Research on Radiation Emergency Medicine

Nobuyuki Sugiura, Ph.D.

Director of Research Center for Radiation Emergency Medicine

E-mail: kinkyu_unit@nirs.go.jp

Dr. Sugiura succeeded Dr. Akashi as Center Director on August 1, 2011*. Dr. Sugiura is a health physicist and his major interests are: 1) dose estimation in radiation emergency medicine; and 2) biokinetics of radionuclides. He started his research career at the former JAERI in 1991 after receiving a Ph.D. from the University of Tokyo. He successively worked as a research associate at the University of Tokyo and as a professor at Kinki University before getting the present position.(*Dr. Akashi, an executive director of NIRS, served as an acting director of the Center from April 1 to July 31, 2011.)

The roles and objectives of the Center

This center has been assigned as the National Center for Radiation Emergency Medical Preparedness and Response by the Nuclear Disaster Prevention Plan of the Japanese government since 1980. The Center is responsible for, and has established a solid system for dealing with radiation emergencies from a medical viewpoint. Our required missions are as follows:

1) To receive victims exposed to radiation and/or contaminated with radioactive materials who require specialized diagnosis and treatment.
2) To dispatch a radiation emergency medical team to local emergency medical headquarters.
3) To facilitate exchange of information, research activities, and human resources, by constructing networks in cooperation with other organizations who can deal with a radiation emergency.
4) To maintain and reinforce an efficient radiation emergency medicine system under usual conditions.
5) To promote technical development and research on radiation emergency medicine.
6) To develop skilled personnel for dealing with radiation emergencies.

As an additional objective, we are carrying out fundamental research on radiation emergency medicine.

The subjects are listed here and details are presented following the list.

1. Establishment of the system and related operations suitable for the national core center for radiation emergency medicine
2. Development of radiation emergency medicine in Asia
3. Research on the diagnosis and treatment of combined radiation hazards with injuries or burns, including dose estimation

Establishment of the system and related operations suitable for the national core center for radiation emergency medicine

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

In June 1980, the Nuclear Safety Commission (NSC) came up with a guideline entitled "Off-site Emergency Planning and Preparedness for Nuclear Power Plants". The radiation emergency system is organized around the NIRS Hospital and Hiroshima University Hospital, which are designated as the "local tertiary radiation emergency hospitals" for eastern and western divisions of Japan, respectively. For emergencies, local governments have selected healthcare centers near nuclear facilities as primary radiation medicine centers and local main hospitals as secondary radiation emergency hospitals. The local tertiary radiation emergency hospitals prepare their system for receiving heavily exposed patients who require advanced and specialized care and they liaise with local governments and organizations over the transport of those patients. In 2000, the NSC published guidelines for radiation emergency medical preparedness and revised them in 2008 to clarify the role of hospitals for radiation emergencies.

From January 2004 the Research Center has served as a liaison institution of WHO/REMPAN (Radiation Emergency Medical Preparedness and Assistance Network).

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

NIRS established the Radiation Emergency Medical Assistance Team (REMAT) program in January 2010. During 2010, the first activity year of the REMAT program, team members participated in not only many domestic drills but also international exercises or events such as at APEC as a comprehensive expert team dealing with radiation and nuclear accidents. Verification of the status and use of equipment and testing of a communication network between the on-site team and support team at NIRS have also been performed during REMAT activities. In March 2011, a nuclear accident occurred at TEPCO's Fukushima Daiichi Nuclear Power Plant. Responses to the accident have become a very important mission for NIRS and NIRS has been coping with the accident and its consequences since the first day. REMAT has played a central role in these activities. Details of NIRS responses to the accident are described elsewhere.

1) Network System

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

Radiation Emergency Medicine Network Council

A cooperative system has been developed between specialized medical institutions and specialists in various places in Japan to cope with severe injuries caused by radiation exposure including gastrointestinal disorders, hematological disorders, and skin disorders.

Chromosome Network Council

With the standardization of chromosome analysis methods and with the improvement of biological dosimetric techniques, a system of cooperation with specialists to evaluate radiation doses by analysis of chromosome aberrations has been established.

Physical Dosimetry Network Council

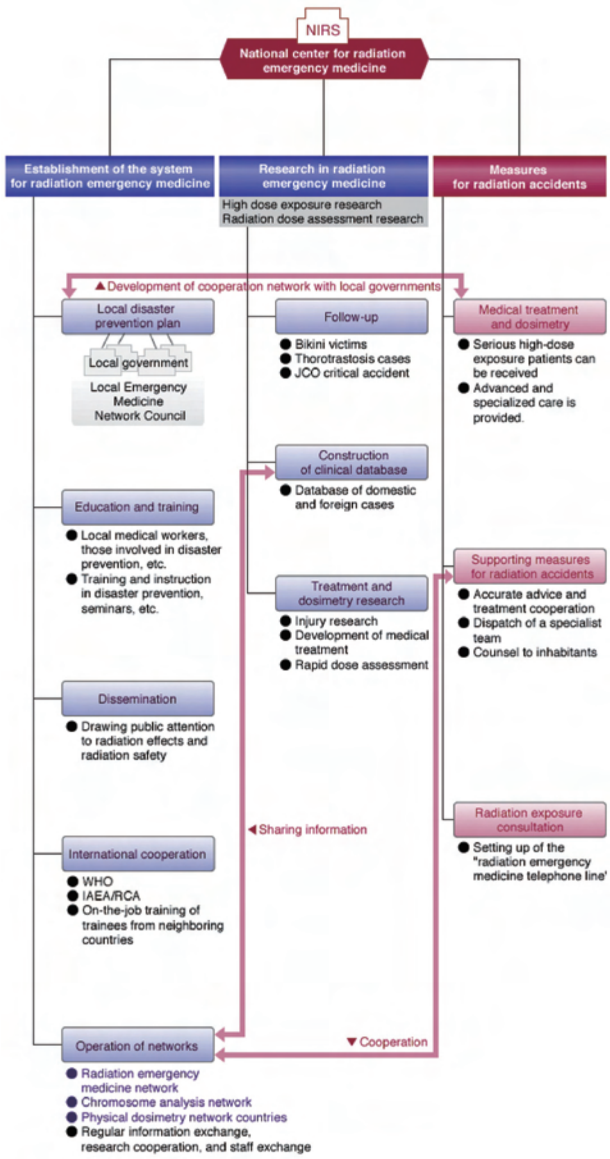
A network has been established to perform rapid and accurate dose estimation and evaluation of contamination in the event of a radiation accident in nuclear or radiation facilities.

Local organizational system for radiation emergency medicine

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

2) Training

The primary goal for training is the development of radiation emergency medicine skills for medical professionals and disaster response personnel; these include doctors and nurses involved in treating victims from a nuclear disaster (NIRS Course "Radiation emergency medicine"), first responders, and nuclear establishment employees (NIRS Course "Radiation emergency medicine for first responders"). Because the numbers of applicants for both courses increased after the Fukushima accident, the number of times to hold each course has been increased.



Development of radiation emergency medicine in Asia

1) Training courses for foreign medical professionals organized by NIRS

Upon a request from the Korea Institute of Radiological & Medical Sciences (KIRAMS), the NIRS Training Course for Korean Medical Professionals on Radiation Emergency Medical Preparedness was held from September 19-21, 2012.

2) International seminars/workshops

The NIRS/IAEA workshop on medical response to nuclear accidents in Asia was held from March 21-23, 2012 and March 11-13, 2013.

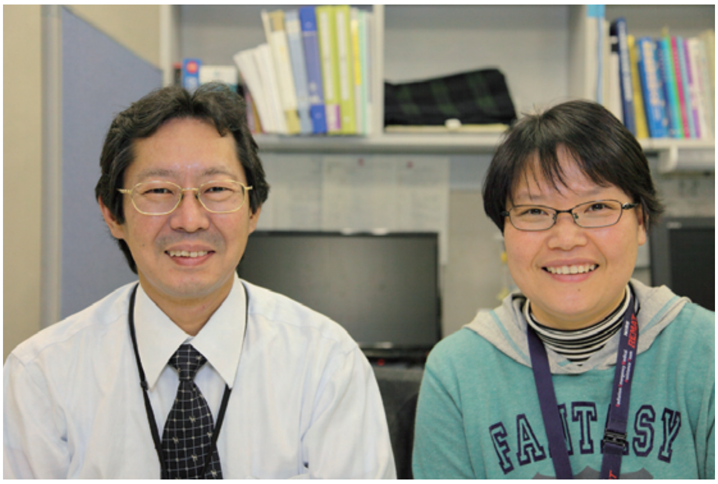
Reorganization of REMAT

On March 1, 2013, REMAT was reorganized with exclusive duty staff for the purposes of supporting patients of nuclear power disasters and to carry out and maintain duties based on the modified urgent radiation exposure medical care system. And the new center will concentrate on research activities relevant to practical emergency radiation medicine.

Highlight

Acute toxicity of uranium and the effects of decontamination agents in a simulated wound model of rodents

Yasushi Ohmachi, Eunjoo Kim
E-mail: y-omachi@nirs.go.jp



In the area of radiation emergency medicine, we have made basic and applied studies for clinical use of chelating agents in removing radionuclides, especially alpha emitters like plutonium or uranium that are incorporated into the body

Experimental decontamination therapy

To evaluate decontamination effects of chelating agents on removal of uranium, a mouse model of simulated wound contamination and a high through-put (HTS)method for bioassay of tissue contents of uranium were established (Fig.1).

The HTS method refers to the methodology used to estimate the concentration of uranium in tissue samples. In this study (Fig.2), the concentration of uranium in the kidney and the urine of the mouse was measured with an inductively-coupled plasma-mass spectrometer (ICP-MS, SII SPQ0700-II) after separating uranium from matrix components using the closed vessel microwave digestion system (CEM Discover SP-D). This digestion system can digest up to 0.3g(dry wt.) tissue sample in 10minutes including cool down time and the ICP-MS can measure at least 10 samples per hour. The method which combined the digestion system and the ICP-MS made it possible to increase the amount of throughput by as much as 5 times compared to a conventional method.

Studies on the removal of uranium contamination clarified thatpamidronate and zoledronate, which are 3rd generation bisphosphonates widelyusedin clinical practice, were as effectiveas etidronate, a known positive bisphosphonate (Fig.3). These agents were clarified to suppress uranium-induced nephrotoxicity both clinically and pathologically with reduction of uranium content in the kidneys. In addition, in order to find more effective chelating agents, wehave been collaborating with researchers at home and abroad.In the past two fiscal years, some newly synthesized agents have been tested in this wound model.

Biomarkers for uranium nephrotoxicity

Immediate detection of uranium toxicity is important to decide how clinical therapy should be contacted for contaminated patients. To find better biomarkers to detect acute uranium nephro-

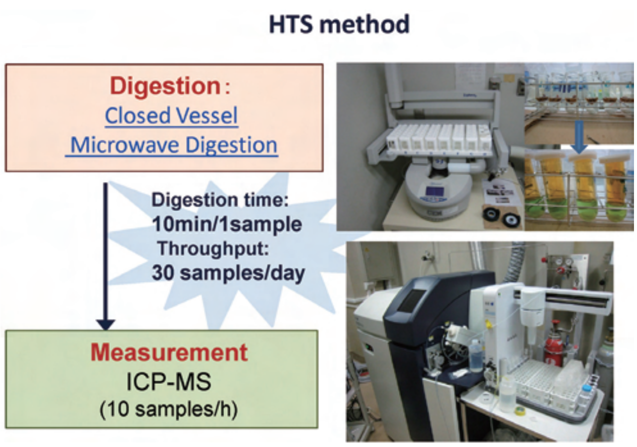


Fig.1

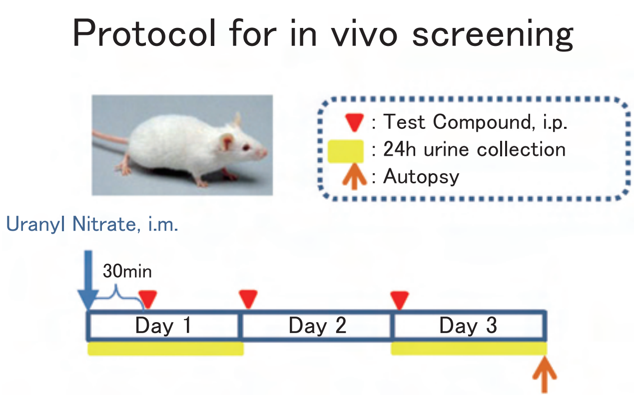


Fig.2

toxicity, several molecules in urine were tested using uranium-contaminated rats. Kidney Injury Molecule-1 (KIM-1), albumin and β2-microbloblin were found to be more sensitive clinical indicators in comparison to conventional clinical markers, blood urea nitrogen and serum creatinine (Fig.4).In addition to those urinary biomarkers, we have been estimating the suitability of using urinary mRNA for early detection of uranium toxicity.

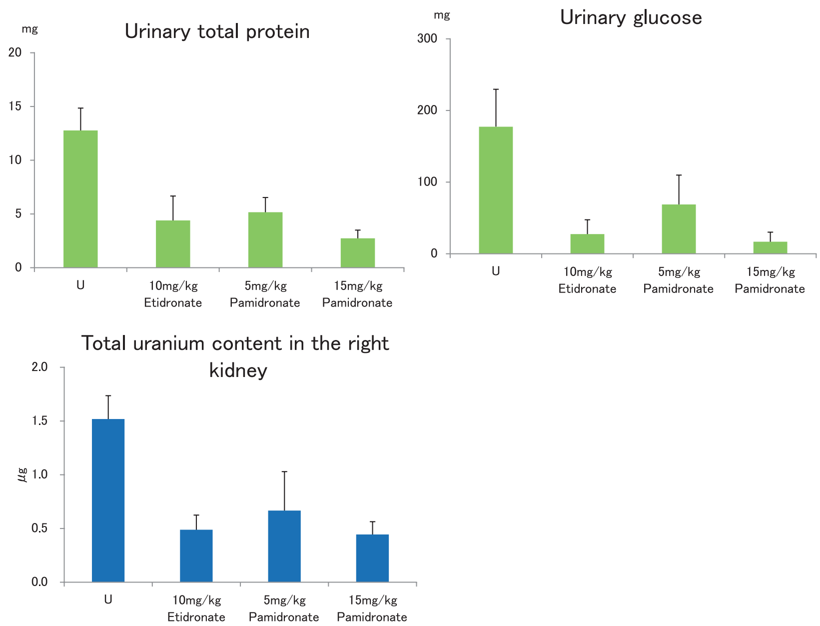


Fig.3 Pamidronate protects against acute uranium uephrotoxicity in mice

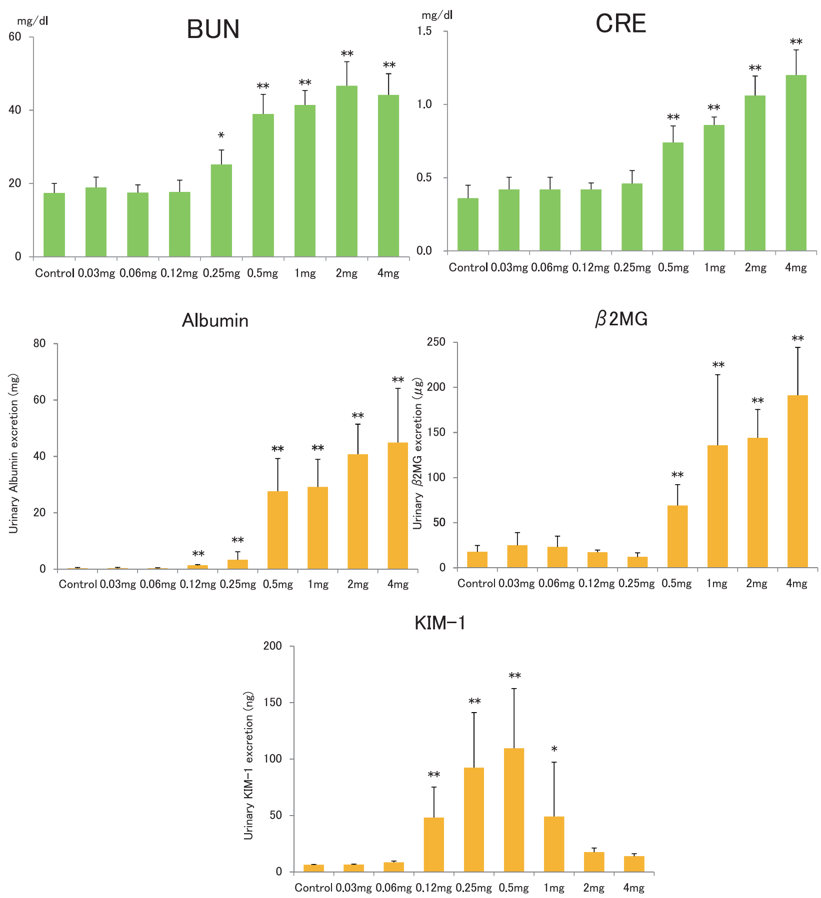


Fig.4 Kidney injury molecule-1 as well as albumin and β2-microglobulin are sensitive indicators in uranium-induced acute renal injury in rats.

Highlight

Novel therapeutic strategy using mesenchymal stem cell derived exosomes for radiation damage treatment

Masaharu Hazawa
E-mail: masaharu@nirs.go.jp

After accidental exposure to a high dose of ionizing radiation (IR), providing proper therapeutic strategies for patients with acute radiation syndrome (ARS) remains a major problem. At relatively high doses, gastrointestinal and vascular syndromes emerge in a dose-dependent manner, which lead to multi-organ dysfunction. A recent report showed that transplantation of mesenchymal stem cells (MSCs) improved wound repair from severe radiation damage and also suppressed uncontrolled successive inflammation waves in a local severe radiation victim [1]. Although precise mechanisms have not been clarified, therapeutic effects of MSCs are believed to depend on secreted factors from MSCs rather than differentiating capacity into regenerating tissue.

We are investigating the biological function of exosomes, one of the secreted factors, for radiation injury using a human bone marrow-derived MSC line (Fig. 1A). Exosomes are bilipid membrane vesicles (30-100 nm in diameter) released into the extracellular milieu. Exosomes contain bioactive proteins and RNAs; therefore they regulate biological function in exosome-receiving cells (Fig.1). Besides effects about modulating biological functions in receiving cells by exosomes, extremely high stability of this vesicle has also been shown. The contents of exosomes (such as proteins and RNA) are protected from degradative enzymes and chemicals. Moreover, exosomes have biological activity even after storage at-20℃ for 6 months [2]. Thus, biological aspects of exosomes have since emerged as not only ‘intracellular communication’ but also ‘therapeutic application.’ Indeed, it has been shown that exosomes derived from MSCs under normal culture conditions have therapeutic effects for cardiac infarction [2].

We recently found that exosomes of MSCs cultured under normal conditions have therapeutic effects against radiation injury (Figs.2 and 3); exosomes could support survival of radiation-damaged rat small intestinal epithelial cells (IEC6) (Fig.3). Surprisingly, we also found that exosomes of MSCs cultured in restricted conditions conversely enhanced radiation-induced cell death, and vice versa (Fig.3). Thus, exosome functions of MSCs strongly depend on the environmental conditions surrounding the MSCs.

Perspective

Comparing exosomes exhibiting contradictory effects allows us to clarify key factors for modulating cellular viability of radiation damaged cells, and these factors themselves also could be applied to ARS treatment. Moreover, it also allows us to manipulate the biological function of exosomes by clarifying the intracellular mechanism leading to key factor production. Our research could lead to effective and practical therapeutic strategies using MSC transplantation combined with proper agents.

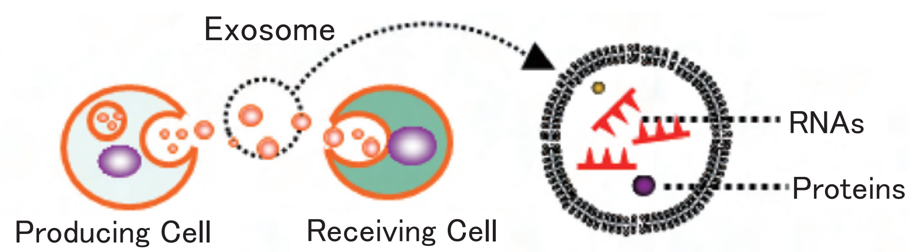


Fig.1 Exosomes are composed of bilipid membrane vesicles and contain RNAs and proteins.

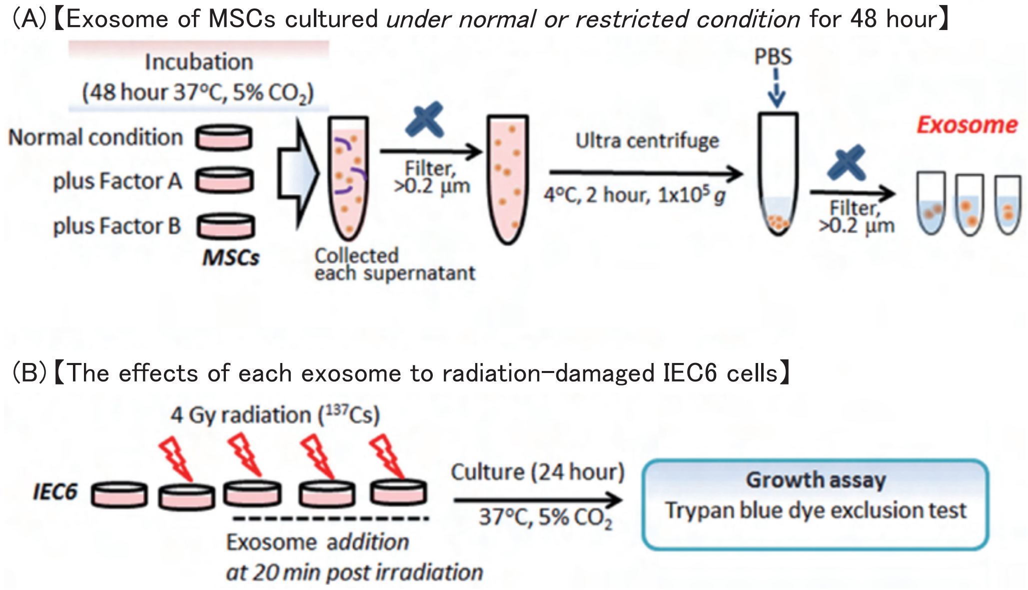


Fig.2 Experimental procedures. (A) Exosome derived from MSCs cultured under each restricted condition was collected by ultra-centrifuge methods. (B) IEC6 cells were treated with each exosome collected in (A) at 20 min post 4 Gy irradiation. After culturing for 24 hours, each cell was analyzed by the trypan blue dye exclusion test.

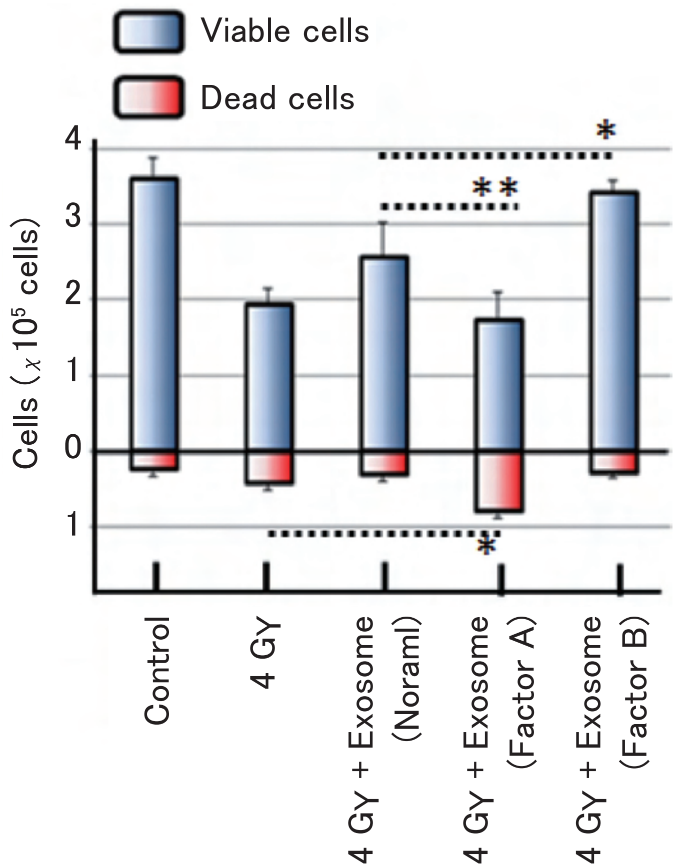


Fig.3 Biological effects of MSC-derived exosome against radiation-damaged IEC6 cell growth. The detailed procedure was shown in Figure 2B. Statistical analysis was conducted using *student-t* test. *: p<0.05, **: p<0.01.

