Ken Higashimoto*, Urano Takeshi*, Kazumitsu Sugiura*, Hitomi Yatsuki*, Keiichiro Joh*, Wei Zhao*, Mayumi Iwakawa, Hirofumi Ohashi*, Oshimura Mitsuo*, Norio Niikawa*, Tsunehiro Mukai*, Hidenobu Soejima*: Loss of CpG Methylation Is Strongly Correlated with Loss of Histone H3 Lysine 9 Methylation at DMR-LIT1 in Patients with Backwith-Wiedemann Syndrome, *American Journal of Human Genetics,* 73, 948-

956, 2003

2. Stefano Bonassi*, Monica Neri*, Cecilia Lando*, Marcello Ceppi*, Yi Ping Lin*, Wushou Peter Chang*, Nina Holland*, Micheline Kirsh Volders*, Errol Zeiger*, Michael Fenech*, Sadayuki Ban: Effect of smoking habit on the frequency of micronuclei in human lymphocytes: results from the Human MicroNucleus project, Reviews in Mutation Research : *A Section of Mutation Research,* 543, 155-166, 2003

11. Roster of Researchers

Status of March 31, 2004

Yasuhito Sasaki, M.D., PhD., President
Toshihiko Ozawa, PhD., Executive Director
Yoshiro Miki, Executive Director

○***Research Center for Radiation Safety***
Sentaro Takahashi, Ph.D., Supervisory Director

Research Promotion Office
Sentaro Takahashi, Ph.D., Head [1)]
Hiroko Ito

Director of Special Research
Shigeo Uchida, Ph.D., Head of Special Research

Biospheric Assessment for Waste Disposal
Shigeo Uchida, Ph.D., Head [1)]
Keiko Tagami, Ph.D. [1)]
Nobuyoshi Ishii, Ph.D. [1)]
Yasuo Nakamaru, Ph.D. [4)]

Nakaminoto Laboratory for Marine Radioecology
Masashi Kusakabe, PhD.,Director
and 7 staffs

Low Dose Radiation Effects Research Project
Toshiaki Ogiu, M.D., Ph.D.Director
Yoshiya Shimada, Ph.D., Vice-Director

Biological Effects of Neutrons
Toshiaki Ogiu, M.D., Ph.D. Team Leader [1)]
Yasushi Ohmachi, D.V.M., Ph.D.
Shin Saigusa, Ph.D.[3)]

Radiation and Environmental Carcinogenesis
Yoshiya Shimada, Ph.D. Team Leader [1)]
Mayumi Nishimura
Tatsuhiko Imaoka, Ph.D.
Shizuko Kakinuma, Ph.D.[3)]
Yoshikazu Kuwahara, Ph.D.[4)]

Genetic Effects on Radiation Carcinogenesis
Hideo Tsuji, Ph.D. Team Leader
Tomoyasu Higashi, M.S.
Hiroko Ishii, Ph.D.
Takanori Katsube, Ph.D.

Hereditary Effects of Radiation
Masatake Yamauchi, Ph.D. Team Leader

Radiation effects on Germ Cells
Tadahiro Shiomi, Ph.D. Team Leader
Masahiko Takahagi, Ph.D.
Takeshi Yasuda, Ph.D.[4)]

International Space Radiation Laboratory
Kazunobu Fujitaka,Ph.D., Director
Takashi Nakamura, Ph.D. [2)]
Toshisuke Kashiwagi, Ph.D. [2)]
Masahide Furukawa, Ph.D. [1)]

Radiation measurements in space
Hiroshi Yamaguchi, Ph.D., Team Leader
Masashi Takada, Ph.D.
Yukio Uchihori, Ph.D.
Nakahiro Yasuda, Ph.D. [3)]
Hisashi Kitamura, M.S. [2)]
Mieko Kurano [2)]

Radiation protection in space.
Kazunobu Fujitaka, Ph.D., Team Leader[1)]
Hiroshi Yasuda, Ph.D.
Susumu Kinpara, Ph. D.

Cellular and molecular effects in space
Ryuichi Okayasu, Ph.D., Team Leader
Kumie Nojima, B.S.
Masao Suzuki, Ph.D.
Chizuru Tsuruoka[2)]
Maki Okada[2)]

Preventive medicine in space
Satoshi Fukuda, D.V.M., Ph.D., Team Leader
Haruzo Iida
Naoko Yayoshi, D.V.M.[2)]

Environmental Radiation Protection Research Group
Nobuhito Ishigure, Ph.D., Director
Masashi Kusakabe, Ph.D., Vice-Director [1)]

Radionuclide Behavior around the Living Environment
Kunio Shiraishi, Ph.D., Team Leader [1)]
Sarata Kumar Sahoo, Ph.D. [1)]
Shinzo Kimura, Ph.D.

Internal Exposure
Yoshikazu Nishimura, D.V.M.,Ph.D., Team Leader [1)]
Yoshito Watanabe, Ph.D. [1)]
Shino Homma-Takeda, Ph.D. [1)]
Masae Yukawa, Ph.D. [1)]

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Takashi Nakano, Ph.D. [1)]
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[2)] Visiting Researcher
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Hiroko Enomoto [1)]

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