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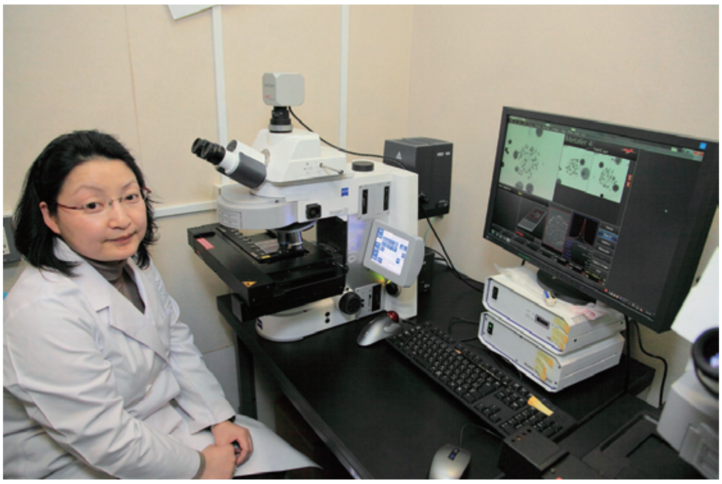
Highlight

Sensitive and rapid detection of centromeric alphoid DNA in human metaphase chromosomes by fluorescence *in situ* hybridization using peptide nucleic acid (PNA) probes and its application to biological radiation dosimetry

Yumiko Suto, Momoki Hirai, Miho Akiyama

E-mail: y-suto@nirs.go.jp



Summary

We conducted a rapid and sensitive fluorescence *in situ* hybridization method using peptide nucleic acid* probes (PNA-FISH) to evaluate the yield of multicentric chromosomes induced in cultured human peripheral blood lymphocytes (PBLs) by high-dose gamma-irradiation. The PNA-FISH allowed us to unequivocally determine centromeres in complexly rearranged chromosomes, thus validating its usefulness in biological dosimetry.

Introduction

Radiation exposure causes DNA strand breaks that lead to chromosome aberrations. Among them, the yield of multicentric chromosomes, as represented by dicentric chromosomes (dicentrics), is considered to be a reliable, sensitive, and specific indicator of recent acute exposure to ionizing radiation. In the dicentric chromosome assay (DCA) using the conventional Giemsa-staining method, the frequency of dicentrics per PBL from a radiation-exposed individual is applied to a dose-response curve that has been established by in vitro exposure experiments, and then his/her exposure dose can be estimated.

A PNA-FISH method using centromeric and telomeric repeat sequences was proposed as an alternative methodology that detects dicentrics accurately [1] (Fig.1). For conducting large-scale biodosimetric examinations, the DCA using the automated scoring of PNA signals would be greatly helpful. However, because of the complicated genomic organization of the centromere, the distribution of alphoid DNA in chromosomes has not been fully investigated. We used our modified technique to detect chromosomal sites of alphoid DNA and evaluated the yield of dicentrics induced in cultured human PBLs by high-dose gamma-irradiation.

Distribution and size variation of alphoid DNA in human chromosomes

By our protocol, centromeric regions can be detected in hybridization times as short as 1-2 h, with the detection efficiency of 100% [1]. The results of PNA-FISH with the centromeric probe on R-banded human chromosomes are shown in Figs.2 (a) and (b). Alphoid DNA sites were present in the centromeric regions of all chromosomes, although the hybridization signal intensity varied

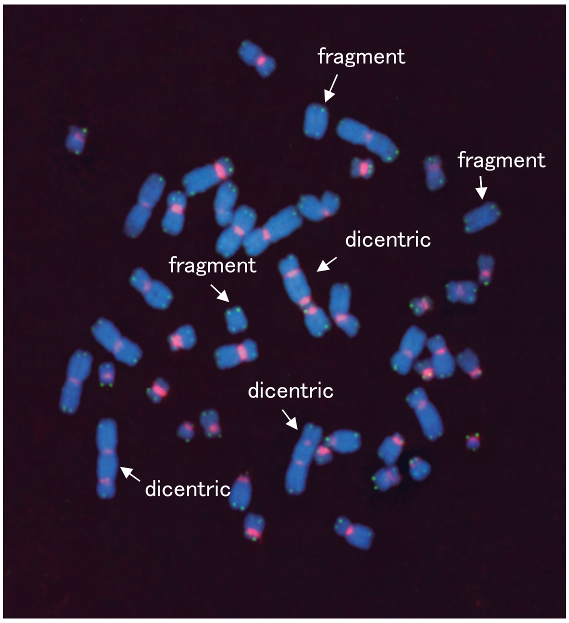


Fig.1 Metaphase chromosomes hybridized with centromeric (red) and telomeric (green) PNA-probes counterstained with DAPI (blue). (Modified from [1].)

*Peptide nucleic acid (PNA) is a nucleic acid mimic that contains a pseudo-peptide backbone composed of charge neutral and achiral N-(2-aminoethyl) glycine units to which the nucleobases are attached via a methylene carbonyl linker. PNA hybridizes with high affinity to complementary DNA sequences, forming PNA-DNA complexes.

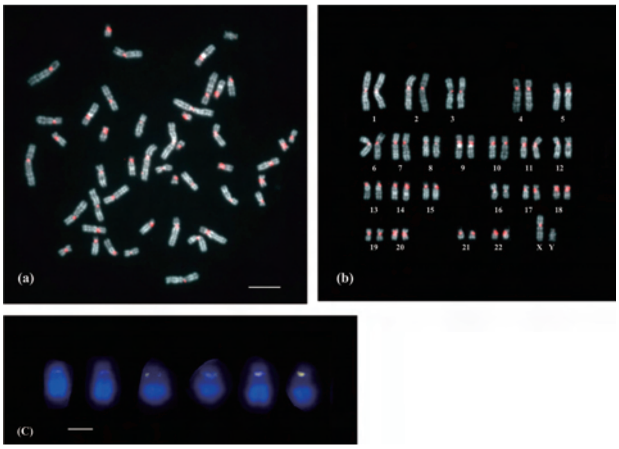


Fig.2 Examples of PNA-FISH using the centromeric probe on non-irradiated human metaphase chromosomes. (a) Hybridization signals of a Cy3-conjugated centromeric probe (red) on R-banded metaphase chromosomes (gray-scale) from a male donor. Scale bar = 10 μm. (b) R-banded karyotype reconstructed from (a). (c) Size variation in the hybridization signals (white) of Y chromosomes from 6 males. Scale bar = 1 μm. (Modified from [2].)

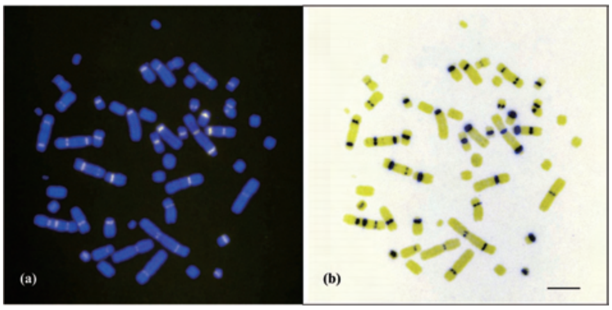


Fig.3 A metaphase plate obtained from cultured peripheral blood lymphocytes after 20-Gy gamma-ray irradiation. (a) Hybridization signals are highlighted in white on DAPI-stained chromosomes (blue). (b) The negative image of the same metaphase plate as (a) generated by image processing software. Scale bar = 10 μm. (Modified from [2].)

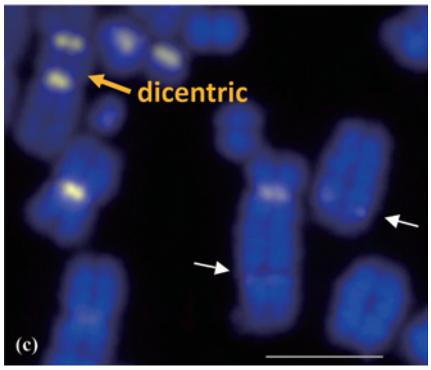


Fig.4 Partial metaphase plate showing interstitial minor signals (arrows). Scale bar = 5 μm. (Modified from [2].)

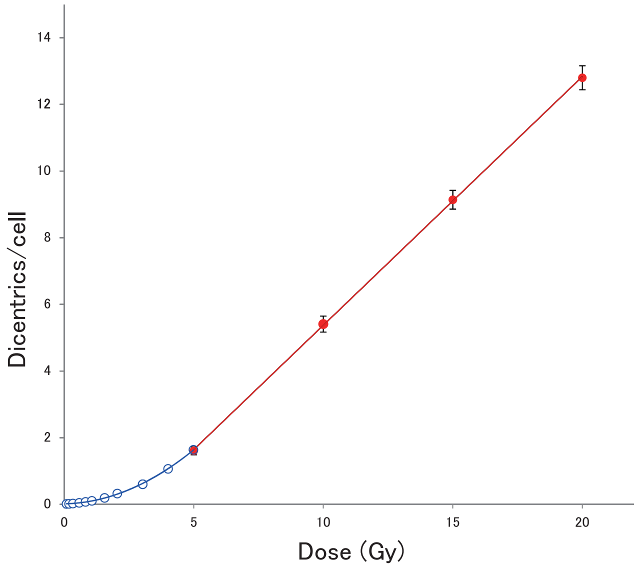


Fig.5 Dose-response curve of peripheral blood lymphocytes irradiated with ^{60}Co gamma rays *in vitro*. Data of dicentric yields by the conventional DCA (0-5 Gy exposures, unpublished data) and those by the DCA combined with the PNA-FISH method (5-20 Gy exposures [3]) are summarized.

between chromosomes. In addition to the inter-chromosomal variation, we detected possible inter-individual variation in the size of alphoid DNA sites, which had been difficult to precisely analyze by conventional molecular and cytogenetic methods (Fig. 2 (c)).

Application of PNA-FISH to biological dosimetry

Centromeres in radiation-induced multicentric chromosomes are difficult to determine by the conventional Giemsa-staining technique, especially when complicated chromosome rearrangements are induced by high-dose irradiation. By PNA-FISH, centromeric regions of lymphocytes irradiated *in vitro* with ^{60}Co gamma rays were rapidly detected in chromosomes (Fig.3). However, chromosome breakage occurring in the vicinity of alphoid sequences outside the functional centromere unit may produce additional minor signals (Fig.4). The development of sophisticated software specific for the image analysis of PNA-FISH is necessary.

Interestingly, the distribution of dicentrics per cell in the high-dose range was different from that in the low-dose range (Fig. 5) [2, 3]. To our knowledge, this is the first report on the evaluation and characterization of the yield of multicentric chromosomes induced by high levels of irradiation, as high as 20 Gy, using PNA-FISH. It should also be noted that the dicentric yield determined by the conventional Giemsa-stain analysis did not differ from that determined by the PNA-FISH analysis, contrary to another published report.

References

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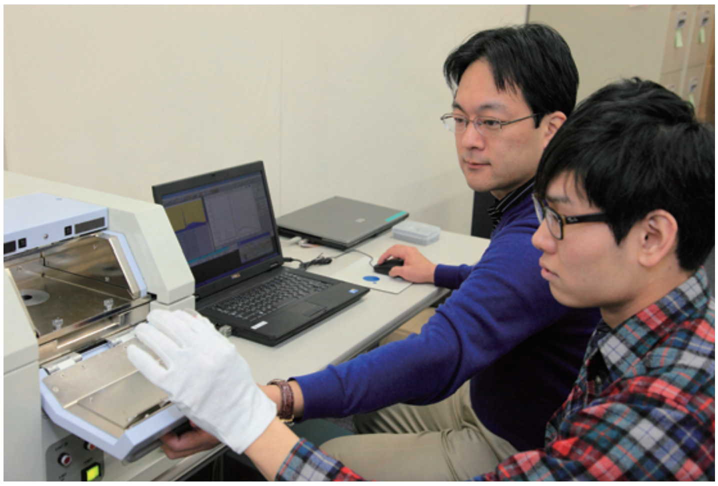
Highlight

Evaluation of wound contamination with heavy atoms by x-ray fluorescent spectrometry

Hiroshi Yoshii
E-mail: yoshii@nirs.go.jp



In the nuclear fuel industry, internal contamination by alpha particle-emitting actinides is a serious health problem for workers. Since the most common pathway of actinide intake inside the body is inhalation, wearing masks is necessary to prevent it; however, compounds containing actinides that deposit on healthy skin seldom enter the body. On the other hand, wound contamination by actinides is a serious problem, because it can easily cause internal contamination and intake from wounds cannot be neglected. The evaluation of the wound contamination with actinides is, therefore, necessary. Plutonium is especially known to adversely affect the body for a long time by physiologically accumulating in lung and bone. Elemental analysis is required to determine the atomic species of contaminating compounds of the wounds and decide the therapeutic strategy.

The standard method for rapid evaluation of wound contamination by alpha particles is to measure the number of particles. Although information on atomic species can be obtained after chemical purification of the samples, which takes a few days, a rapid distinction between plutonium and other actinides is too hard to provide. We have proposed x-ray fluorescence (XRF) analysis as a new technique to give a rapid diagnosis for the presence of plutonium in a wound. X-ray fluorescence analysis provides qualitative and quantitative analyses of atoms instead of radioactivity, and therefore it should be effective for nuclei having a long half-life such as plutonium and uranium, because the number of atoms per unit radioactivity is large in those atoms.

We established a methodology to rapidly evaluate the wound contamination from heavy atoms using a portable XRF analyzer. For easy handling during development of the method, we used stable lead as heavy atoms contaminating the wound; however we expect that the established method will be easily extended to actinides in the future.

Two types of wound models, dry and bleeding wound models, were prepared to develop the methodology for evaluation of lead contamination in wounds by XRF (Fig.1). The dry wound model used several epoxy resin skin phantoms, which was made by mixing epoxy resin (crystal resin, Nissin Resin Co., Ltd., Yokohama, Japan) with several concentrations of lead-containing white oil paint solution. Lead-containing white oil paint solution consisted of white oil paint (Silver White, Kusakabe Co., Ltd., Saitama, Japan) containing 60.5 % lead and solvent for oil paints (Odorless

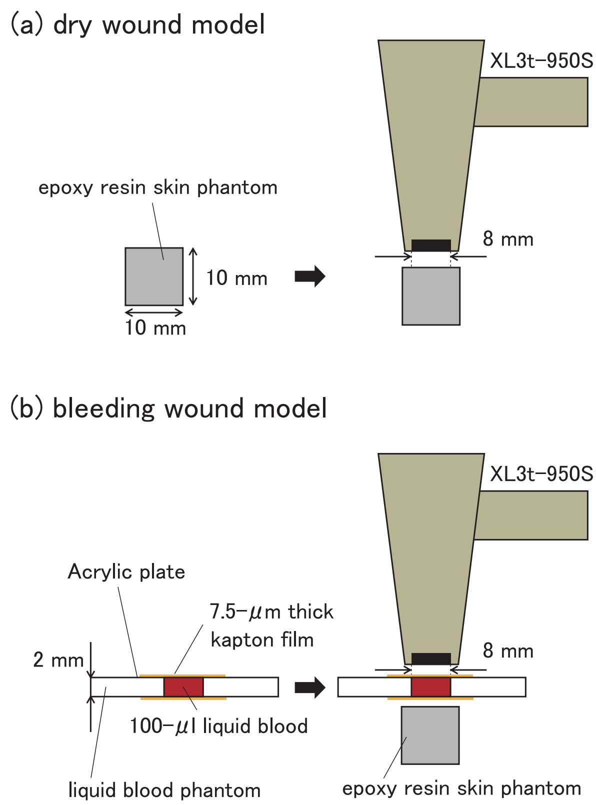


Fig.1 Schematic structures of epoxy resin skin phantom and blood phantom with overviews of the observations of the dry and bleeding wound models.

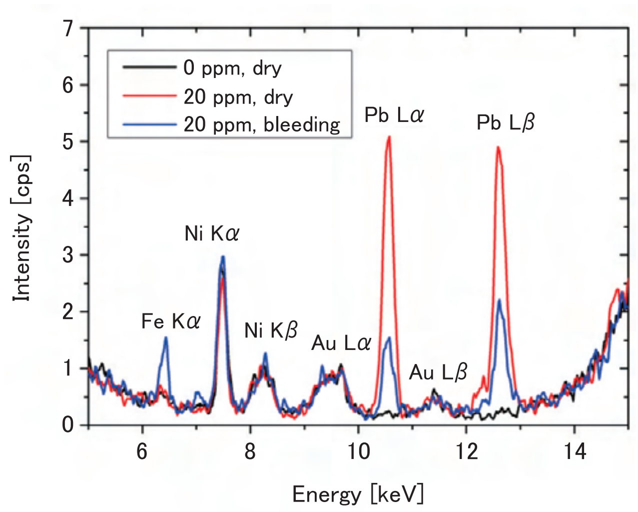


Fig.2 The measured XRF spectra for the dry wound model using 0 ppm and 20 ppm lead phantoms and the bleeding wound model using the 20 ppm lead phantom in the energy range from 5 to 15 keV.

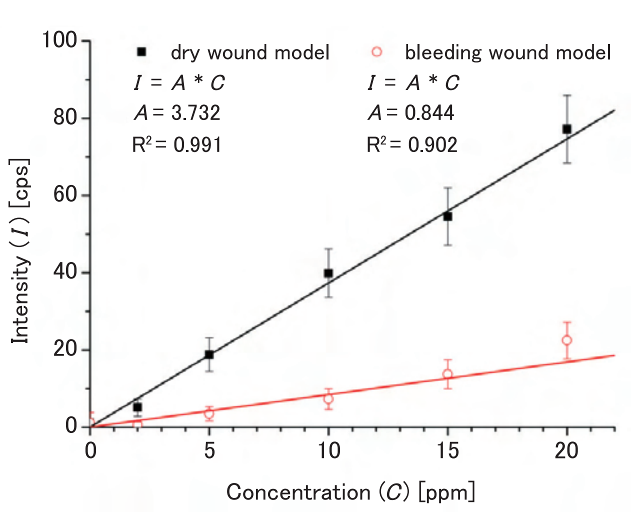


Fig.3 Correlation between concentration of lead in epoxy resin skin phantoms and Pb Lα peak intensity.

Petroleum, Holbein Works, Ltd., Osaka, Japan) for dilution to the desired lead concentration. The concentrations of lead in the produced phantoms were 0, 2, 5, 10, 15, 20 ppm, and both diameter and height of the epoxy resin skin phantoms were 10 mm. The density of the epoxy resin skin phantoms, 1.06 g cm^{-3}, is similar to that of the human skin. The bleeding wound model was constructed by putting a blood phantom containing liquid blood on each of the epoxy resin skin phantom. For production of the blood phantom, small well acrylic cases were prepared. The acrylic cases, which had a thickness of 2 mm, each had an 8-mm hole bored into them, and both sides of the hole were sealed with 7.5-μm thick kapton films. The volume of the hole was, therefore, 100 μL. Liquid blood (Mouse Blood, Kohjin bio Co., Ltd., Tokyo, Japan) was enclosed in each acrylic case to make the blood phantom.

We employed the XL3t-950S (Thermo Fisher Scientific Inc., Billerica, MA) as the XRF device. In the measurements, the x-ray tube voltage was set to 50 kV, the current was set automatically, and the main filter of the XL3t-950S was chosen. Accumulation times were set to 5 s. According to the users' manual of this device, equivalent dose of skin is estimated as less than 16.5 mSv for a 5 s exposure time when the device is applied to the skin surface. In addition, the equivalent dose limit of human skin is recommended by the ICRP as 500 mSv per year for workers [1].

Fig.2 shows the measured XRF spectra for the dry wound model using 0 ppm and 20 ppm lead phantoms and the bleeding wound model using the 20 ppm lead phantom at the energy range between 5 to 15 keV. Device-derived peaks, Ni Kα and Kβ, Au Lα and Lβ, were found in the spectrum for the dry wound model using the 0 ppm lead phantom (background spectrum). Two peaks were also clearly found for both dry and bleeding wound models using the 20 ppm lead phantom and they could be identified as for Pb Lα and Lβ, respectively. The blood-derived peak of Fe Kα appeared for the bleeding wound model.

In the present measurements, minimum detection limits (MDLs) obtained by the method similar to that of Gherase *et al*. [2] as concentrations corresponding to three times the uncertainty of the peak areas for the 0 ppm phantom for the dry and bleeding wound models, were 1.8 and 9.6 ppm, respectively. The presently obtained MDL for the dry wound model was comparable to reported MDLs for polyester resin skin phantoms containing arsenic and selenium amounts of 1.05 and 0.88 ppm, respectively [2]. In previous measurements [3], the detection limit in a naked bone phantom containing lead was 3.3 ppm, which was evaluated using two times the uncertainty. MDLs are usually given using three times the uncertainty, and MDL was estimated as about 5 ppm for the study [3]. The present MDL value for the dry wound model is sufficiently low; this difference is mainly caused by the difference of the densities of the phantoms.

In conclusion, we proposed the basic methodology for evaluation of lead contamination in a wound by using the portable XRF device. Low MDL and short diagnostic time were achieved. Further measurements using various thicknesses of blood phantoms are required to improve accuracy of evaluation. In the long term, we expect this methodology will be applicable to evaluation of wound contamination from actinides (uranium and plutonium).

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Highlight

The status of radiation emergency medical systems in Japan since the accident at TEPCO Fukushima Daiichi NPP

Hideo Tatsuzaki, Masaya Hasegawa
E-mail: tatsuza@nirs.go.jp

Local organizational system for radiation emergency medicine (REM)

In Japan, the medical system for radiation emergencies has been constructed in accordance with the disaster prevention plans of local governments where nuclear facilities are located. The medical system has a three-layered arrangement of hospitals i.e., primary, secondary and tertiary level hospitals. NIRS is designated as both a regional and national tertiary level hospital under that scheme (Fig.1). Within the framework of each local nuclear disaster prevention plan, establishment of a co-operative system by each local government with NIRS is mandatory and the plan must specify the steps to be taken in the effective medical care and smooth transfer of patients from an accident site to the appropriate level of medical facilities, with appropriate radiation protection management.

One of the missions of NIRS is to enforce the radiation emergency medical system in Japan. As the tertiary level hospital of REM in Japan, NIRS continues to play an important role for increasing effectiveness of the organization through co-operative work with primary and secondary level hospitals.

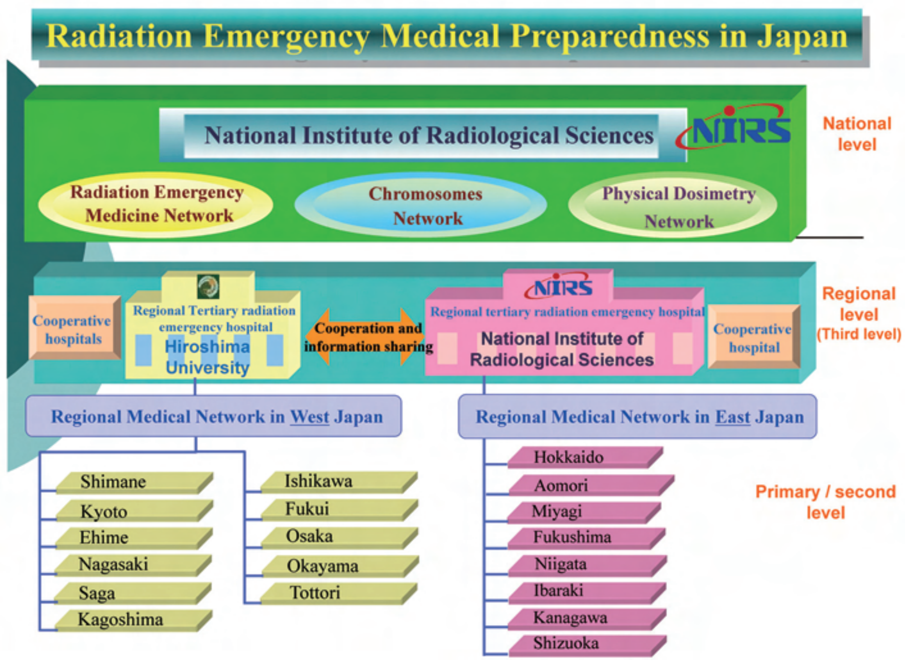


Fig.1 Organizational System of Radiation Emergency Medical in Japan

Fig.2 Meeting with local REM members in 2011

Fig.3 Annual General Meeting on Radiation Emergency Medicine in 2012

As a part of this project, NIRS has been annually holding conferences for co-operation in REM in each prefecture having nuclear power plants or related facilities in eastern Japan.

Since the accident at Tokyo Electric Power Company (TEPCO) Fukushima Daiichi NPP, the central government, the Fukushima government, and other local governments together with hospitals and NIRS have been taking tremendous actions to deal with the situation according to the systems mentioned earlier. Based on the lessons learned from the accident, however, it has become apparent that local nuclear disaster prevention plans need to be reexamined in the context of the current organizational system of REM.

In order to reflect the experiences from the TEPCO Fukushima Daiichi NPP accident to local plans, conferences were held in 8 NPP located prefectures in Eastern Japan, namely Hokkaido, Aomori, Miyagi, Fukushima, Niigata, Ibaraki, Kanagawa, and Shizukoka. Participants were medical staff from primary or secondary radiation emergency medical hospitals, fire brigade officials, Self Defense Forces officials, local governments, and NPP companies. In FY2011, the conferences focused on presenting the response of NIRS and local governments to the Fukushima accident; and then the participants discussed problems recognized from the accident and considered future REM systems (Fig.2).

NIRS also organized the annual general meeting of local governments on REM in Tokyo in February 2012 (Fig.3). Medical professionals and administrative officers from 19 NPP located local governments who are responsible for dealing with radiation and nuclear accidents attended the meeting. NIRS and Fukushima Medical University made presentations on their activities in Fukushima Prefecture. After the presentations, revision of REM guidelines, and issues such as patient transfer and stock pile of internal decontamination agents such as Prussian Blue and DTPA were discussed, reflecting on experiences after the accident.

In addition to these subjects ,installation of whole body counters (WBCs) was discussed i.e., where WBCs should be located at places other than secondary level hospitals based on the explanation of the new operational guideline by the Nuclear Safety Commission succeeded by the Nuclear Regulation Authority (NRA) from September 2012. Officials from the relevant ministries and agencies such as the Ministry of Education, Culture, Sports, Science and Technology (MEXT), the Ministry of Defense (MOD), the Fire and Disaster Management Agency (FDMA), Japan Coast Guard and the National Police Agency also attended this meeting as observers.

Three Network Meeting

NIRS organizes three experts' networks, namely Chromosome Analysis Network, Physical Dose Assessment Network, and Radiation Emergency Medical Network.

The Chromosome Analysis Network has shared the experiences of each member in response to the TEPCO Fukushima Daiichi NPP accident, and it was recognized that the biodosimetry results well agreed with those of personal dosimeters. The network also checked cooperation among the member organizations, increased the number of members in order to geographically cover all Japan, and the number of experts that would be working in five years. The importance of training of new experts through training courses to maintain the expertise was stressed.

Physical Dose Assessment Network

In the meetings of this network, experts discussed screening levels used for the NPP accident, and calibration and maintenance of WBCs.

Experts from NIRS visited 9 hospitals with WBCs and discussed the problems in operation and maintenance and then suggested possible solutions.

A workshop entitled "Status and ideal status of WBC in radiation emergency medicine ---Based on TEPCO Fukushima Daiichi NPP Acci-dent---" was held at NIRS on March 5, 2012, co-organized by NIRS and MEXT. There were 82 participants including the network members and ten lectures were presented (Fig.4). The workshop clarified the limitations of transfer phantoms, discussed the need of standardization, and discussed ways to explain results to people after WBC measurements.

Radiation Emergency Medical Network

The meetings of this network discussed reestablishment and maintenance of REM systems and proper responses for low dose exposure to residents during disaster mitigation. Furthermore, in order to facilitate smooth acceptance of contaminated patients by hospitals anywhere in Japan, the network announced its "Request

Fig.4 Physical Dose Assessment Network; Whole body counter workshop

Fig.5 Specialist committee for the questionnaire

from the Radiation Emergency Medical Network to staff members in medical facilities regarding patients' management related to TEPCO Fukushima Daiichi NPP Accident" via the NIRS home page.

24-hour Response System

As a third level radiation emergency medical hospital, NIRS has a function to support other facilities or professionals. As an instrument for direct support, NIRS has been operating a telephone line consultation system for professionals. This system operates 24 hours a day, 7 days a week. A staff member of the Research Center receives calls during working hours, and the system connects callers to staff members of the Research Center who are responsible at night or on holidays. In FY 2011 and FY 2012, 92 consultations were carried out (as of January 31, 2013).

Survey of REM in Japan

In FY 2012, to increase the effectiveness of the organizational system of REM in Japan, NIRS carried out an extended survey for investigating the current situation of REM in terms of human resources, facilities and equipment. A questionnaire was sent to the organizations where NPPs were located such as : local governments throughout Japan; primary and secondary level hospitals throughout Japan; and local firefighting head offices in eastern Japan. Answers to the questionnaire were used to clarify the status and points for improvement in each organization. This research project was supervised by specialist committees (Fig.5) consisting of disaster medical care specialists, crisis management specialists, radiation protection specialist and REM specialists.

Responses were received as follows: 19 local governments out of 19; 92 hospitals out of 123; and 177 firefighting head offices out of 202. These represented reply rates of 100%, 75% and 88%, respectively. Through this survey, various types of key information were gathered concerning all resources relevant to REM. Therefore, it will now be possible to further clarify the problems and identify solutions within the organization of REM in Japan. As one type of key information, the availability of REM equipment among hospitals was found to be as indicated in Table 1.

Exercise

Disaster Medical Center-NIRS Joint Exercise

The Disaster Medical Center (DMC)-NIRS Joint Exercise was conducted on August 23, 2012 (from 9:51 to 20:54) at NIRS, DMC, and on roads between them. The DMC is the national center for disaster medicine. NIRS has an agreement with the center to cooperate in case of NIRS accepting severely injured patients.

Table 1 Availability of REM equipment in primary and secondary level hospitals

# of deployment	GM tube-type Survey Meter	NaI Scintillation	Ionization Chamber	Active Personal Dosimeter	WBC	Thyroid Monitor	Others	TTL	% to TTL
Secondary Level Hospitals	181	129	56	943	18	18	63	1,408	72%
Primary Level Hospitals	79	39	48	362	2	1	20	551	28%
TTL	260	168	104	1,305	20	19	83	1,959	100%

Median value							
Secondary Level Hospitals	5	3	2	20	1	1	1
Primary Level Hospitals	1	1	1	6	0	0	1
TTL	2	1	1	10	1	1	1

Fig.6 Exercise on decontamination

The objective of the exercise was to make staff aware of the transportation and medical management in both hospitals in case a contaminated patient must be transported to DMC after initial treatment at NIRS (Fig.6).

Two special cars for REMAT (Radiation Emergency Medical Assistance Team) were used for the exercise. Twelve players and 15 exesercise controllers or observers joined the exercise from the NIRS side. Many important lessons were identified during the exercise, for example a need to improve the communication system during transportation.

Over all, this exercise was thought to be important as the first joint exercise with an agreement hospital. The cooperation between two hospitals were strengthened. Additionally, many staffs of DMC recognize the procedure and meaning of accepting patients contaminated with radioactive substances.

Hachinohe City Hospital-NIRS Joint Exercise

The Hachinohe City Hospital-NIRS Joint Exercise was conducted from September 4 to 7, 2012 at the City Hospital and NIRS. The Hachinohe City Hospital (HCH) is a secondary level radiation emergency hospital located in Aomori Prefecture, in northern Japan. The Rokkasho reprocessing plant for nuclear fuels and nuclear power plants are located near the HCH; thus this hospital is well-prepared for accepting contaminated patients.

Fig.7 REMAT car dispatched to Hachinohe City Hospital

Twelve members from NIRS joined the exercise. The exercise consisted of movement between two hospitals by a REMAT car (Fig.7), lectures and drills for the HCH staff members, calibration of a WBC at HCH, radiation protection practices in a treatment area, internal contamination dose assessment, and communication exercise using on-board systems. Forty resident doctors and 20 other medical workers participated in the lecture and drill. The lecture, “Radiation protection for REM” and the drill for using survey meters were given by 10 people from NIRS. As a part of internal contamination dose assessment, an inter-comparison between the WBC on the REMAT car and that of the HCH was performed.

Some of the HCH workers did not have enough knowledge on radiation exposure, radiation protection, or dose measurements, thus instructions from NIRS staff on survey meters and radiation protection gear, were thought to be essential. This experience confirmed that assistance by NIRS in exercises at other medical facilities is important and will play an important role in establishing the REM system.

Highlight

Improvement of radiation emergency medical systems in Asia

Hiroko Ino, Hideo Tatsuzaki*

*E-mail: tatsuza@nirs.go.jp

Background

Radiation can enable the improvement and development in many fields. Radiation, however, should be used in controlled environments with strict regulations. Well trained and educated personnel who handle radioactive substances are also fundamental to safe operation. Although these principles are effective to maintain peaceful and safe use of radiation, they do not guarantee absolute safety such as in case of emergency situations. Therefore, countermeasures to mitigate and control radiation and nuclear accidents must be prepared since accidents are still a possibility. When victims are exposed to radiation or contaminated with radioactive substances, the medical workforce must treat them with proper understanding of radiation. A radiation emergency medicine (REM) team is multidisciplinary team consisting of medical staff, radiation dosimetry and radiation safety experts who provide appropriate medical response to radiation or nuclear accident victims. Trained specialists are the basis of REM. Unlike other medical fields, it is difficult for medical and related personnel to accumulate experience in REM because of the rare occurrence of such incidents. For this reason, thorough training of the REM staff is the key for ensuring the capability to handle incidents.

NIRS activities for REM

NIRS is the only comprehensive research institute in Japan for studying radiation and its effects on humans, and it has also been designated as the only national tertiary radiation emergency hospital. When the JCO criticality accident occurred in 1999 in Ibaraki Prefecture, NIRS received three victims who had experienced high radiation exposure. Aside from this case, NIRS workers have dealt with past radiation-related emergency situations and in each incident, besides provision of medical care and medical follow-up, researchers have identified the radionuclides, carried out dose assessments, and provided reporting of information to the government and general public.

As preparation for radiation and nuclear emergencies, NIRS has been providing a variety of educational opportunities such as training courses, seminars, and lectures to national medical staff and first responders to maintain and enhance the establishment of REM preparedness in Japan.

In addition to these domestic activities, NIRS has cooperated in a wide variety of activities of the IAEA and the WHO, and contributed to the establishment of a global radiation emergency medical network based on the institute's abundant experiences. NIRS has sent medical experts to third world countries where there are patients of radiation accidents. Additionally as common practice, NIRS has sent REM experts to conduct international training courses as invited lecturers and also to participate in expert meetings for compiling universal REM guidelines. All of these dispatches were requested by the responsible international organizations.

Activities for promoting REM in Asia

Since 2001, NIRS has conducted international training courses and workshops on REM for medical personnel from various Asian countries where the use of radiation has been increasing. (Fig.1) These activities are aimed at training medical professionals directly who will be in charge of REM in their respective countries. These programs basically consist of lectures which include the experience acquired in the JCO accident and the most up-to-date information on REM obtained from NIRS's global activities, desktop drills and practical drills. Most of these global activities were organized in cooperation with IAEA and/or WHO. For the past 12 years (to January 2013), the total number of medical specialists who joined NIRS training courses and workshops from Asian countries was 365. The participants have gone on to share the knowledge and skills which they obtained during the training courses and workshops with medical REM professionals in their home countries.

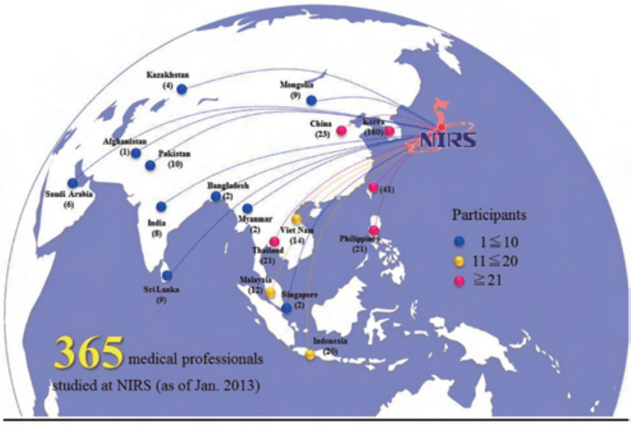


Fig.1 Number of medical specialists who joined NIRS training courses and workshops

Fig.2 Lecture scene from the symposium session.

As the next step for supporting REM in Asia, NIRS established the Radiation Emergency Medical Assistance Team (REMAT®)* in January 2010. The workforce configuration of REMAT® includes physicians, nurses, radiation protection experts, and health physicists. All of the team members are staff of NIRS. REMAT® would have two parts. The dispatch team supports medical care for REM on-site overseas. At the same time, the supporting team at NIRS provides assistance to the on-site REMAT® team. The strong point of REMAT® is its ability to make an immediate response to support REM in other countries. At the request of international organizations or foreign governments, the president of NIRS can make an immediate decision to send a team. REMAT® is equipped with the most advanced portable, radiation measurement equipment, communication devices, in addition to some medicines. Since its establishment, REMAT® has maintained mobile equipment by testing its capability both in Japan and overseas and it has been kept ready to function 24-7.

*REMAT® is a registered trademark of NIRS.

What NIRS did for REM in Asia in 2011 & 2012

Although the activities of REMAT® were intended to ensure a rapid response to radiation emergencies abroad, the preparation paid off at the time of the TEPCO (Tokyo Electric Power Company) Fukushima Daiichi Nuclear Power Station accident in March 2011. NIRS was ready to send the first REMAT® team before the government ordered the dispatch in the early hours on March 12. Besides on-site activities, other staff members at NIRS provided a variety of other responses to the accident. For example in the early phase, NIRS accepted four victims who had dealt with the accident and received both internal and external contamination.

While some activities like REMAT® which were developed before the Fukushima accident functioned well, it is true that activities related to REM could have been performed more smoothly if people including medical staff and first responders had better understanding of radiation. This situation made people realize again that human resource development and education are very important for REM. Working from this background, NIRS has organized a symposium, a training course, and a workshop which are described below. These have been aimed at sharing the information which NIRS staff obtained in their activities for the TEPCO Fukushima NPS accident and at continuing the training for the medical professionals in Asia.

Symposium on the Accident of TEPCO Fukushima Daiichi Nuclear Power Station-What was seen and not seen by others?-

NIRS organized this symposium on August 26, 2011. It was co-organized by the Radiation Emergency Assistance Center/Training Site (REAC/TS) and in co-operation with the U.S Department of Energy (DOE), National Nuclear Security Administration (NNSA), and IAEA.

Although various issues associated with the accident became widely known as time went by, there were very few opportunities for foreigners living in Japan to get correct information and explanation about the ongoing problems. The symposium focused on three topics namely "Response system for REM in Fukushima", "Contamination of environment and foods", and "Public communication and social problems". Two medical doctors and two health physicists from REAC/TS and IAEA joined NIRS staff for presentations. These topics were discussed and analyzed from the viewpoint of REM experts. It was particularly notable that nine persons from seven foreign embassies in Tokyo attended the symposium (Fig. 2).

Workshop on REM in Asia 2012 and Training Course on REM for Korean Medical Professionals

These two events have been promoted as continuing activities for Asian medical workers during the past decade.

The workshop on REM in Asia 2012 was entitled "NIRS Workshop on Medical Response to Nuclear Accidents in Asia 2012" and held from March 21 to 23, 2012. It was organized by NIRS with co-operation from IAEA. A total of 17 participants from China, India, Indonesia, Korea, Malaysia, Mongolia, Pakistan, Philippines, Saudi Arabia, Sri Lanka, Thailand, and Viet Nam attended.

The training course on REM for Korean medical professionals, entitled "NIRS-KIRAMS Joint Seminar on Radiation Emergency Medicine 2012", was hold at the request of the Korea Institute of Radiological & Medical Sciences (KIRAMS) which is the core organization for REM in Korea. The 19 participants were medical professionals and administrators who are involved in REM in Korea.

Although both of these programs consisted of lectures, desktop drills, and practical drills along with discussions as in past training courses, information on several issues identified in the aftermath of the TEPCO Fukushima NPS accident were newly added.

Development of Fundamental Technologies in Radiological Science

Masami Torikoshi, Ph.D.

Director of Research, Development and Support Center

E-mail: torikosi@nirs.go.jp

The Research, Development and Support Center wasestablished in 2011 to support and promote research activities of NIRS. It consists of one unit and three departments: the Planning and Promotion Unit, Department of Technical Support and Development, Department of Safety and Facility Management, and Department of Information Technology. The unit and each department are briefly introduced as follows.

The Planning and Promotion Unitfunctions as the secretariat of the center and is the hub linkingthe departments to the administrative sections of NIRS's overall Department of Planning and Management and Department of General Affairs. The unit has an Education Section which offers many courses of education and training for human resource development. The section has had more than 10,000 attendees sinceits establishment in 1960.

The Department of Technical Support and Development has three sections: Radiation Engineering Section, Radiation Measurement Research Section and Laboratory Animal and Genome Sciences Section. The Radiation Engineering Section maintains the facilities for radiation generators and many devices which are used for experiments. There are seven gamma-ray generators, six X-ray generators and two Cockcroft-Walton accelerator systems which consist of proton accelerators and beamlines. One of the Cockcroft-Walton accelerator systems is used to generate neutron fluxes for research experiments on the biological effects of low dose radiation. The other Cockcroft-Walton accelerator system has three beamlines; two beamlines are used as atomic element analyzers and the third beamline is used to deliver focused proton beams as a few microbeamsto individual cells. Both systems were damaged in the 2011 Great East Japan Earthquake. The latter system experienced more serious damage; the vacuum condition of the accelerator itself broke, the magnets for steering and focusing proton beams moved from their original positions and some beamlines were badlybent. The members of the Radiation Engineering Section fixed them which took about 10 months. These radiation generators are used not only by the researchers of NIRS but also by the researchers from outside NIRS.

The synchrotron accelerator HIMAC is used for carbon ion radiotherapy for cancer and there are also three cyclotron accelerators usedfor radio-pharmacy development related to molecular imaging. HIMACand these cyclotrons are managed and maintained by the Department of Accelerator and Medical Physics of the Research Center for Charged Particle Therapy.

The Radiation Measurement Research Sectiondevelops various radiation detectors. After the Fukushima Daiichi Nuclear Power Plant accident occurred, we began developing some detectors for surveying high level radiation areas in FukushimaPrefecture: these are a gamma-camera which can selectively detect the radiation from ^{137}Cs radioisotope and a detector system which can find out hot-spots were very high levels of radiation are located. We are aiming at commercializing these items.

The Laboratory Animal and Genome Sciences Section supports researchers in conducting animal experimentsof the highestlevel quality. Seven species of animals for animal experiments are available. In this section, we breed more than 15,000 mice and 2,000 rats a year and have developed genetically modified mice in order that researchers can conduct even more advanced experiments. Since some mice and rats are bred in SPF conditions, it is very important to sterilize the area periodically and keep it clean all the time. We control the SPF areas very strictly.

The Department of Safety and Facility Management has four sections: Safety and Risk Management Section,Safety Control Section, Radiation Safety Section,and Facility Management Section. Only the last two sections are introduced here. In NIRS, about 1,600 persons including NIRS's direct employees, researchers from outside NIRS, and contracted workers are registered as radiation workers who can work in the 20 radiation-controlled areas in NIRS. NIRS must instruct them regarding radiation safety and security before entering a radiation-controlled area for the first time. There are more than 400 kinds of radioisotopes used for experiments on radiobiology, radiation medicine and so forth. And NIRS also has many radiation generators as

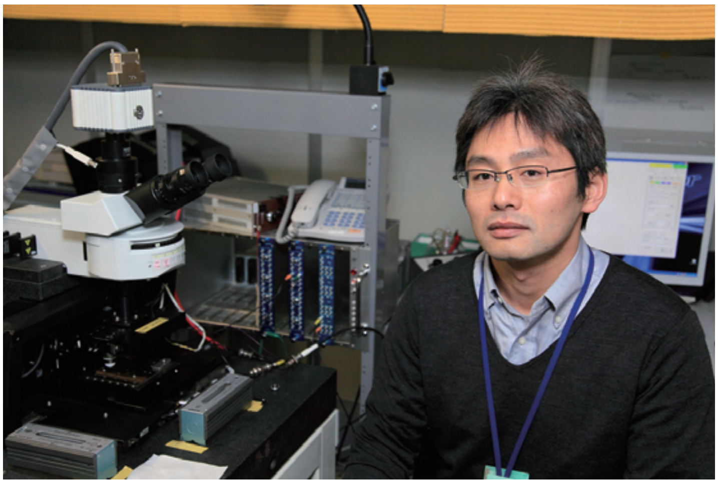
mentioned above. All items concerned with radiation have to be controlled strictly by rules. The Radiation Safety Section is charged with controlling all of them in accordance with the rules. There are about 50 buildings on the NIRS campus. The Facility Management Section maintains the buildings and their equipment such as elevators, air conditioners, etc., and the campus infrastructures such as electric power lines, telephone systems, gas lines, water supply lines, and so on. NIRS was established in 1957, so some buildings are very old and a few were damaged considerably in the March 2011 earthquake. Some of them have had to have seismic strengthening. This section has also been managing construction of a new building which will be used for human resource development. The Radiation Emer-gency Medicine Cooperative Research Facility has one building in which the use of actinide nuclei is allowed for research on radiation emergency medicine. This facility is the only one of its kind in Japan in which researchers can use, for instance, plutonium in animal experiments. Therefore, this building has to be strictly controlled to keep the inside of the building at a negative pressure according to the radiation safety law. In this case, the ventilation system of the building is maintained by the Radiation Safety Section in cooperation with the Promotion Section for Radiation Emergency Medicine Cooperative Research Facility of the Research Center for Radiation Emergency Medicine instead of the Facility Management Section because of existence of the strict rules.

The computer network system is one of the main infrastructures of NIRS. This network system has more than 1,100 users daily and about 4,000 computers are connected to it. The Department of Information Technology is responsiblefor maintenance and development of the computer network system. The administrative sections have many computer-aided service systems, for instance, personnel management, accounting procedures, patent database, etc. These service systems are maintained by the relevant section in principle, but Department of Information Technology has undertaken various jobs such as improving the systems or adding new functionsto them. Now an institutional repositoryisbeing developed to replace the conventional database system used for registration of achievements of NIRS research activities. We plan to release it in December 2013. This department is also managing the library of NIRS and publications such as a research reports, proceedings and so on. One of the most important missions of this department is to secure information security. We instructed users on to keeping security in an e-learning exercise in the summer of 2012.

Highlight

Research and development of focused proton microbeam irradiation system, SPICE for radio-biological studies

Teruaki Konishi
E-mail: tkonishi@nirs.go.jp



There is continuing interest in the use of microbeam irradiation systems designed to deliver a defined number of charged particles on a single cell with a resolution of a few micrometers. Irradiation of an exact number of charged particles on a single cell means that the limitations of the Poisson distribution of the number of charged particles can be overcome. This is especially important in low-dose regions because a small number of charged particles per cell will inevitably lead to large fluctuations in the cell population in a broad-beam irradiation field. Moreover, microbeams are particularly useful in the field of radiation-induced non-targeted effects, so called bystander effects that are considered to be one of the major effects in the low-dose region. In addition, microbeams with beam sizes of less than a few micrometers enable irradiation of a desired site within the cell.

Our microbeam irradiation system, the Single Particle Irradiation system to CEll (SPICE) provides a 3.4 MeV proton microbeam focused with a quadrupole magnetic lens on an upward vertical beam line. The construction of the prototype of SPICE began in 2003 with the primary goal of targeting 2,000 cells per hour with a 2-μm diameter proton microbeam. After improving the vertical beam line structures and accelerator stability, a beam size of 10 μm was obtained in 2006. Further optimization of the beam focusing system and improvements on the stability of the bending magnets led to the beam size being reduced to approximately 5 μm. In 2008, an automated cell recognition system for targeting cell nuclei in a 2.5 mm×2.5 mm area of the cell dish was also completed[1]. Now, after additional improvements, SPICE provides a beam size of approximately 2 μm in diameter, and its irradiation procedures are fully automated with high-throughput irradiation of 3,000 cells in a 5 mm×5 mm area in a single dish within 15 min after placing the cell dish on the micro-positioning stage.

SPICE was severely damaged by the Tohoku-oki Earthquake on March 11th 2011, and was out of operation for about a year and a half. We have successfully reconstructed the facility and it is now operational with system refinements. At present, SPICE is the only proton microbeam facility at which a single-ion single-cell irradiation can be performed on mammalian cells with stability and high throughput using an upward vertical beam of 2-μm diameter, focused with a magnetic quadrupole triplet lens. Fig. 1 is a microscopic image of the plastic track detector that indicates the beam size of the microbeam. The 2-μm diameter beam size enables us to irradiate the nucleus or cytoplasm of a single mammalian cell; and the number of protons irradiating a single nucleus can be controlled to be one to several thousand with a precision of 99%. SPICE is convenient and stable and all procedures are controlled automatically by the operation system except for setting the preset number of protons during the standard microbeam irradiation targeting monolayer cells. This is good for radiation biologists who are not familiar with microbeam experiments, but is also very time consuming.

A variety of irradiation modes have been established for radiation-induced bystander effects, cytoplasm irradiation, and so on. The default targeting pattern mode is single position irradiation at the center of the cell nucleus for all nuclei with the same preset number of protons or for each nucleus to be irradiated with a different number of protons. In addition to the default mode, three types of optional targeting modes are provided for a variety of radiobiological studies: a fractional population targeting mode, a multi-position targeting mode for nucleus irradiation, and a cytoplasm targeting mode. In the fractional population targeting mode, which is useful for bystander-effect studies, the percentage of irradiated cells among all cells is a set value. With a multi-position targeting mode, we can change the dose distribution in the targeted cell nuclei, and with cytoplasm targeting mode, we can target only the cytoplasm of the targeted cells. A schematic drawing is shown in Fig. 2. In addition, a time-controlled irradiation mode for targeting thick biomaterials has also been established, and this mode has been demonstrated with zebrafish embryos[2]. Representative images when targeting zebrafish embryos are shown in Fig. 3.

SPICE provides a stable microbeam for 3 h, and under the stan-

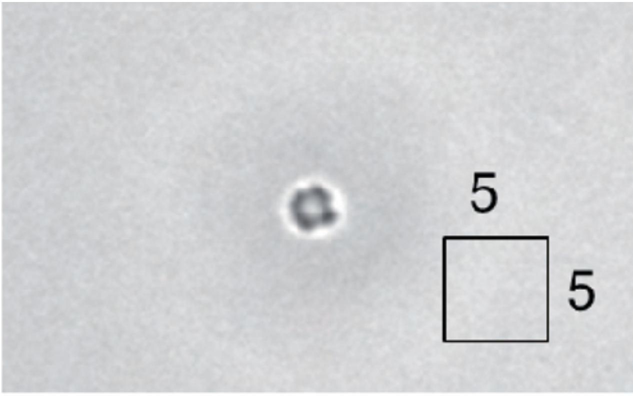


Fig.1 Beam profiles recorded on a CR-39 plastic detector after irradiation with 100 protons. The square is 5 µm×5 µm.

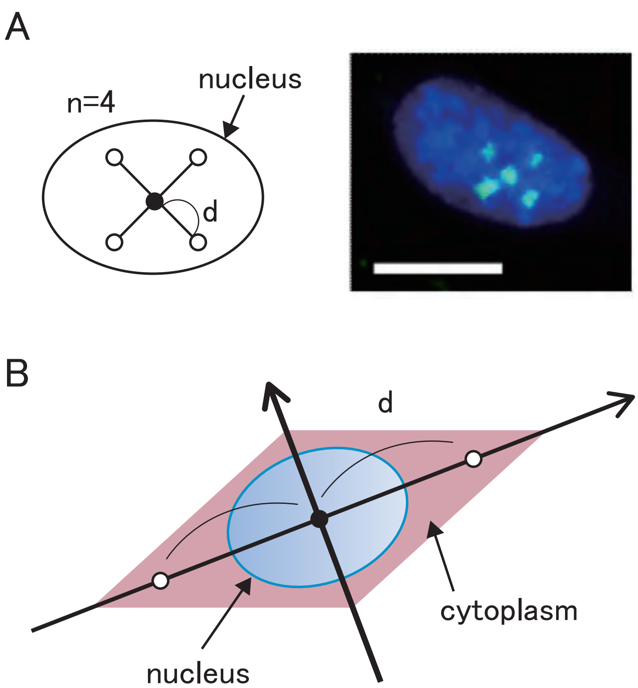


Fig.2 Schematic diagrams of the optional targeting modes. (A) The multi-position targeting mode: the center of the cell nucleus is shown by the solid circle, and off-center positions at a distance of *d* µm (up to 20 µm) are shown by the open circles. The configurations for different numbers of off-center positions, n (= 1, 2, 3, or 4) are selectable. An example target pattern of n=4 with center position is shown on the left. The image on the right is the WI-38 human normal fibroblast cell targeted with 200 protons per each position with *d* = 3 µm and n=4 with the center of the nucleus. Green-fluorescent spots indicate γ-H2AX, a marker for DNA double strand breaks. (B) The cytoplasm targeting mode: the two open circles on the major axis are the distance *d* from the center [3].

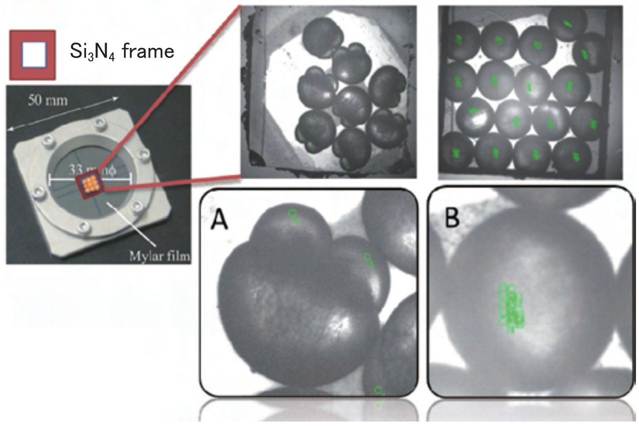


Fig.3 Specially designed dish for zebrafish embryo irradiation, with a Mylar film as the substrate for the embryos and a rectangular frame (Si_3N_4) attached to the center of the Mylar film by Vaseline to restrict the movement of the embryos. A and B represent embryos of 0.75 hpf and 5 hpf, respectively. (hpf: hours after fertilization)

dard irradiation protocol conditions, 3,000 cells in a cell dish can be irradiated within 15 min, meaning that 12 dishes can be irradiated in 3 h. Overall specifications of SPICE have been reported in the literature [3]. Since 2009, SPICE has been administrated as a “Joint-use Facility for Collaborative Research,” and thus researchers outside NIRS can apply for beam time of SPICE after their research proposals are approved.

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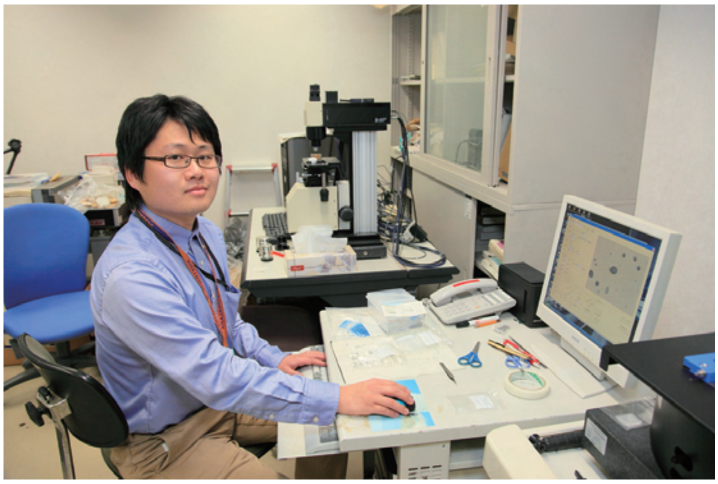
Highlight

Research development of selective and precise measurement technologies of secondary high-LET particles in the radiation mixed fields

Satoshi Kodaira
E-mail: koda@nirs.go.jp



The secondary particles produced by the nuclear interactions of high energy photons, protons and heavy charged particles play significant roles for extra radiation exposure to not only patients during the medical treatment but also astronauts during space missions at lower-Earth orbits and beyond. For example, proton beams can deposit a dose to surrounding healthy tissue through nuclear reactions with the production of secondary short range, high-LET (high-linear energy transfer) target fragments. The LET of such particles extends from about 20 keV/μm up to several thousand keV/μm, meaning that their biological effectiveness is relatively high compared to primary protons. To fully understand the possible risks from the secondary target fragment component, including the induction of secondary cancers, the experimental verification of the dose contribution from the secondary target fragments is necessary.

For the precise measurement of secondary high-LET particles, we have developed two technologies with CR-39 plastic nuclear track detectors. CR-39 detectors are commonly used as heavy ion detectors with a detection threshold of ~5 keV/μm; this means that they do not register tracks from primary protons with energy greater than ~12 MeV and thus are insensitive to primary protons in the radiotherapy beam. To cover the very high-LET region of a proton beam around its Bragg peak and of a carbon ion beam, we have developed a two-step chemical etching method for CR-39 plates with PEW-x solution [17wt% KOH + *x*wt% C_2H_5OH + (83-*x*) wt% H_2O] as the pre-etching solution and 7N NaOH solution as the post-etching one. This method allows us to control the LET detection threshold of CR-39, further enabling selective measurement of particles as a function of LET as shown in Fig. 1 [1, 2].

In the conventional method for the analysis of CR-39 detectors using an optical microscope, it is difficult to measure secondary high-LET tracks due to the short range (≤10 μm) of such tracks, because those tracks are mostly lost when chemical etching removes the surface layer to a thickness of several tens of micrometers. We have established a precise LET spectrum measurement method for short range tracks by controlling the chemical etching to an extremely shallow layer of ~ 1μm. The produced minute nuclear tracks are precisely measured with an AFM (atomic force microscope) replacing the conventional optical microscope as shown in Fig. 2. Under the AFM measurement conditions, CR-39 detectors were calibrated using low energy (< 6 MeV/n) and high energy (>100 MeV/n) heavy ion beams at HIMAC. The exposed CR-39 plates were etched in a 7 N sodium hydroxide solution at a temperature of 70℃ for 1 h. The AFM (Dimension V; Veeco) equipped with a 125 μm cantilever having a typical tip length of 10 μm was operated in the tapping mode. The cantilever was oscillated near its resonant frequency (~300 kHz) which allowed the whole detector surface to be scanned. The AFM images for

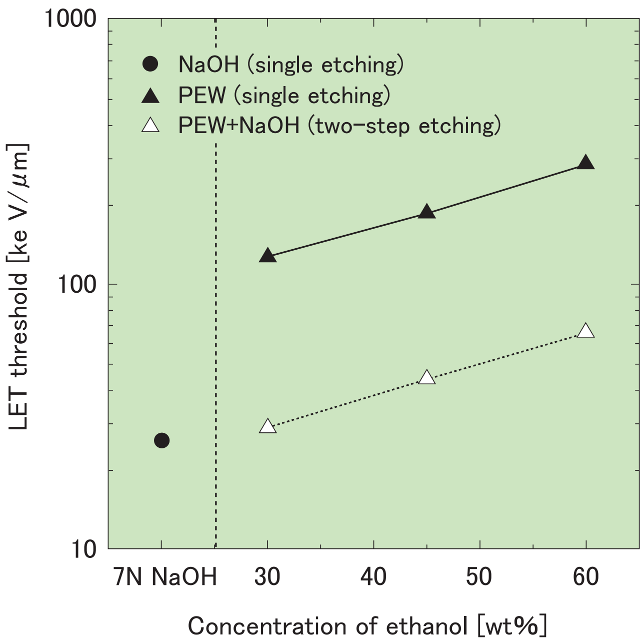


Fig.1 Variations of LET detection threshold as a function of ethanol concentration in PEW-x pre-etching solution.

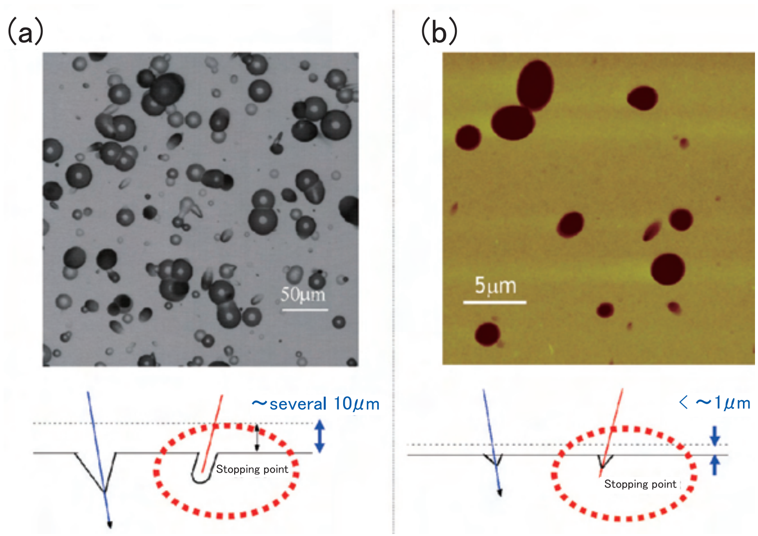


Fig.2 Comparison of secondary particles measurements by (a) conventional optical microscopy of micron-size tracks enhanced by deep etching and (b) atomic force microscopy of non-size tracks by extremely shallow etching. In the conventional method, short range tracks are etched away which means LET information is lost. AFM method allows to measure precisely LET of short range tracks without over-etching problems.

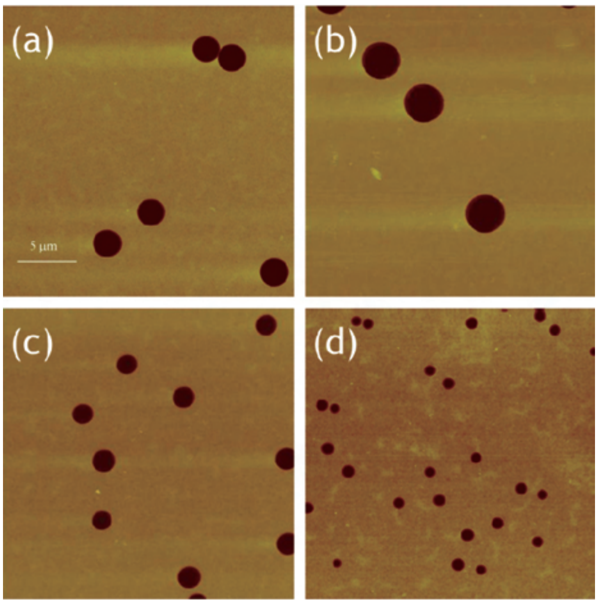


Fig.3 25 μm×25 μm AFM images of nuclear tracks formed on CR-39 detectors from: (a) 415.8 MeV/n Fe, (b) 2.49 MeV/n Ar, (c) 4.18 MeV/n N and (d) 5.62 MeV/n He[3].

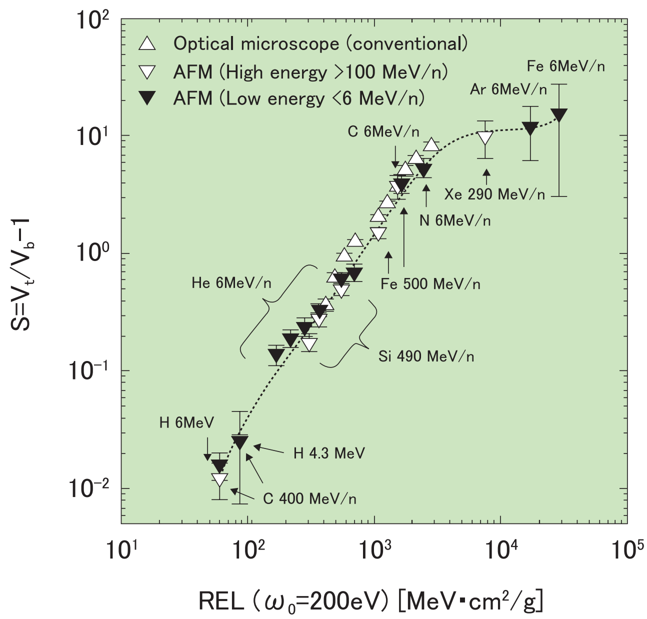


Fig.4 Track response data measured by AFM as a function of REL (ω_0= 200 eV)[3].

the track diameter measurement, which gives CR-39 response (S), were scanned as 25 μm×25 μm sizes with 1024×1024 pixels. The scan rate was 1.5 Hz. Fig. 3 shows typical AFM images of nuclear tracks from (a) 415.8 MeV/n Fe, (b) 2.49 MeV/n Ar, (c) 4.18 MeV/n N and (d) 5.62 MeV/n He. The accuracy of measurement was 24.4 nm/pixel. The response curve for the conversion from track response (S) to restricted energy loss (REL) with the δ-ray cut off energy of 200 eV, which can be converted to LET in water, was obtained as shown in Fig. 4. We found that the track response in CR-39 can be scaled with a universal function over a wide energy range from low energy (a few MeV/n) to high energy (~500 MeV/n) by the AFM measurement method[3]. The reported results will be applied to the evaluation of the secondary short range particle tracks produced by target fragmentation reactions in the radiation field used in not only radiation cancer therapy but also space radiation fields.

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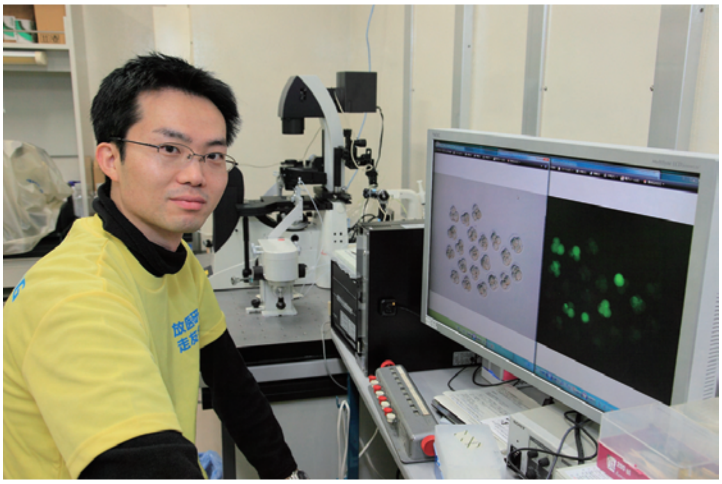
Highlight

Analysis of lysosomal function in preimplantation mouse embryos

Satoshi Tsukamoto
E-mail: s_tsuka@nirs.go.jp



Lysosomes were discovered more than half a century ago by Dr. Christian de Duve, a professor at Rockefeller University and a 1974 Nobel Prize recipient in Physiology or Medicine. Lysosomes are now recognized as the ubiquitous and acidic organelles responsible for the turnover of cellular constituents. One of the main functions of lysosomes is to degrade cellular constituents. Therefore, they contain more than 50 hydrolases (phosphatases, nucleases, glycosidases, proteases, peptidases, sulphatases and lipases) which function only in an acidic environment[1]. It is known that many materials are delivered to lysosomes for digestion via several pathways—phagocytosis, endocytosis, and autophagy. Lysosomal function is critical for cellular homeostasis, since lysosomal defects can be linked to several diseases leading to cellular damage, such as Danon disease and Neimann-Pick disease, which is characterized by the accumulation of undigested materials. In addition, current research suggests that lysosomal activity decreases during aging, which can result in the accumulation of toxic materials, such as damaged organelles, protein aggregates, and lipofuscin, indicating that lysosomal activity is essential for maintaining cellular integrity.

Infertility has become a medical issue recognized world-wide. It has long been believed that oocyte/embryo quality decreases with maternal aging (after an age of 35 years in humans) and that the resulting low quality could be one of the major reasons for female infertility. However, little is known on the molecular mechanisms involved in oocyte/embryo quality control. Preimplantation development is a developmental process where a fertilized oocyte develops into a blastocyst (Fig.1). Once fertilized, the embryo rapidly develops into the blastocyst through several mitotic events, a process taking about 4-5 days in mice and 5-6 days in humans. Considering the rapid development, bulk degradation via lysosomes could be critical for eliminating residual materials in the oocyte and recycling them for synthesis of new products that are essential for transition from differentiated oocytes to totipotent embryos. Recently, we showed that autophagy, in which the cytoplasmic contents are sequestered by the autophagsomes and fused with the lysosomes, followed by the degradation of those

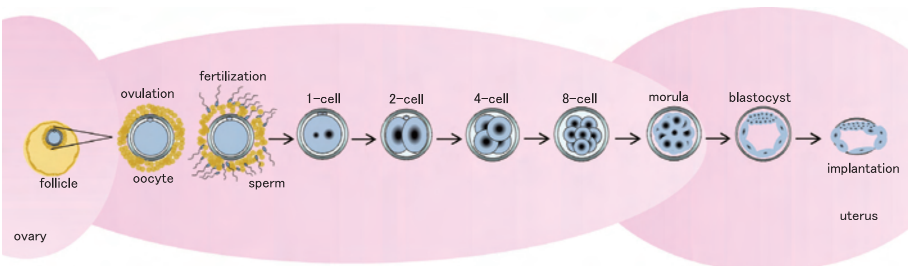


Fig.1 Preimplantation embryo development.
Oocytes are grown and maturated in the ovary. After ovulation, fertilization occurs when the sperm fuses with the oocyte. Once fertilized, the embryo develops rapidly into a blastocyst through several mitotic events, followed by attachment to the wall of the uterus (implantation). During implantation, the embryo is composed of approximately 100 cells. The time required for preimplantation development differs among animal species: 4-5 days in mice and 5-6 days in humans.

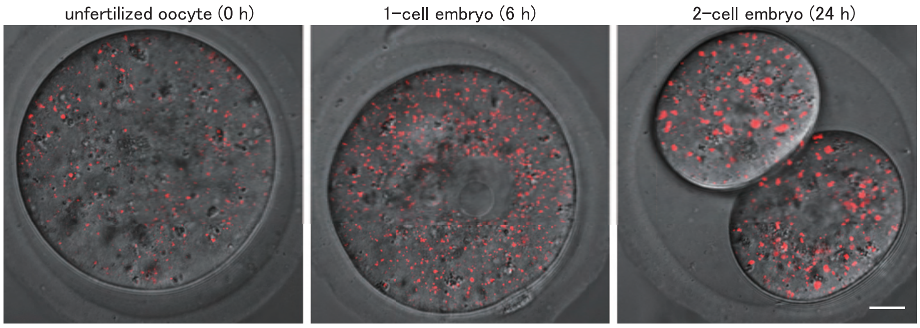


Fig.2 Distribution of lysosomes in mouse oocyte and embryos.
Lysosomes in unfertilized oocyte and 1-cell and 2-cell embryos were labeled with LysoTracker Red, specifically for staining of the lysosomes, and observed under a confocal laser fluorescence microscope. Note that the size and number of lysosomes changes after fertilization. (h) represents time after fertilization. The scale bar is 10 µm.

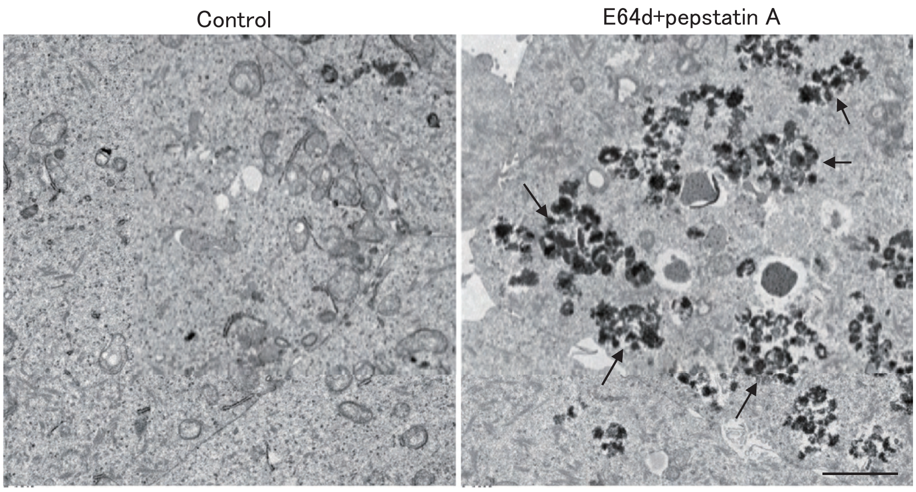


Fig.3 Lipofuscin accumulation in lysosome-defective embryos.
Early embryos were co-cultured with both E64d and Pepstatin A, which inhibit lysosomal proteases, and were analyzed by electron microscopy. Large numbers of lipofuscins, indicated by arrows, were observed in the co-cultured embryos, while no visible lipofuscins were observed in the non-treated (control) embryos. The scale bar is 2 µm.

contents, was highly activated shortly after fertilization[2]. These observations shed light on the importance of lysosome-mediated degradation in early embryo development.

Our laboratory has focused on the lysosomal function during preimplantation development. We recently found that the size and number of lysosomes changes dramatically after fertilization[3] (Fig.2). Consistent with this observation, the level of mature cathepsin, which is one of the major lysosomal hydrolases, was high during early embryo development. We also showed that lysosomal dysfunction caused an accumulation of lipofuscin (Fig. 3), which is a toxic material and a hallmark of ageing, and that these embryos were not able to develop further. These observations indicate that lysosomal activity and its function are critical for preimplantation embryo development. Based on our observation, we are developing a method for monitoring the lysosomal activity in developing embryos. If this technique is established, we might be able to determine which oocytes and embryos have relatively high (good) or low (poor) development potential, since we speculate that the lysosomal activity will correlate with embryo viability. Because lysosomal function is conserved in different species, our developing technique will be applicable to not only laboratory mice but also other animal species, including humans.

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Highlight

Immunogenicity of the differentiated cells derived from induced pluripotent stem cells

Ryoko Araki, Masahiro Uda, Yuko Fujimori-Hoki, Miki Nakamura, Shunsuke Ando, Misato Sunayama, Mayumi Sugiura, Hisashi Ideno, Akira Nifuji, Masumi Abe

E-mail: a_ryo@nirs.go.jp

Technology using induced pluripotent stem cells (iPSCs) holds great promise in regenerative medicine. Because iPSC technology allows researchers to obtain embryonic stem (ES)-like cells from patients directly, no immune rejection is expected when the tissues derived from iPSCs are transplanted. However, recently, immunogenicity of iPSCs was claimed, while similar immunogenicity was not observed in ES cells (Zhao *et al., Nature* 474, 212-215, 2011). This is quite an important study, since it directly affects the future of regenerative medicine. Heated arguments have arisen about the study (Okita *et al., Circulation Research* 109, 720-721, 2011; Yamanaka, *ISSCR* 2011), because the report involves several big concerns: only one line of ES cells (ESCs) was examined; there was no assessment of the developmental ability, of which partiality elicits immune responses; and immunogenicity was evaluated by using the iPSCs themselves.

Here we established many lines of integration-free iPSCs and ESCs from an inbred mouse strain C57BL/6 to obtain a conclusion on this issue[1, 2]. The fully reprogrammed state and their developmental ability were verified by the germline transmission test through chimeric mouse formation for most of the lines.

First, we conducted a teratoma formation test for seven iPSC lines and five ESC lines; full developmental ability was observed for the five out of the seven iPS cell lines and four of the five lines of ES cells. Although slightly efficient formation was observed in iPSCs, little difference in incidence was observed basically between iPSCs and ESCs (Fig. 1).

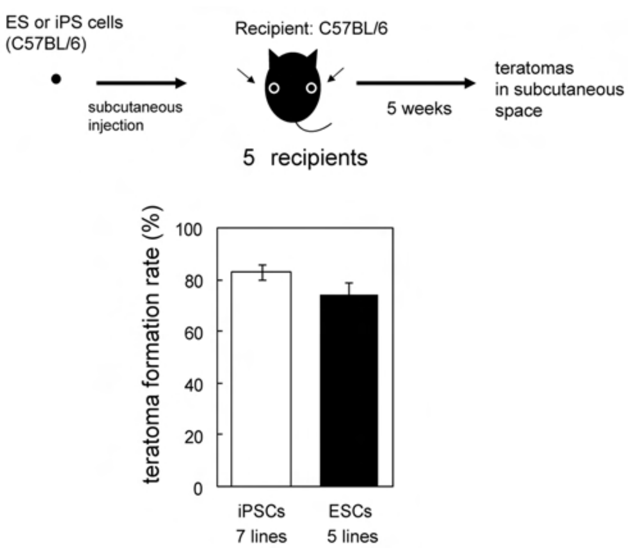

Fig.1 Teratoma formation
Arrow heads indicate teratomas. Seven iPSC and five ESC lines were analyzed. SEs are shown.

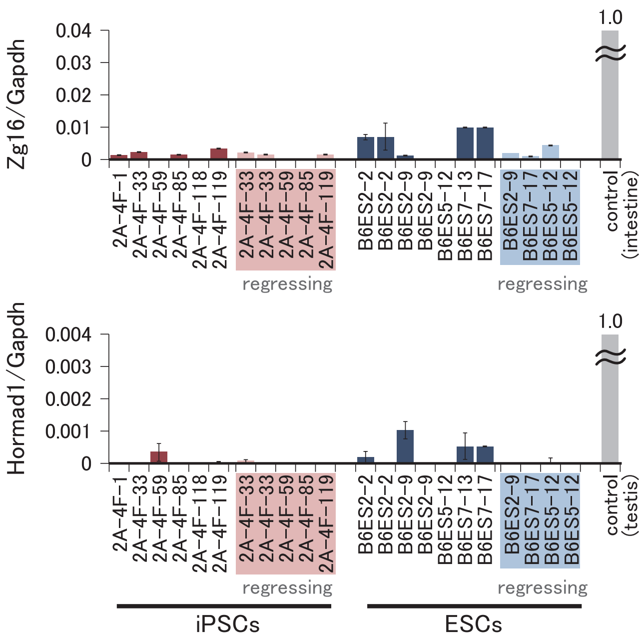

Fig.2 Expressions of *Zg16* and *Hormad1* genes in teratomas[2].

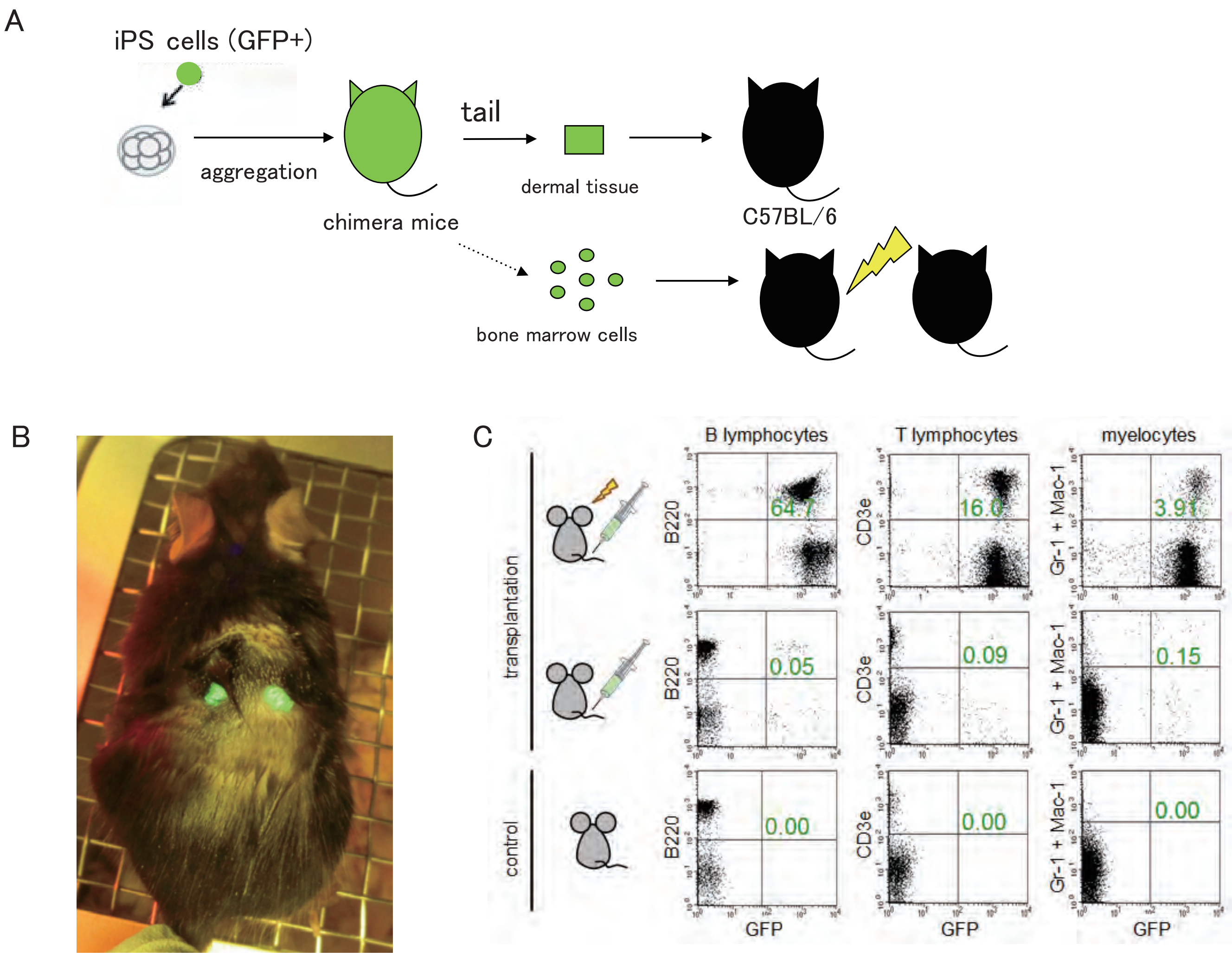

Fig.3 Transplantation experiments of skin and bone marrow.
(A) Schematic diagram of the method. (B) Grafted skin by GFP iPSCs. (C) Long-term reconstitution of bone marrow by GFP positive iPSCs [3].

Three germ layers were observed in the teratomas. In addition, although we investigated T cells for detecting immune responses, we could not detect meaningful T-cell-infiltration not only in the teratomas derived from iPSCs but also from ESCs. We also examined the expressions of *Zg16* and *Hormad1* that were demonstrated as the causative genes for their immunogenicity but their expressions in the teratomas derived from iPSCs were lower than those in ESCs (Fig. 2). Thus, contrary to the previous report, even using a large number of ESCs and iPSCs, we could not detect any differences between these two types of pluripotent stem cells.

Because iPSCs or ESCs would be converted into specific tissues and transplanted into a recipient body, not transplanted pluripotent stem cells themselves directly, evaluation of immunogenicity must be performed on the differentiated tissues, not iPSCs or ESCs themselves. Therefore, second, we assessed the immunogenicity of the terminally differentiated cells derived from iPSCs and ESCs, skin and bone marrow. In our study, donor tissues were prepared from chimera mice developed from either iPSCs or ESCs; we used 100% chimeric mice only that were generated by aggregation with GFP-mice embryos to completely exclude the recipient derived cells from donor tissues. Tissues that were confirmed to be GFP-negative were used for subsequent transplantations. Consequently, even in the cases focusing on these differentiated cells, we also observed little difference between the tissues derived from iPSCs and those from ESCs not only in incidence but also in T-cell response. Almost all transplantations were successful and very few T-cells were observed within the transplanted tissues in both cases using the two types of pluripotent stem cells. Skin transplantation was successful for iPSCs and ESCs derived tissues and the engraftment was maintained for more than 6 months. Transplantation of bone marrow cells into recipient mice without X-ray irradiation was also successful and hematopoietic reconstitution was achieved four months later, indicating an engraftment of long-term hematopoietic stem cells.

Thus, in the present study we could not observe or distinguish the immunogenicity of iPSC-derived tissues from those derived from ESCs [3].

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Fukushima Project Headquarters

Masami Torikoshi, Ph.D.

Deputy Director

E-mail: torikosi@nirs.go.jp

The Fukushima Project Headquarters was established in May 2012 to support restoration and revitalization of Fukushima Prefecture following the nuclear accident at the Fukushima Daiichi Nuclear Power Plant (NPP). The headquarters manages three research projects and five sections. The projects are Radiation Effect Accumulation and Prevention Project, Project for Environmental Dynamics and Radiation Effects, and Project for Human Health. The headquarters also manages other research activities related with these projects. Background to the establishment of the headquarters and these projects are introduced briefly here. Details of each project are given in the following section.

Following the nuclear accident, NIRS has been dispatching medical staff to Fukushima Prefecture to assist in medical care of contaminated persons. By request of the Japanese government, several researchers have been staying at various organizations, such as the Cabinet Office, Nuclear Regulation Authority, and so on. These workers are required to give scientific advice about radiation effects on human health. Furthermore, the Fukushima Prefectural government and many municipal governments seriously need information about radiation and its effects on human health because they do not have any idea what measures they should take regarding radiation exposure caused by the NPP accident. So NIRS has dispatched many researchers to give talks about radiation and its effects on human health. One day after the NPP accident occurred, an NIRS worker found misleading information about radiation on an internet site. So, NIRS began sending out correct information on radiation and its human health effects and we provided simple measures to avoid unwanted exposure in an internet first. Using the internet was found to be one of the strongest ways to transmit information—both true and false. NIRS workers prepared messages through the internet in “Question and Answer” format so that people could easily understand complicated topics. A few special telephone lines were added to communicate with individuals who were uneasy about the health effects due to radiation exposure. This consultation was operated by seven staff members by turn for 24 hours a day, seven days a week for the first two weeks after the occurrence of Fukushima Daiichi NPP accident.

However, a year after the accident the situation has changed from the emergency stage. The emission of radioactive materials from Fukushima Daiichi NPP was almost stopped. The Japanese and municipal governments started decontamination work in a few areas. The emergency evacuation preparation zone was opened and some residents began coming back to their homes from temporary evacuation places. In years to come, more and more people will begin living in their homes as before the accident. But there is a concern that they may be exposed to low dose radiation from the surrounding environment, especially mountain and forest areas which have undergone hardly any decontamination. Many parents raising young children and pregnant women are uneasy and nervous about the health effects of radiation and contamination of foods, water, playgrounds for children and so forth in daily life. NIRS recognized that the needs and concerns of these people should be address to assist them in the next stage of recovery from the NPP accident. Therefore, the Fukushima Project Headquarters was established to manage and support all activities of NIRS assisting in the restoration of the areas affected by the NPP accident in Fukushima Prefecture.

In high radiation background areas, people will continuously receive low doses over many years into the future. This situation is very different from the exposure situation in which high doses are delivered in a short interval of time such as the case of the atomic bombs in Hiroshima and Nagasaki. It has been reported that the health effects of radiation at a lower dose rate are less than the health effects of radiation at high dose rate even at the same total dose. From the viewpoint of radiation protection a dose and dose-rate effectiveness factor (DDREF) is used to estimate the health effects caused by exposure of low dose at a low dose rate. The ICRP recommends the DDREF is 1/3 for an adult human. However, for children it is not very clear what value is the most suitable for the DDREF. In the Radiation Effect Accumulation and Prevention Project researchers are focusing on clarifying the DDREF for fetus and infant because many parents of young children and many pregnant women may be concerned about what extent radiation affects the health of children and fetuses. There are two ways to approach the DDREF; one is the direct way in which the factor is determined by animal experiments with mice and rats, and the one is an indirect way in which the mechanisms are investigated for why a low dose and a low dose rate exposure have smaller effects on human health. What most people want to know is whether they can reduce the effects of radiation on their health or not. NIRS researchers have found that dietary mice have a longer life time than mice which are not on a diet. This finding is independent of being exposed to radiation or not. This study will be done again with expanded experimental conditions to cover various cases.

Most people are concerned with whether health effects will actually appear in the future, and if yes what they will be and when they will appear. There is no way except by an epidemiological study to directly clarify how exposed radiation doses affect human health. In the Project for Human Health, we started an epidemiological investigation with the cooperation of first responders who worked at Fukushima Daiichi NPP controlling the accident in the early stage. We will monitor their health for a long time by referring to their certificates of health and by asking for their medical history and information about their lifestyle such as smoking and drinking habits, etc. The information is being collected in a database to analyze the correlations between health conditions and the doses they received. If correlations are found between occurrence of some disease and the dose, we will inform this fact to the persons or the organizations to which they belong. Our final goal is to use the information for health care to prevent occurrence of disease or to find it at the early stage. Furthermore, we expect that future radiation protection activities will apply these epidemiological study results as a basis for responsible laws.

Fukushima Medical University is one of the largest medical centers in Fukushima Prefecture. It is carrying out a long-term health management survey for all people of Fukushima Prefecture. One section of this project is in cooperation with NIRS researchers and will estimate the external exposure dose which residents in Fukushima Prefecture received during the first four months after March 11, 2011.

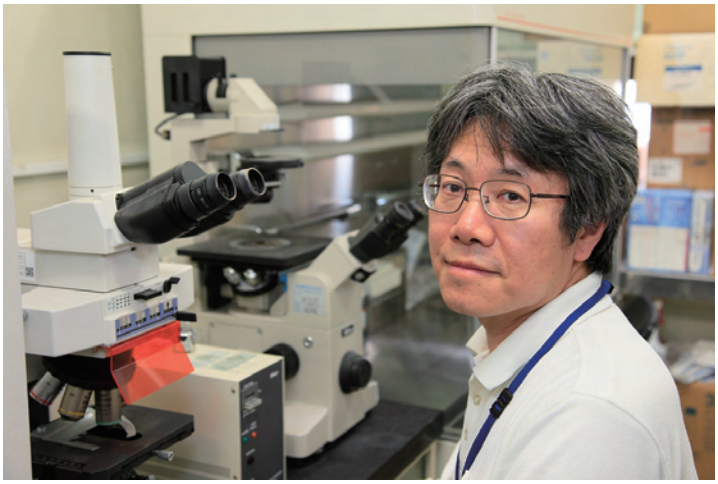
Members of Project of Environment Dynamics and Radiation Effects are entering the restricted area to collect small animals and plants.

Many residents from evacuation areas are afraid that they will be exposed to high radiation dose again, or that they will ingest radioactive materials from foods and water. Radionuclides may migrate to residential areas from the surrounding environment such as mountains and forests with time. In order to estimate long-term radiation doses of the residents from the surrounding environment during their daily life, we started dose estimation oriented collection of environmental samples as one mission of the Project for Environmental Dynamics and Radiation Effects. In addition, high contamination levels of the environment suggest possible effects of radiation on non-human biota and ecosystems. Although drastic effects such as the “red forests” in contaminated Chernobyl areas have not been observed, long-term studies are required to estimate the environmental effects. We are collecting biological samples such as pine, wild mouse, and salamander in heavily contaminated areas, and are planning to estimate radiation effects using different endpoints (e.g. growth rate, reproduction and chromosome aberration).

Highlight

Effects of the Fukushima Daiichi Nuclear Power Plant accident in wildlife of Fukushima Prefecture

Yoshihisa Kubota
E-mail: y_kubota@nirs.go.jp



Tremendously large quantities of radionuclides were released into the environment following the nuclear accident at the Fukushima Daiichi Nuclear Power Plant in March 2011. In such a situation, it was quite important to study the environmental effects of the accident as well as the effects on human health; this importance reflects the change in the way people now think about the environment. During the past two decades, the need to evaluate the influence that radiation has on the environment itself has been pointed out by researchers while the interest in environmental problems has increased worldwide among people in general, although the way of thinking that "environment should be protected by the radiation protection system of humans" has been supported for many years by the International Commission on Radiological Protection (ICRP). The frameworks on environmental protection against radiation have already been established in international organizations such as ICRP.

Garnier-Laplace *et al.* [1] calculated radiation exposure dose of rodents inhabiting Iitate Village, Fukushima using soil monitoring data reported from the Ministry of Education, Culture, Sports, Science and Technology and the dose evaluation tool (ERICA Tool) developed by a research project of the EC. They suggested a possible decline of the fecundity based on the criteria of the environmental protection framework of radiation given in ICRP Publication 108 [2]. It is essential to make a radiation effect study on the wildlife inhabiting Fukushima Prefecture to answer the question of whether or not the environment is really affected by radiation. Many researchers are trying to demonstrate environmental effects (on individual health, population size, biodiversity of species, and ecosystems) of radiation derived from the Fukushima NPP accident. However, there are only a few reports which have proved any biological effects of radiation in the wildlife. It seems difficult to find easily any biological consequences in wildlife of Fukushima Prefecture except for wildlife inhabiting the very restricted highly contaminated areas. In highly contaminated areas within the exclusion zone, genetic effects such as chromosome aberration and gene mutation, higher tumor incidence, population size reduction by reproductive failure may happen.

Based on the radiation sensitivity, we selected several animals and plants from many types of wildlife as research objects since it is reasonable to consider that radiation effects can be more easily observed in more radiosensitive wildlife. Wild mice, salamander, medaka fish, Japanese cedar and pine tree were chosen because these animals and plants are known to have comparatively large genome size and consequently radiosensitive characteristics. They are also commonly found throughout Fukushima. In particular, we are focusing on the study of radiation effects seen in wild mice caught in Fukushima (Fig.1). Tanaka *et al.* [3] demonstrated the increased chromosome aberration in lymphocytes of laboratory mouse (*Mus musculus*) exposed chronically at a dose rate of 20mGy/day, but they saw an extremely slight effect at a dose rate of 1mGy/day. The highest value of the dose rate we measured in Fukushima with an ionization chamber type survey meter was 60-80 μSv/h. Rough dose estimation predicts that wildlife inhabiting the ground surface of such a highly contaminated location may receive a dose of more than 1mGy/day by external exposure only and an elevated level of chromosomal aberration might be observed in wild mice there. Therefore, we are trying to demonstrate the chromosomal aberration in wild mice (mainly two species, wood mouse (*Apodemus speciosus*) and small field mouse (*Apodemus argenteus*), both are unique species in Japan) captured in a highly contaminated area of the exclusion zone. As shown in Table 1, the methods applicable to laboratory mice to detect unstable or stable chromosomal aberration cannot be applied to wild mice because of genetically distant relationship. Only C-band staining can be applied to small field mice (Fig.2). At present, centromere FISH probes for wood mice and small laboratory mice are being developed. The multi-color FISH with centromere FISH probes in combination with the telomere FISH probe is expected to make the detection of unstable chromosomal aberrations possible and much easier. The study is taking place now; however substantial results will not come until next year.

Fig.1 Wood mouse captured in a Fukushima forest

This year, we started to give a chronic low-dose rate exposure to a Tohoku salamander captured in Fukushima. This is being done in the long-term irradiation facility of NIRS. Fertilized egg, wintering larva and adults are now being chronically irradiated at various dose rates. The effects of irradiation will be examined on hatching, growth, fecundity, etc.

Even if some kind of changes are observed in wildlife inhabiting highly contaminated areas of Fukushima, it will be necessary to demonstrate that the changes that occurred are really due to radiation exposure. Evacuation from the highly contaminated areas has made the study of radiation effects on the environment more complicated and difficult because human activities had largely influenced the environment. To that end, it is necessary to measure radioactivity concentration in the wild animals and plants themselves and in the environmental media they were inhabiting to calculate the radiation exposure dose or dose rate as precisely as possible.

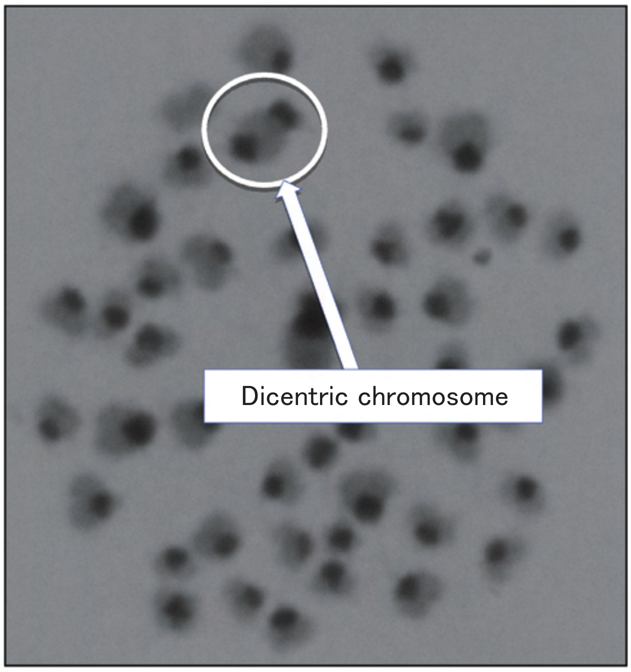


Fig.2 Dicentric chromosome detected by C-band staining in the lymphocyte of a small field mouse

Table 1 Interspecies Comparison of method to detect chromosomal aberration

	Unstable type (Dicentric) Centromere-FISH	Unstable type (Dicentric) C-band	Stable type (Translocation) FISH or Multi-FISF
Laboratory mouse	○	○	○
Wood mouse	×	×	×
Small field mouse	×	○	×

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Highlight

Project for human health (Workers' health follow-up team)

Shinji Yoshinaga
E-mail: yosinaga@nirs.go.jp

Highlight

A lot of workers were involved in emergency response and stabilizing operations and many continue to be involved in recovery operations and associated activities not only at the site of the Fukushima Daiichi Nuclear Power Plant but also in the surrounding areas. These workers include employees of Tokyo Electric Power Company (TEPCO) and its contractors, policemen, fire fighters, members of Self-Defense Forces, etc. According to the available data published on the website of TEPCO, the maximum and average cumulative effective doses until December 31, 2012 among TEPCO and its contractor workers were about 680 and 12 mSv, respectively, which are much lower than those among the Chernobyl recovery operation workers as shown in Fig.1. For TEPCO and its contract workers, a long-term health care system was designed by the Ministry of Health, Labour and Welfare (MHLW) of Japan, and it is implemented by law. Under this health care system, data on radiation doses and health examination results for these workers are stored in a database at the MHLW. However, less attention has been paid to radiation exposures and associated health risks among the other emergency and recovery operation workers, and information on the levels of radiation doses among them is not officially available.

Numerous epidemiological studies have been conducted by

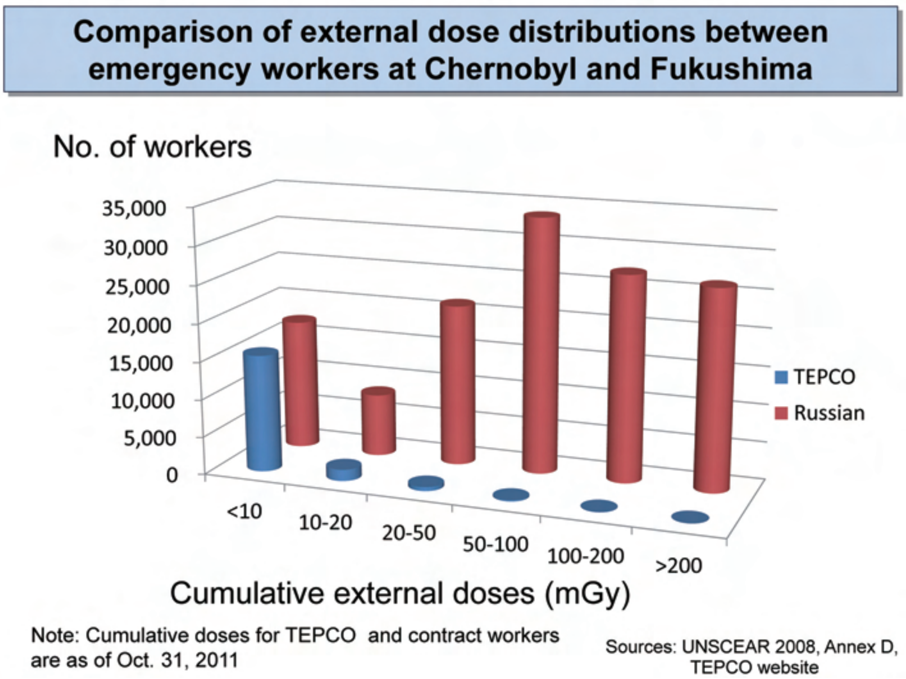

Fig.1

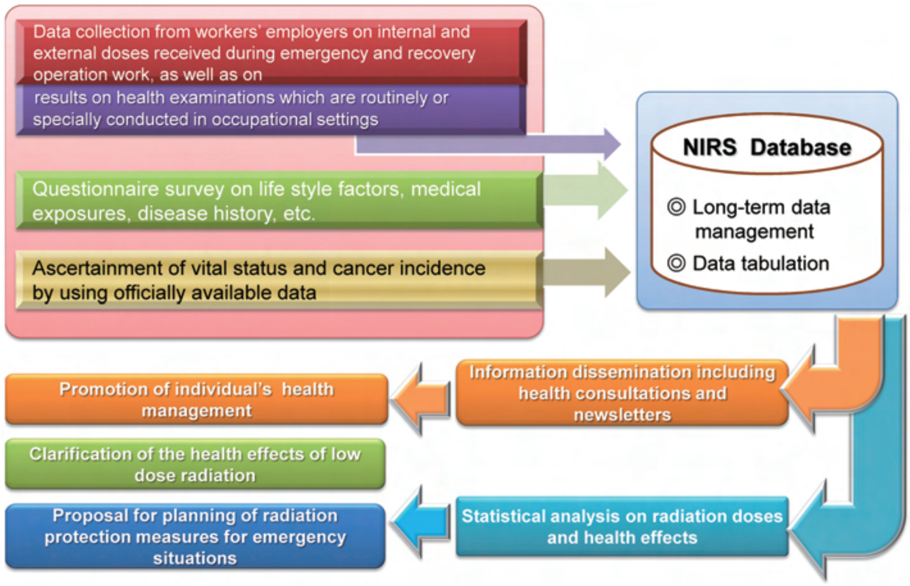

Fig.2

using the national registries for Chernobyl emergency workers as well as for the general public in Belarus, the Ukraine, and the Russian Federation. These studies show that there are increased risks of several diseases including leukemia and cataracts among workers who received higher doses, and thyroid cancer among people who were exposed during childhood and adolescence at the time of the accident. For the emergency workers of TEPCO and its contractors as well as for the general public, the World Health Organization has published two reports on preliminary dose estimation and on health risk assessment resulting from the accident in Fukushima Daiichi NPP. Although the level of radiation doses for the workers involved in the accident seems to be too low to detect any demonstrative increase of health effects, workers' health is likely to be a matter of social concern as well as a matter of each individual's own concern. There has no such survey for the emergency and recovery operation workers while the Fukushima Health Management Survey for residents of Fukushima has been initiated by Fukushima Prefecture in order to monitor their long-term health, promote their future well-being, and investigate health effects of chronic exposure to low dose radiation. In cooperation with experts in various fields from other institutes and universities in Japan, we have designed a follow-up project for those workers involved in emergency and recovery operations after the Fukushima Daiichi NPP accident as shown in Fig.2.

Data on internal and external doses received during emergency and recovery operation work will be collected from workers' employers. Data on results of regular and special health examinations will be also collected periodically from workers' employers. Based on the lessons learned from studies of recovery operation workers after the Chernobyl accident and other occupational studies which have often shown mixed results, life style factors including smoking, and other possible confounders should be taken into account. In the planned study, we will collect such data using a questionnaire at the beginning of the follow-up and subsequently every 3-5 years. Information on disease history for both cancer and non-cancer diseases will be also collected through the same questionnaire. Mortality and cancer incidence are the main endpoints of the follow-up, so various available sources including vital statistics, cancer registry data, etc. will be used to ascertain the endpoints. These data will be stored in a database at NIRS and be analyzed. Information on the progress of follow-up and related topics will be provided to the workers through newsletters.

In FY 2011-2012, we had discussions with persons in charge of health care of emergency and recovery operation workers at relevant organizations about the importance and feasibility of follow-up, and made an agreement with two organizations for conducting the follow-up. In addition, we have designed the structure and functions, especially in terms of security of the database for long-term follow-up. So far, more than 600 workers have been registered in our database, and most of them have completed the baseline questionnaire survey. Additional workers will be included in the follow-up in FY 2013. The findings from the follow-up study are expected to be reflected in workers' health care, as well as in planning of radiation protection measures for emergency situations.

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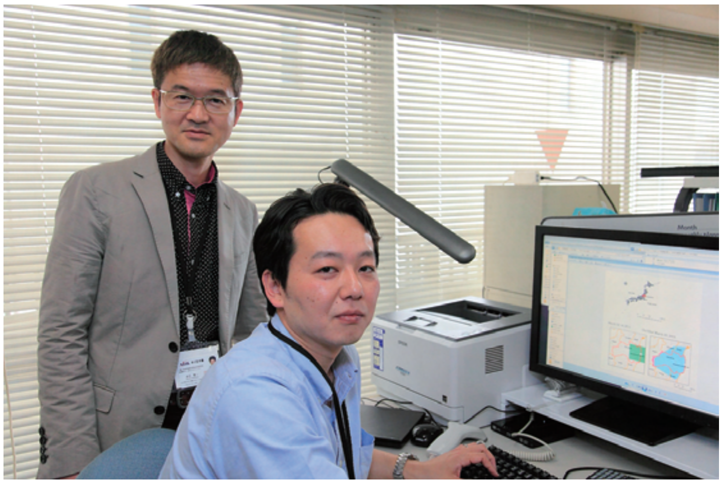
Highlight

NIRS external dose estimation system for Fukushima residents after the Fukushima Daiichi Nuclear Power Plant accident

Shunsuke Yonai
E-mail: yonai@nirs.go.jp



Introduction

After the Fukushima Daiichi Nuclear Power Plant accident, the interest in doses from radioactive nuclides released by the accident has been increasing especially among Fukushima residents. Also, the involved organizations have recognized that it is very important to estimate the doses of residents for proper health management of individuals. NIRS started to develop the external dose estimation system for Fukushima residents at the end of March 2011. At first, this system was developed for the evacuees who had lived in the restricted area, the deliberate evacuation area and the evacuation-prepared area in case of emergency. On the other hand, the Fukushima Prefectural government and Fukushima Medical University decided to do a health management survey for all Fukushima residents (about two million people) at the end of May 2011, to support management of their health conditions which were affected by the accident.[1]. External dose was considered to be one of the necessary items for health management, and the NIRS external dose estimation system was adopted in the survey. Here we briefly describe the algorithm of the NIRS external dose estimation system and the present statuses of the system and the survey.

Algorithm of the NIRS external dose estimation system

In our system, the external effective dose between March 12 and July 11, 2011 can be estimated by superimposing the individual behavior data of each day on the daily dose rate map of that day. The data flow in the external dose estimation system is shown in Fig.1. The behavior data of Fukushima residents were supplied by Fukushima Medical University. These data included: 1) place, i; 2) time to stay at i, t_i ; 3) time to move from i to $i+1$, $t_{move,i\rightarrow i+1}$; and 4) type of building at i, k_i. In practice, t_i was divided into the time to stay in the building at i, $t_{in,i}$ and the time to stay outside at i, $t_{out,i}$.

Daily external dose rate maps used in our system were composed of divisions of approximately 2 km × 2 km (2.5 min in latitude × 1 min in longitude) based on the second mesh (7.5 min in latitude × 5 min in longitude) defined by the Geospatial Information Authority of Japan. The maps were constructed based on two kinds of data. One kind is the hourly effective dose rate maps simulated by the System for Prediction of Environmental Emergency Dose Information (SPEEDI) with the source term calculated by the MELCOR code by the Nuclear and Industrial Safety Agency (NISA),[2], which was used from March 12 to 14, 2011. These data were an alternative to monitoring data, because the number of measurement points was not sufficient to construct the dose rate maps in that period. Since the dose rate maps used in our system were daily maps, they were averaged over a day. Also, the area outputted by this SPEEDI simulation was limited to 98 km × 98 km, which is painted in green in Fig.2, and had the divisions of 1 km × 1 km. Therefore, the dose rate maps generated by SPEEDI were reconstructed by dividing in proportion to the area size of our system with commercially-available mapping software. The other kind of data was monitoring data released by the Ministry of Education, Culture, Sports, Science and Technology (MEXT), which was used between March 15 and July 11, 2011. These data were supplied as a set of numerical values by MEXT. The monitoring data, which were scattered in the map, were converted to spatially-continuous data by using the Natural Neighbor method and then the daily dose rate in each division of approximately 2 km × 2 km was obtained by averaging the values in that division. Since the monitoring data by MEXT did not cover some seaside and boundary areas between Fukushima and Niigata Prefectures (pink-colored areas in Fig.2), the values of their neighbor on the right or left were used alternatively. As a result, our system can estimate the dose received in the area painted in pink and blue in Fig.2 after March 15, 2011. Unfortunately, the monitoring data on March 15 were not sufficient to construct the dose map. On the other hand, these SPEEDI results could not simulate the available monitoring data completely. Therefore, the dose rate map on March 16 was used for that on March 15. We confirmed

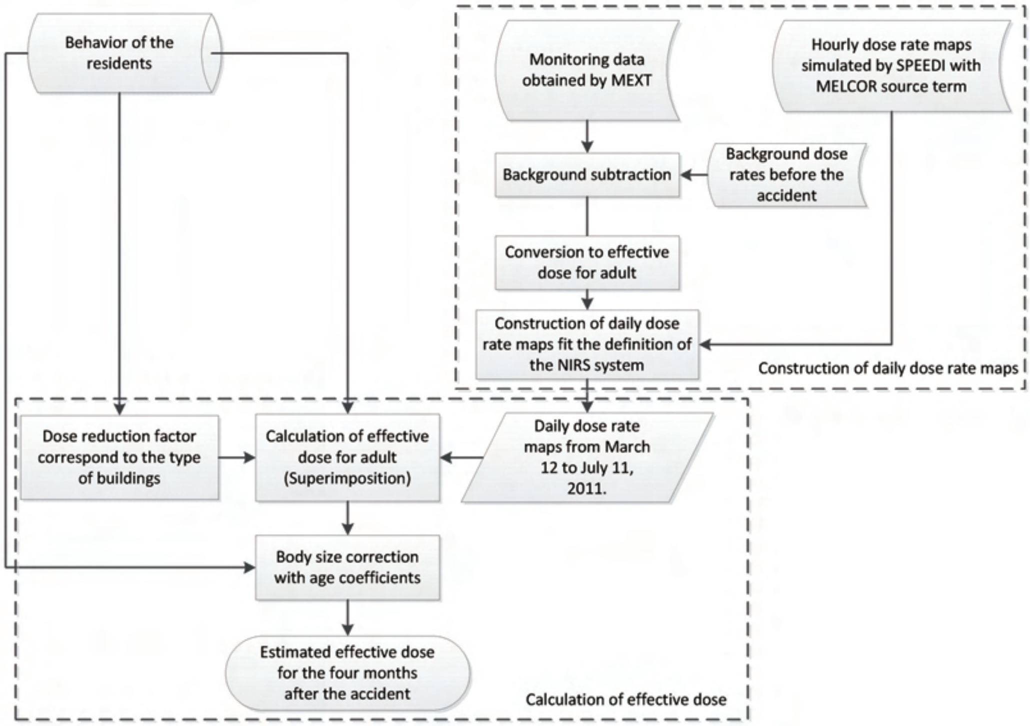


Fig.1 Data flow in the NIRS external dose estimation system. (Sci. Rep, 3, 1670, 2013)

Fig.2 Areas of dose rate maps used in the NIRS external dose estimation system. (Sci. Rep, 3, 1670, 2013)

that the alternative approach did not lead to a significant underestimation by comparing results with the available monitoring data. In fact, it led to an overestimation at most points. Moreover, two corrections were performed for daily dose rate maps between March 15 and July 11, 2011: background subtraction and conversion from ambient dose equivalent to effective dose for adult. The background dose rate of 0.03 μSv/h (in effective dose) was used for the background subtraction, which was the median value reported by Fukushima Prefecture before the accident. The monitoring data were multiplied by the conversion coefficient from ambient dose equivalent, $H^*(10)$ to effective dose for adult, E. The conversion coefficient was calculated for the main radionuclides discharged from the Fukushima Daiichi NPP, which was expected to contribute to the external dose, based on E/ϕ for isotropic irradiation (ISO) and $H^*(10)/\phi$ shown in ICRP Publication 74. As a result, the value of 0.6 was adopted as the conversion coefficient in our system, which was the rounded value of 0.59, the maximum value among the radionuclides. Finally, the effective dose rate maps (for adult) were obtained as a function of time and location, $d(h,m)$, where h and m are the date and the division number, respectively, in a time series from March 15 to July 11, 2011 in all parts of Fukushima Prefecture and a part of four neighboring prefectures (Miyagi, Yamagata, Tochigi, and Ibaraki).

The external effective doses were calculated for three different situations: staying indoors/outdoors and moving from one place to another. When a person stays indoors, the dose reduction should be considered because buildings have a shielding effect against radiation exposures depending on their material and thickness of the walls. In IAEA TECDOC 225, representative reduction factors for cloud, r_c, and ground, r_g, sources are shown. From March 12 to 14, radionuclides in the plume released from the power plant contributed to the dose rates in the environment. On the contrary, on March 15 radionuclides on the ground were major sources of the exposure dose rates because of rain or snow falls in Fukushima. Therefore, in our system, the reduction factors for cloud source in TECDOC 225 were used between March 12 and 14, and the factors for deposited radioactivity were used between March 15 and July 11, 2011.

Dose rates during a move may change depending on the location. In our system, the dose during a move is simply calculated as the product of averaged value of effective dose rates in the regions before and after the move and the time of the move. Then, the effective doses on the date, h, for stay and move ($E_{stay,h}$, $E_{move,h}$) can be expressed as the following equations, respectively,

$$E_{stay,h}=\sum_{i}\{d(h,m(i))\times[t_{in,i}\times r_{c/g}(k_i)+t_{out,i}]\}$$

$$E_{move,h}=\sum_{i}\left\{\frac{d(h,m(i))+d(h,m(i+1))}{2}\times t_{move,i\rightarrow i+1}\right\}$$

where the division number including the place, i is $m(i)$, and the dose reduction factor correspond to the type of the building, k_i is $r_{c/g}(k_i)$. Finally, the effective dose from March 12 to July 11, 2011, E, can be obtained with the following equation.

$$E=\sum_{h}(E_{stay,h}+E_{move,h})$$

Additionally, a body size correction was performed by Fukushima Medical University using age coefficients supplied by us, because the external effective dose depends on body size even in the same radiation field due to the self-shielding effect. The age coefficients, C_{age}, for the main radionuclides discharged from the Fukushima Daiichi NPP, could be obtained from the ratios

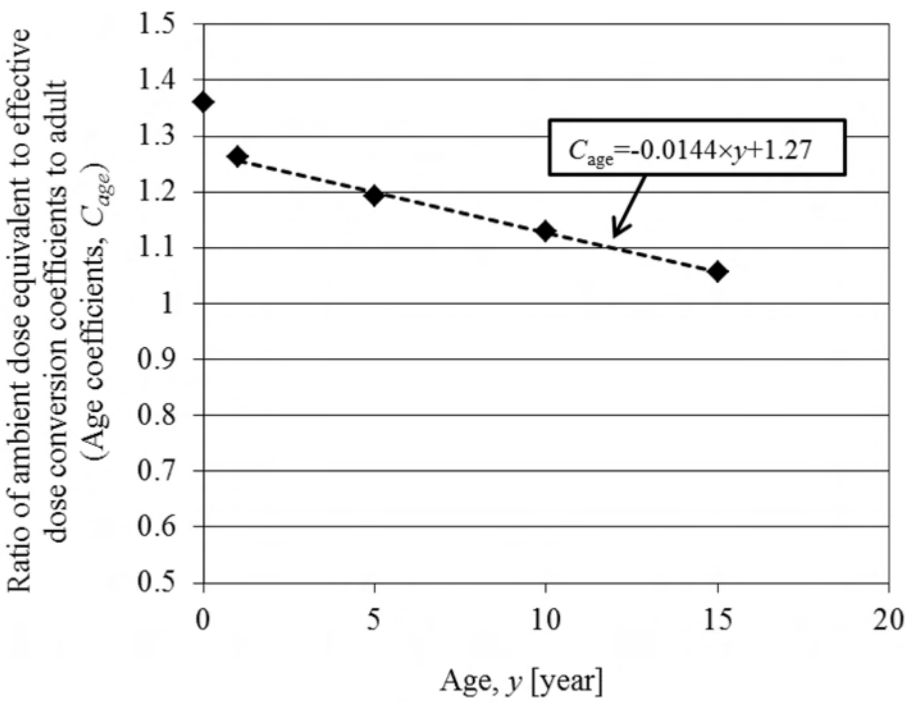


Fig.3 Ratios of ambient dose equivalent to effective dose conversion coefficients for each age group to adult (Age coefficients, C_{age}). The maximum values in the main radionuclides released from the Fukushima Daiichi NPP were adopted.

of ambient dose equivalent to effective dose conversion coefficients for children to adult calculated based on published data[3] as shown in Fig.3. By adopting the maximum values among the radionuclides, age coefficient for infants was 1.36 and age coefficients in the age range from 1 to 15 years old could be expressed as the following linear function of age, y.

$$C_{age} = -0.0144 \times y + 1.27$$

Present statuses of the system and the survey

NIRS and Fukushima Medical University reached a work consignment agreement regarding the external dose estimation for Fukushima residents in April 2012, and since then our system has been used only for the Fukushima health management survey. Fukushima Medical University digitizes the questionnaire results on behavior of the resident, and the digitized outputs without personal identifiable information are sent to us. To date, we have completed effective dose estimations of about four hundred thousand residents, which represent all the data sent to us by Fukushima Medical University, with our system. The estimated results were provided to the Fukushima residents individually by Fukushima Medical University, and a summary was sequentially reported by the Commission on the Fukushima Health Management Survey.

Conclusion

We developed the NIRS external dose estimation system for Fukushima residents to estimate the external effective doses for the first four months after the Fukushima Daiichi NPP accident. This system has been adopted in the Fukushima Health Management Survey, and the estimated results were provided to the Fukushima residents, individually. The estimated results include various uncertainties such as the vagueness of the residents' memories; however, our dose estimation can be very useful as the first approximation of the external effective doses to Fukushima residents by the accident.

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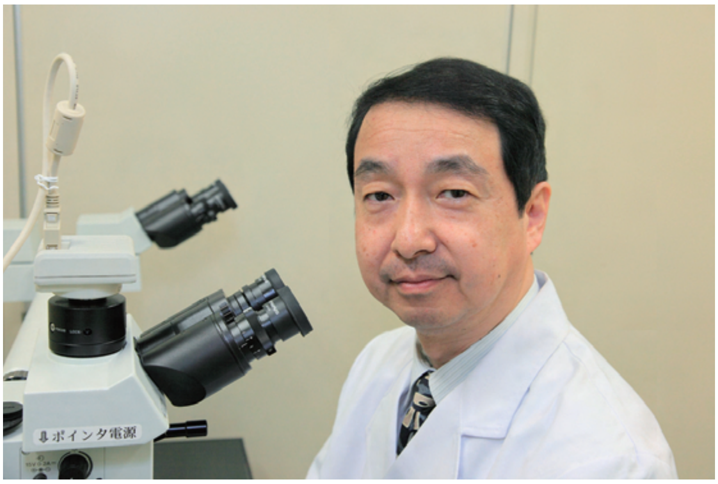
Highlight

Research project for biological effects of low-dose-rate radiation and risk mitigation

Yutaka Yamada, Kimihiko Sugaya, Tatsuhiko Imaoka, Takamitsu Morioka, Yi Shang, Shizuko Kakinuma, Yoshiya Shimada
E-mail: yt_yamad@nirs.go.jp



The residents of Fukushima Prefecture have been suffering psychologically, economically and socially from the accident at TEPCO's Fukushima Daiichi Nuclear Power Plant, which happened in 2011. Specifically, people who live in areas of high background levels of radiation feel uneasy about their health. Attention is, in particular, focused on unborn children and young children. With the current radiation protection system, it is assumed that the dose of low-dose-rate radiation accumulates, but with the reduction factor (dose and dose-rate effectiveness factor: DDREF) of 2. However, the following questions remain unresolved: 1) Is the dose-rate effect for children the same as that for adults? 2) Can the dose-rate effect be explained in part by the reduced accumulation of radiation-induced damage in stem (progenitor) cells or elimination of damaged stem cells? 3) Could the cancer risk after childhood exposure be reduced by subsequent control of diet?

The purpose of the project described here is to elucidate the effects of low-dose-rate radiation and its underlying mechanism, and then to provide possible measures to mitigate the risks based on findings using animal models. At first, the effects of the low-dose-rate radiation on life shortening and cancer induction are examined for juvenile exposure in comparison with adult exposure. Secondly, the accumulation of radiation effects in the stem cells of the skin and mammary glands is evaluated. Thirdly, inhibitory effects of calorie restriction and anti-oxidant food ingredients on radiation-induced cancer are investigated.

Long-term animal experiments have become considerably difficult to perform on a large-scale, because of financial and ethical reasons. Unfortunately, many local archives of the past animal experiments have been lost when investigators retired. In the 1990s, however, animal samples were collected into shared international archives for future re-examination of data using novel methods or hypothesis; re-examination now would facilitate the effective utilization of research resources in the U.S, Europe and Japan. Samples and the data provided by the present project will be incorporated into these international archives, and be available in collaborative investigation with domestic and foreign research organizations.

Risk analysis for effects of low-dose-rate exposure

Male and female B6C3F1 mice in the juvenile (1 week of age) and adult (7 and 15 weeks of age) stages were gamma-irradiated at low-dose-rate for 4 consecutive weeks, and life shortening and incidence of leukemia and solid cancers are being investigated. The dose rate was 0.026 mGy/min and 0.105 mGy/min (total exposure dose of 1 Gy and 4 Gy, respectively) (Fig.1). The effect on the induction of mammary tumors (SD rats) and brain tumors (*Ptch1*$^{+/-}$mice) is also being examined. The dose-rate effectiveness factor (DREF) will be estimated in comparison with the data of single irradiation exposure. The survival of these animals is now being followed.

Accumulation of radiation effects on tissue stem cells

The present radiological protection system assumes full accumulation of the stochastic effect (especially, induction of carcino-

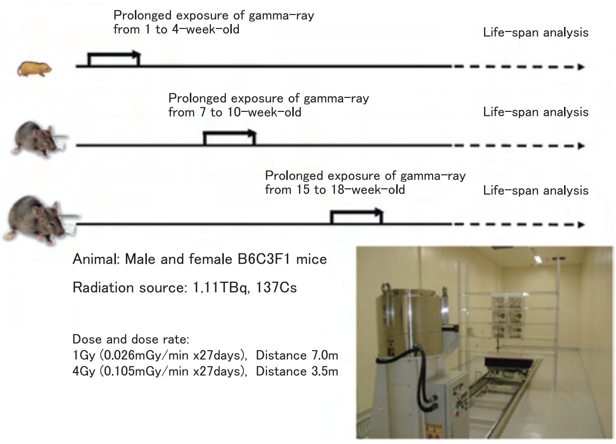


Fig.1 Experiment design and set-up of low-dose-rate exposure

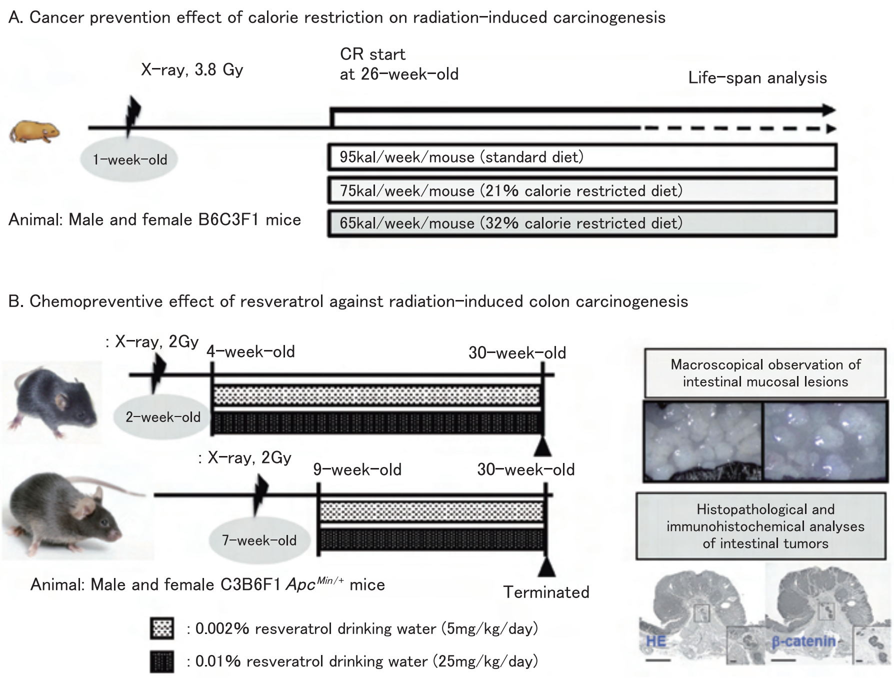


Fig.2 Experiment designs. (A) Calorie restriction, (B) Resveratrol

genesis) of ionizing radiation. Given that long-lived tissue stem or progenitor cells are the targets of radiation carcinogenesis, this model system seems reasonable. This means that continuous radiation exposure at low dose rate should impose small but significant health risks. However, epidemiologic studies do not necessarily support this idea. In addition, it was recently hypothesized that the radiation effects after chronic exposure do not accumulate in proportion to the cumulative dose when tissue turnover rate or radiation-induced change in self-renewal activity is taken into account.

1) Study on the damage response of hair follicle stem cells

Hair follicles are self-renewing structures that reconstitute themselves through three cycling stages: anagen (growing phase), catagen (regression phase) and telogen (resting phase). Differentiating keratinocytes constitute the hair matrix with mature melanocytes, pigment-producing cells. Recent findings indicate that keratinocyte and melanocyte stem cells reside in the bulge area of the hair follicle. It is expected that the effects of damage in keratinocyte and melanocyte stem cells in the telogen stage of the first hair growth cycle can be detected as the phenotype of descendant hair follicle structure in the anagen phase of the second hair growth cycle, since newly formed hair follicles are derived solely from keratinocyte and melanocyte stem cells. To study the accumulation of effects by irradiation, 22 to 24-day-old C57BL/10 JHir (B10) mice were exposed to gamma-rays of ^{60}Co, and the radiation effects were examined on 35 to 37-day-old B10 mice. The number of hair follicles and the pigment production in hair bulb are established as the criteria.

2) Study on the cell kinetics and modeling of mammary stem cells

Another focus of study is on the effects of radiation on mammary stem cells. The mammary gland is a highly susceptible organ to radiation induction of carcinogenesis and its stem cells are enriched in a culture of mammary epithelial cells on a non-adherent substrate ('mammospheres'). It is hypothesized here that radiation exposure not only induces oncogenic mutations but also increases the probability of losing self-renewal activity or increases the chance of undergoing differentiation of stem cells, which may lead to a relative decrease in the chance of maintaining affected stem cells. The first goal is to provide a new model using the mammosphere system, which can evaluate the behavior of irradiated stem cells during continuous radiation exposure.

Mitigation of cancer risks from radiation exposure

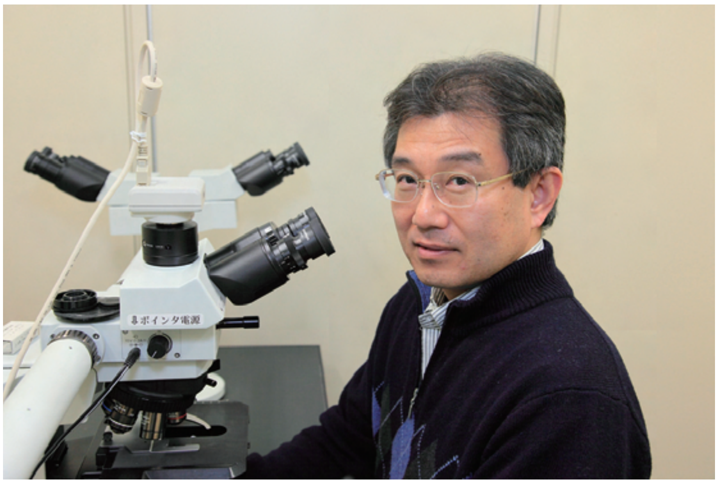
Children are the most susceptible subpopulation to radiation carcinogenesis. After the TEPCO Fukushima Daiichi NPP accident, people became worried about the long-term health effects on children, especially children who live in areas affected by the release of large amounts of radioactive materials. Therefore, it is important to lay a special emphasis on finding a useful remedy to prevent carcinogenic effects of radiation on children.

Calorie restriction (CR) is known to extend the life span and prevent the major causes of morbidity and mortality including cancer. Thus, it may be one of the most potent interventions for decreasing deleterious effects of radiation. Then attention is given to investigating the cancer preventive effects of CR after early-life exposure. Male and female B6C3F1 mice were irradiated with X-rays of 3.8 Gy at one week of age. Then, calorie restrictions of 21% and 32% were started at 26 weeks of age, and will be continued for the natural life span. The life span, incidence and spectra of tumors will be clarified (Fig.2A).

Phytochemicals, a wide variety of compounds produced by plants, are known to prevent many health conditions, including cancer. Resveratrol, a phytochemical, has been demonstrated to have properties that mimic CR. The inhibitory action of resveratrol on early-life exposure to radiation-induced carcinogenesis is being investigated using the mouse model of familial adenomatous polyposis. Male and female C3B6F1 *Apc*$^{Min/+}$ mice were irradiated by X-rays of 2 Gy at 2 and 7 weeks of old, and administration of resveratrol was started 2 weeks after the irradiation. All mice will be autopsied at 30 weeks old, and the preventive effects of resveratrol will be evaluated (Fig.2B).

Research on Evaluation of Medical Exposure

Yoshiya Shimada, Ph.D.
Director, Medical Exposure Research Project
E-mail: y_shimad@nirs.go.jp



In this midterm plan at NIRS, the Medical Exposure Research Project (MER-project) has the mission to investigate the frequencies and doses of domestic medical radiation uses and to summarize the current status worldwide concerning radiation protection in medicine. Based on the dose data together with basic and epidemiological data, medical radiation risk will be estimated. The results will be put into a database. By sharing the data among the involved medical staff and researchers, the MER-project will contribute to provide the scientific and practical basis for the justification and optimization of radiation protection in medicine. These data are supposed to be submitted to the UNSCEAR.

To achieve the above plan, five issues have been currently undertaken: 1. Estimations of examination frequencies and organ doses in X-ray CT, PET, PET/CT, and heavy ion particle therapy; 2. Establishment of an organization for the collection of domestic data on radiation protection in medicine; 3. Estimations of secondary cancer risk of the patients in cervical cancer treatments; 4. Study of radiobiology in radiation use in medicine; and 5. Development of the method for risk-benefit communications in medicine.

For the estimation frequencies and organ doses, the data of X-ray CT examinations for pediatric patients have been collected from DICOM data in the National Center for Child Health and Development (NCCHD) Hospital in cooperation with doctors and radiologists in that hospital by using a program specially developed for this purpose. In Chiba Children's Hospital, the data have also been extensively collected and the data for the recent 4 years on CTDI, DLP and so on were summarized. Phantom measurements of organ doses have been continued in both two hospitals as the basic data for optimization.

For PET diagnoses, the basic physiologically-based pharmacokinetic model (PBPK model) was made to consider the physiological differences among patients.

For heavy ion therapy, dose estimations of patients due to secondary exposures were estimated based on the data of both measurements and Monte Cario simulations.

For the secondary cancer risk estimations in radiotherapy of cervical cancer, organ dose distribution is to be estimated. Gel dosimeters were selected in order to obtain 3D distribution of dose, and the fundamental data on the characteristics of the gel were experimentally obtained. Based on the data of CT images of more than 100 patients, a physical pelvic phantom was developed. The analyses of secondary cancers of 286 cases among 4,181 patients are being performed.

On radiobiology in medical exposures, the differences of the patterns of DNA breaks and repairs were studied in a comparison between young and adult mice. It was found that the speeds of DNA repairs of bone marrow in infant mice were faster than those of adult mice.

Online and off-line data collection system were under development for establishment of the system to follow-up the medical radiation exposure histories of the patients, which is the concept of the IAEA's "Smart Card/SmartRadTrack project".

For the nation-wide exchange of the information on medical exposures, two general meetings of the Japan Network for Research and Information on Medical Exposure (J-RIME) were held in April 2012 and in January 2013. Four working groups (Protection for pediatric patients, Smart Card system, Nationwide survey, and Publicity) were organized in J-RIME and they have been working on various tasks. The J-RIME has published the newsletter "Limelight" three times until the end of the FY2012.

For risk communications, the draft of a pamphlet for mothers of young children was made based on information identified as necessary by medical staff in Chiba Children's Hospital.

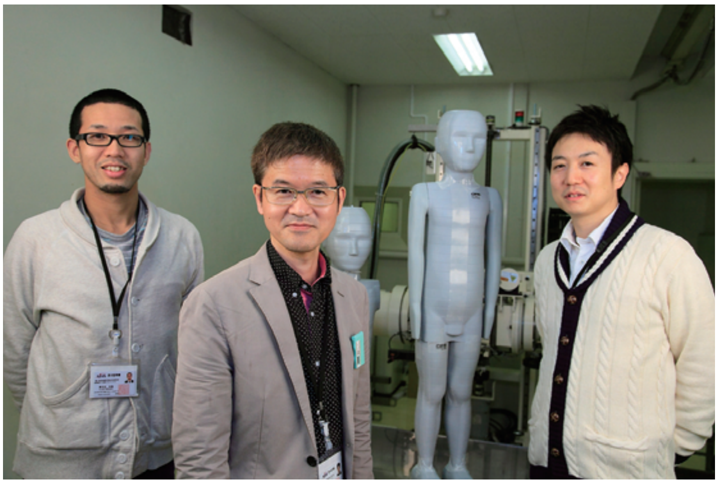
Fig.1 The 4th plenary meeting of J-RIME

Fig.2 Newsletter of J-RIME

Highlight

Investigations on frequencies and doses in X-ray CT examinations in pediatric hospitals

Keiichi Akahane
E-mail: akahane@nirs.go.jp



X-ray CT examinations are the major sources of radiation exposures in medicine for patients. Among them, more attention should be paid to pediatric patients because of their higher radiation sensitivity compared to adults. As one of the research issues of the Medical Exposure Research Project (MER-project), an investigation on frequencies and doses has been performed in two pediatric hospitals, the National Center for Child Health and Development (NCCHD) Hospital, and Chiba Children's Hospital. In addition, dose measurements have also been done by using pediatric anthropomorphic phantoms and glass dosimeters in these hospitals.

In the NCCHD Hospital, about 4,000 X-ray CT examinations are performed every year. For this study, the data of about 40,000 examinations for 10 years were selected. Original software has been developed and applied in the NCCHD Hospital to automatically collect data on the kinds of diagnoses, and patients' data such as gender, age, etc. from DICOM-tag information. In FY2012, the data of the period from May 1st 2002 to February 29th 2012 were extracted and put into the database. For example, the numbers of patients extracted were 163 for 214 chest examinations and 151 for 194 abdomen (pelvis) examinations in 2010. Fig.1 shows the numbers of patients for each age less than 16. The percentage of examinations for head was about 47% of the total examinations.

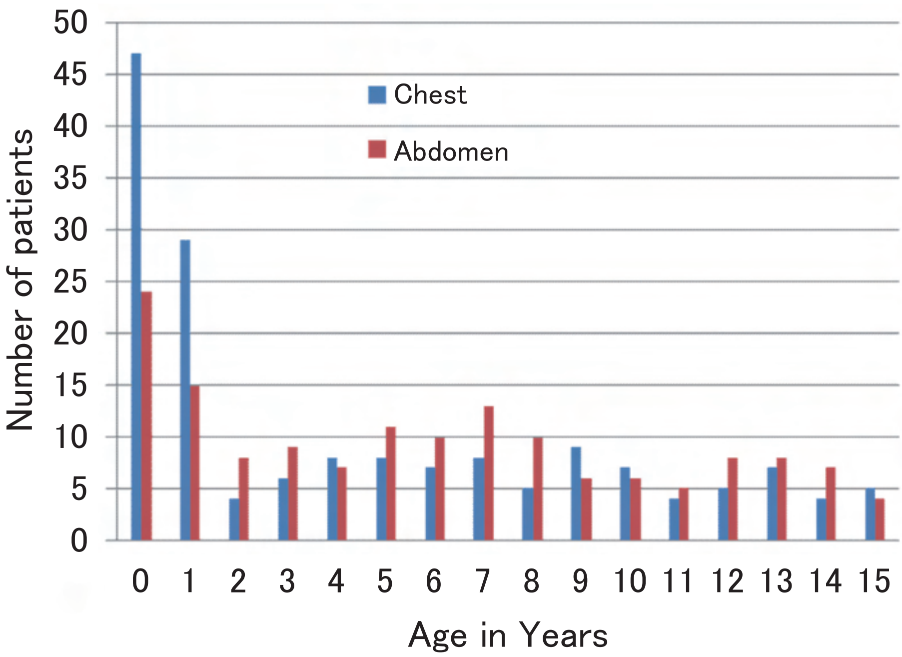


Fig.1 Numbers of patients for each age at NCCHD, 2010.

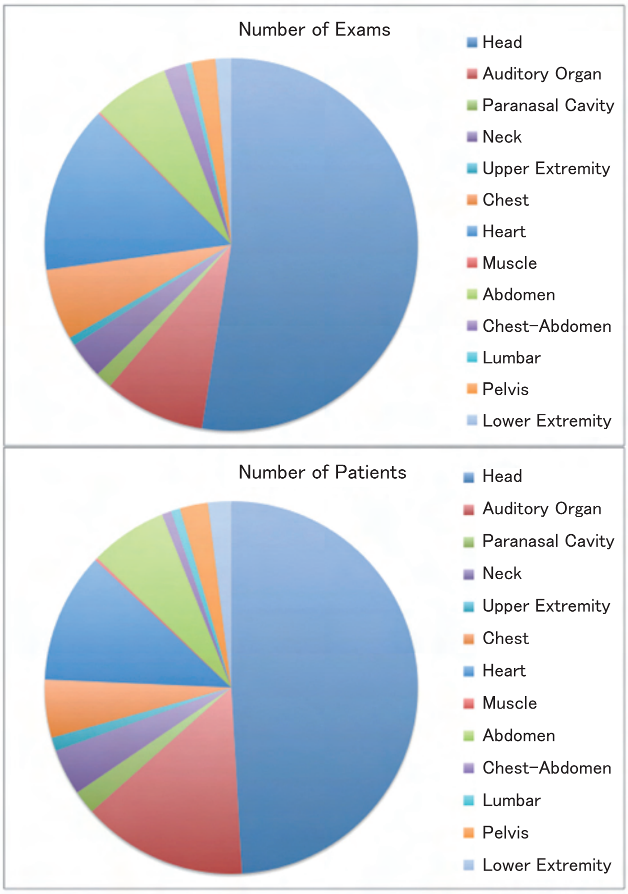


Fig.2 Numbers of examinations and patients in Chiba Children's Hospital

The examinations for abdomen were about 26% of the total, and about half of them were for patients less than 1 year old.

In Chiba Children's Hospital, the number of X-ray CT examinations is about 1,600 per year. About 40,000 exams for 4 years were set for the data analyses. The number of X-ray CT examinations performed in the period from October 2008 to July 2011 was 4,801 (male, 2,767; female, 2,034), and the number of the patients was 2,546 (male, 1,443; female, 1,103) (Fig.1). The largest number of the examinations was for head CT, about 52.5 % of all examinations. The second largest was CT for auditory organs, about 8.7 % of the examinations. The ratios of the numbers of patients were similar to those of the examinations (Fig.2).

Fig.3 Organ dose measurements using anthropomorphic phantoms and glass dosimeters

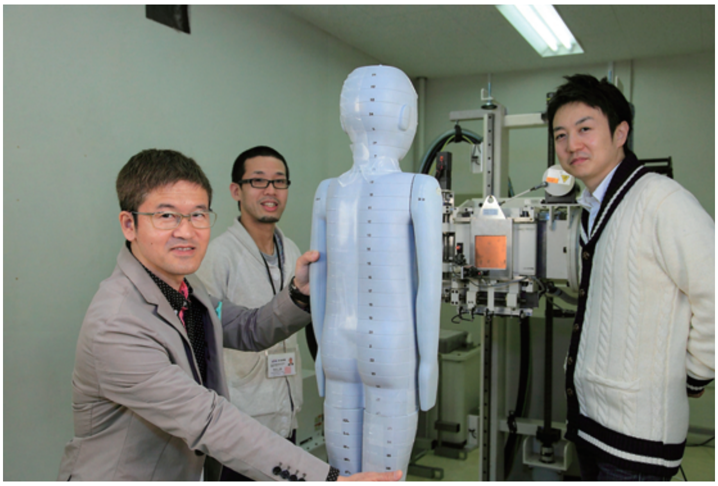
The organ doses in CT examinations were also planned for considering optimization in radiation protection. By using anthropomorphic pediatric phantoms and glass dosimeters, organ doses have been directly measured under the exposure conditions in daily uses in NCCHD hospital (Fig.3).

These data will be referred to in establishing the diagnostic reference levels for pediatric patients in CT examinations.

Highlight

Estimations of pelvic organ doses in brachytherapy for cervical cancer patients

Keiichi Akahane
E-mail: akahane@nirs.go.jp



Radiotherapy is one of the effective methods for cancer treatments. On the contrary, the secondary cancer incidents have come to be a problem as the survival ratio is increasing in radiotherapies. In NIRS, follow-up for cervical cancer patients has been performed and data on these patients have been stored in a database. For risk estimations of secondary cancers of the organs of not only near but also in the outer region of the cancer, the development of a pelvic phantom was planned that consisted of gel dosimeters, bone equivalent material and PMMA. The data of three-dimensional dose distributions can be obtained using the gel dosimeter.

As a first step, the basic characteristics of the gel dosimeter have been studied. The gel dosimeter was made based on the standard protocol, and put into a water phantom. The phantom was irradiated with Ir-192 gamma rays to study the linearity of dose response comparing with glass dosimeters (Fig.1). After the irradiation, the phantom was scanned by using MRI. Basically, the linearity was confirmed at dose levels of less than 10 Gy (Fig.2).

In the second step, the effects of the wall width of the phantom and permeating oxygen through the wall were observed by using several cylindrical phantoms having different wall widths, because oxygen interferes with the gel phantom measurements. As a result, the MRI artifacts were about 5mm in size , and the effects of oxygen were seen at distances less than 5mm from the wall (Fig.3). For reading of doses in the gel phantom, the volume at a distance of 5mm or less from the wall should be excluded.

Since air is present inside the intestines of patients, as the third

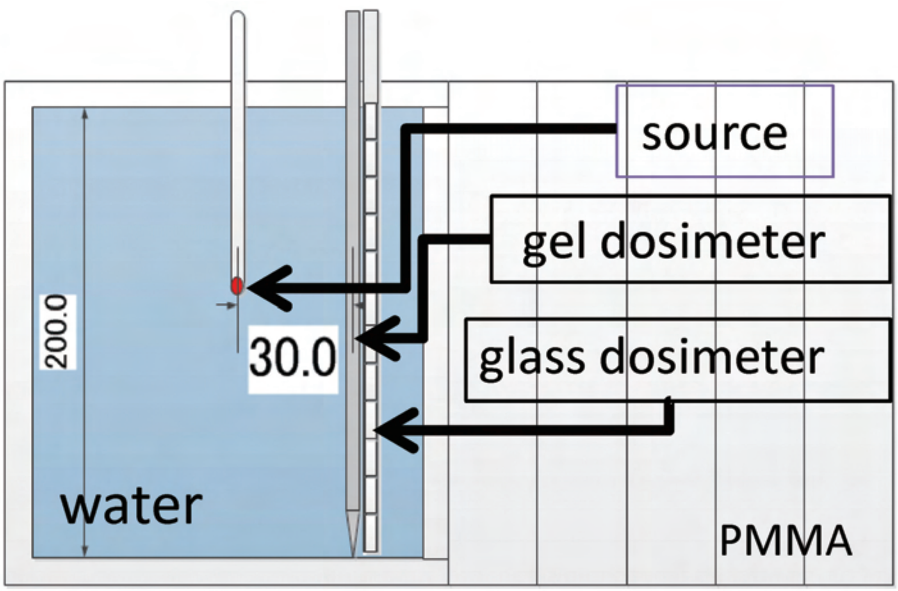


Fig.1 Geometry of the phantom for the measurement of dose range

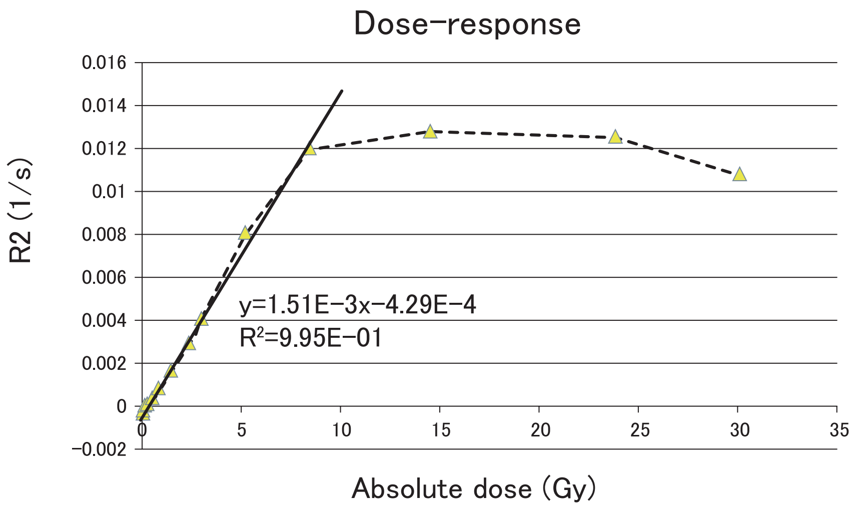


Fig.2　Linearity of the GEL phantom

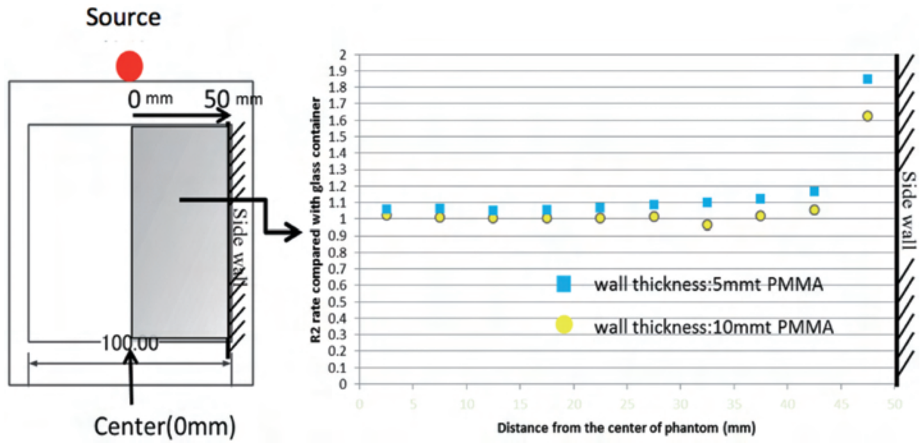


Fig.3　Effects of the wall width of the phantom and permeating oxygen

step, the effects for dose distributions were measured setting CaSO4 as the pelvic bone and air as the gas inside the rectum (Fig.4). The doses of glass dosimeters were similar compered to those of the radiotherapy planning system in the region with no air. The dose maps (distribution) in Fig.5 show a comparison between the system behid (left) and frontforward area (right) around the air region. The doses were about 10 % lower than those of the system behind the air region (Fig.5).

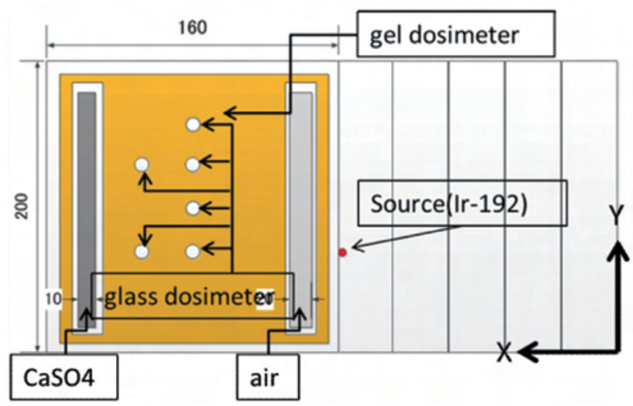


Fig.4　Geometry of the phantom with CaSO4 and air inside

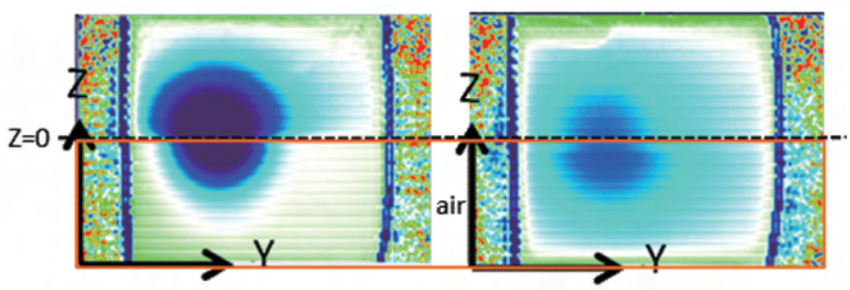


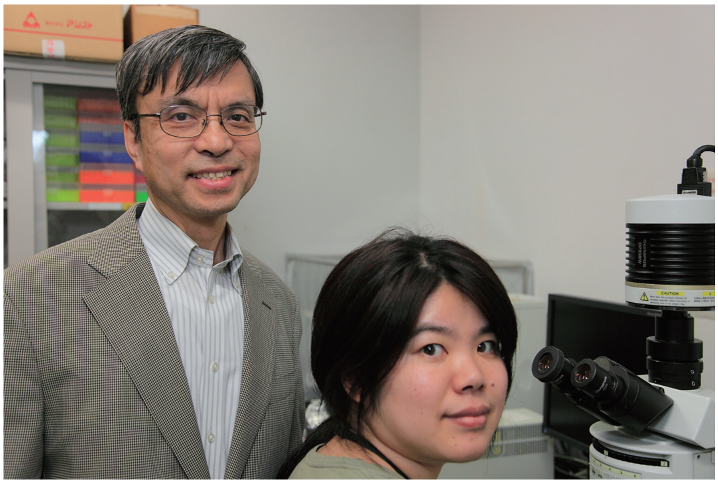
Fig.5　Dose distributions obtained by using gel dosimeter inside the phantom with CaSO4 and air inside

International Open Laboratory

Ryuichi Okayasu, Ph.D.

Scientific Secretary

E-mail: rokayasu@nirs.go.jp



History:

The history of the NIRS International Open Laboratory (IOL) starts in 2008. In March that year, the International Advisory Board which includes internationally renowned research scientists, recommended NIRS have a structure to promote international collaborations with highly regarded scientists from abroad. After various discussions and much planning, the first term of the IOL started in November 2008 with three research units. In particular two persons greatly contributed to this new establishment, namely Dr. Hirohiko Tsujii, then Executive Director for Research and Dr. OhtsuraNiwa, then Deputy Center Director for the Research Center for Charged Particle Therapy. Dr. Tsuiji was particularly keen to start IOL by actively adding this new entity to the NIRS system and Dr. Niwa greatly contributed to the selection and invitation of the worldly recognized scientists. NIRS selected three units for the first IOL term and each unit had a unit leader and a collaborating distinguished scientist. The following units were active for the first IOL term (2 years and 4 months) which ended in March 2011, coinciding with the end of the five year mid-term plan for the whole institute:

1. Particle Therapy Model Research Unit: Prof. Anders Brahme (Karolinska Institute, Sweden), Distinguished Scientist, and Dr. Takeshi Murakami (NIRS), Unit Leader
2. Molecular Particle Radiation Biology Unit: Prof. Penny Jeggo (Sussex University, U.K.), Distinguished Scientist, and Dr. Ryuichi Okayasu (NIRS), Unit Leader
3. Space Radiation Research Unit: Prof. Tom K. Hei (Columbia University, USA), Distinguished Scientist, and Dr. Ukio Uchihori (NIRS), Unit Leader

These first three units actively pursued collaborations with respective foreign institutes under the supervision of the foreign distinguished scientists and produced various useful results. As a result of these efforts, all of the three units obtained "excellent" overall status in the evaluation meeting which was held in June of 2011 with the international review board members. Each unit hold frequent workshops in English with the respective distinguished-scientist, and these workshops were well-attended by NIRS employees as well as researchers from outside NIRS.

Current IOL Status:

The second IOL term started in April 2011 with four research units and it will last for three years. These units were chosen from campus-wide applications at NIRS and they are actively pursuing their collaborative research with foreign institutes at this point. One unique feature for IOL this term is that most of the funding is from donations from the general public and we are particularly thankful to the Chang Yung-Fa fund for their substantial contribution.

The organization of IOL this term is shown Fig.1. Three professors (Profs. Hei, Brahme and Jeggo) are continuing for the second term, and two new professors, Prof. Jac Nickoloff (Colorado State University, USA) and Prof. Marco Durante (GSI, Germany), joined IOL as Distinguished Scientists. The new Director of IOL is Dr. Makoto Akashi, Executive Director for Research at NIRS. The first general meeting, "IOL Research Seminar" was held in November 2011 (Fig.2) and was well-attended;all of the five distinguished scientists were able to attend the conference and very fruitful discussions were had among the audience and speakers. Around this time in 2011, Columbia University and NIRS signed a Memorandum of Understanding (MOU) in the pursuit of further active collaborations in the area of heavy ion therapy and space radiation research; IOL, particularly the Space Radiation Research Unit, played a great role in the signing of this document as the major areas of IOL research are the applications of heavy ions produced in the HIMAC facility here at NIRS. Another highlight of IOL this term is that we were able to hire two appointed scientists for a long period of time:Dr. Walter Tinganelli from GSI, Germanyis staying here more than a year in the Particle Beam Quality Unit,

Director:Makoto Akashi
Vice Director:Tadashi Kamada, Kazuo Sakai
Scientific Secretary:Ryuichi Okayasu
−Chief Advisor:Hirohiko Tsujii−

Space Radiation Research Unit
Prof. Tom Hei (USA)
Yukio Uchihori (NIRS)

Radiation Response Model Unit
Prof. Anders Brahme (Sweden)
Takeshi Murakami (NIRS)

Particle Therapy Molecular Target Unit
Prof. Penny Jeggo (UK)
Prof. Jac Nickoloff (USA)
Akira Fujimori (NIRS)

Particle Beam Quality Research Unit
Prof. Marco Durante (Germany)
Yoshiya Furusawa (NIRS)

Planning Office:Shigekazu Fukuda (Head)
Takashi Fujita
Yukari Mizumura

Fig.1 Organization of current IOL

Fig.2 IOL Research Seminar 2011 (November 2011)

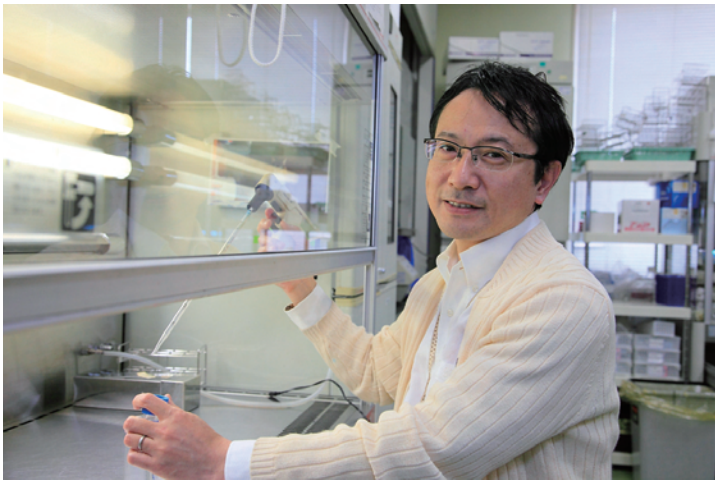
and Dr. Chris Allen, Colorado State University (CSU), USA stayed for eight months in the Particle Therapy Molecular Target Unit. With this new connection to CSU, many graduate students were able to visit NIRS for collaborative experiments. In June of 2012, the NIRS-Colombia University Joint Workshop was held at NIRS hosted by IOL and the Research Center for Charged Particle Therapy, NIRS. Many people attended this exciting conference from all over Japan andthere were many fruitful discussions and exchanges as one of the world's renowned radiation biologists Prof. Eric Hall was invited as a speaker.

In the second IOL term, our name and activities were introduced on the web sites of several foreign institutions such as CERN, Europe and Colorado State University, USA, and the IOL reputation has started to spread internationally. The progress report meeting for the FY 2012 was recently held in January 2013 and had great discussions and exchanges of novel ideas. We do not know what our future holds, but our IOL activities thus far have substantially contributed to the internationalization and improvement of research quality at NIRS.

Highlight

Particle therapy molecular target unit, International open laboratory

Akira Fujimori
E-mail: fujimora@nirs.go.jp



The Particle Therapy Molecular Target Unit was established in 2011 as one of four distinct units under the International Open Laboratory (IOL). It took over a previous international collaboration between Dr. Okayasu (Department Head of the Charged Particle Therapy Research Group) and Prof. Penelope A. Jeggo at the University of Sussex, UK. In 2011, we invited another distinguished scientist, Prof. Jac A. Nickoloff from Colorado State University (CSU), to join us and our unit started as a united team from three international facilities (Fig.1). The specific aim of our research is to study cellular and molecular mechanisms associated with heavy ion irradiation for cancer therapy. Our goal is to clarify the molecular mechanism or determinants of cellular sensitivity to ionizing radiation (IR), particularly to heavy ion particles. In other words, we would like to define important 'target molecules' for particle therapies.

Prof. Jeggo and Prof. Nickoloff are internationally recognized leading scientists in the field of radiation research and molecular biology. Through exchanges with such distinguished researchers, we can work to obtain research outcomes that will promote the use of particle therapy worldwide. Moreover we hope that the present collaboration will 'open' the field of radiation research to more researchers who are concerned with ordinary or different fields of biology.

Because of the 3.11 disasters, the first official IOL meeting was postponed to October 2011. In spite of the tight schedules, all the distinguished scientists were able to gather at NIRS, where everyone had fruitful discussions about experimental approaches with heavy ion particles.

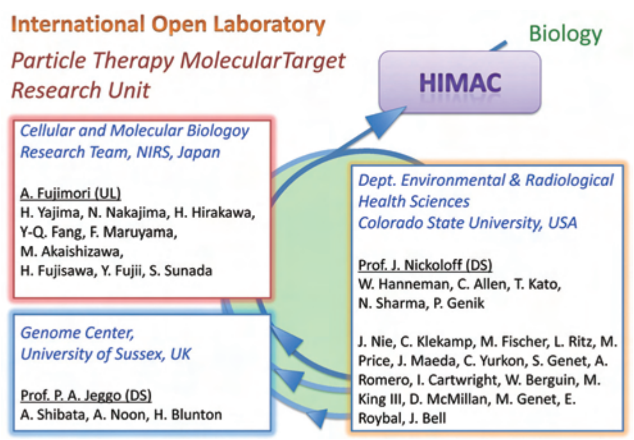


Fig.1 Organization of the Particle Therapy Molecular Target Research Unit.

Since April 2011, we have used HIMAC over 60 times and

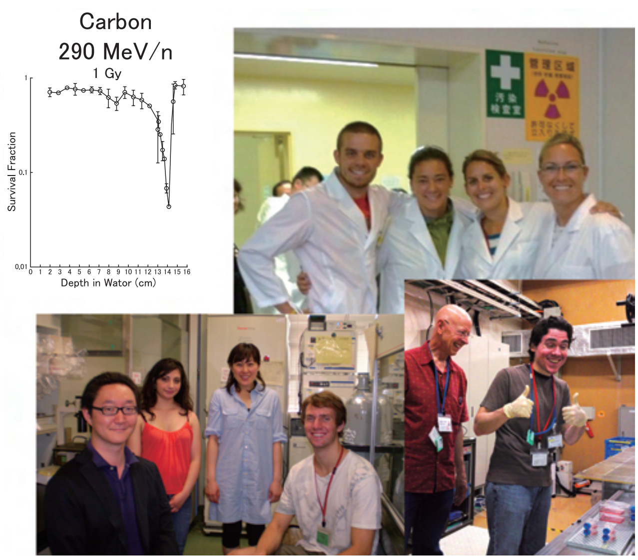


Fig.2 Demonstration of the Bragg peak in biological assays. Pictures of Dr. Kato, Dr. Allen and students from CSU (*Oncol Rep,* 28, 1591-1596, 2012).

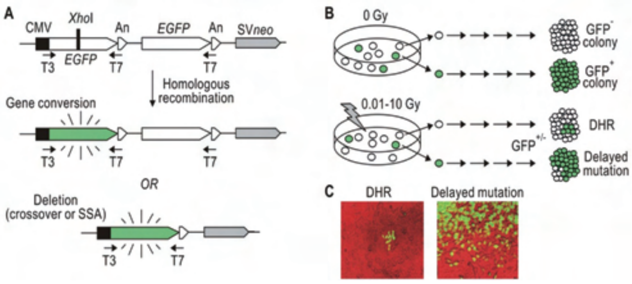


Fig.3 Delayed Homologous Recombination (DHR) induced by low and high LET ionizing radiation in a human cancer cell line [1].

hosted 7 guest researchers and 19 students for running of experiments (Fig.2). Faculty members from both universities gave excellent seminars and Dr. Takamitsu Kato (Assistant Professor, CSU) brought many students to NIRS and guided them in performing biological experiments. The outcomes were published in two papers this year.

In 2012, we invited Dr. Christopher Allen (Assistant Professor, CSU) as an appointed scientist. Dr. Allen stayed in Chiba for 8 months and investigated 'delayed' phenotypes of cell death and mutations, which are induced in cells irradiated with X-rays or particle ion beams. In RKO (colon cancer cells), there is a single copy of a target construct; a couple of tandem-repeated dead GFP genes. One event of homologous recombination (HR) can generate an active GFP gene and repopulate cells with green fluorescence (Fig.3). Similarly to a DNA-double-strand break repair process, the phenotypic conversion happens spontaneously and is induced by IR; however, it can be detected without any targeted DNA strand break and can remain over generations. The RKO system can provide a good model to study how dividing cells lose genome integrity under some stressful conditions [1]. The molecular mechanism under delayed genomic instability (DGI) remains to be clarified. An updated technique using a time-lapse microscope and a cell sorting system will further accelerate our research in the next year.

In the progress report meeting held on January 22, 2013, Prof. Nickoloff presented some highlights from the collaboration as described above. In addition, he referred to the *ASPM* (abnormal spindle-like microcephaly associated) gene as a potential target molecule for future radiation therapy. This conjecture is based on our recent publication, in which we showed that knocking-down ASPM significantly enhanced the radiation sensitivity in glioblastoma cells [2]. Dr. Nakako Nakajima of NIRS presented the characterization of clustered DNA damages resulting from heavy ion particles that can be discriminated from those generated by delta-electrons (Fig. 4). This work was done at the University of Sussex in collaboration with Dr. Atsushi Shibata and Prof. Jeggo. Dr. Nakajima often traveled to Sussex to accomplish the immunocytological analyses using the special confocal microscope in Prof. Jeggo's laboratory. Dr. Hirohiko Yajima of NIRS talked about the resection, an early step in the molecular process of HR followed by DNA double-strand breaks. He demonstrated that phosphorylation of a key molecule CtIP was significantly enhanced in the cells irradiated with higher LET radiation. This can be attributed to a preference of HR over other repair pathways in the surviving cells irradiated with higher LET radiation.

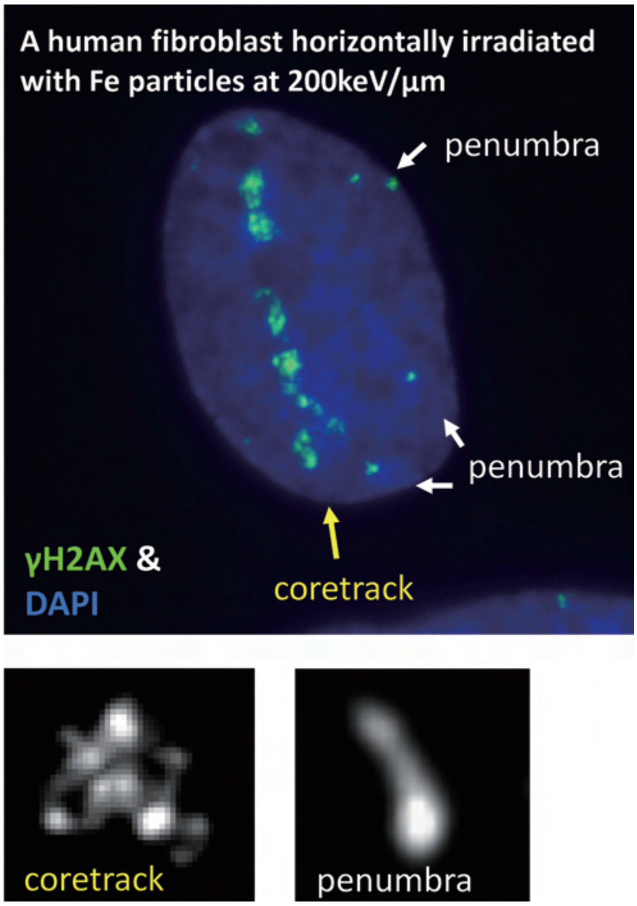


Fig.4 Core track consists of a clusters of γH2AX foci.

Study of biological targets for IR is clinically relevant to radiotherapy. It can strengthen the 'local control' of particle therapy that has been achieved by physical approaches. Cancer biologists are seeking the targets selective to tumor cells. Cellular sensitivity to IR is varied among the cells under different biological situations; cell cycle, circadian, tissue types, stemness or differentiation, etc. A novel cellular response to IR is secretion of prostaglandin E2 (PGE2) in IR-irradiated tissue. There are some tumor cells that repopulate themselves in the chain of PGE2 secretion. This effect is called 'phoenix rising' after the legendary bird that could be reborn [3]. Since the upregulation of PGE2 selectively depends on caspase3, inhibitors of the caspase pathways may control the tumor repopulation. Investigation of 'Phoenix rising' under hypoxic conditions is being undertaken by Dr. Walter Tinganelli, an appointed scientist from the laboratory of Prof. Marco Durante (GSI), under collaboration with the Particle Beam Quality Research Unit.

References

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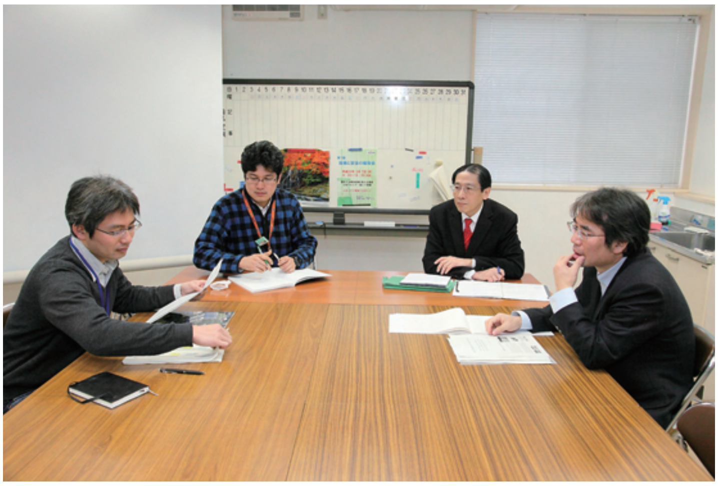
[2] Kato T, Okayasu R, Jeggo PA, *et al.*: ASPM influences DNA double-strand break repair and represents a potential target for radiotherapy, *Int J Radiat Biol,* 87(12), 1189-95, 2011.
[3] Huang Q, Li F, Liu X, *et al.*: Caspase-mediated paracrine signaling from dying cells potently stimulate tumor cell repopulation during cancer radiotherapy, *Nature Medicine,* 17(7), 860-866, 2011.

Highlight

Space radiation research unit, International open laboratory

Yukio Uchihori
E-mail: uchihori@nirs.go.jp



The Japanese experimental module (KIBO) in the International Space Station (ISS) was constructed and has been operated from 2010. After completion of this construction, Japanese astronauts have been staying in the space environment longer than before. Astronauts in the ISS are exposed to space radiation including high energy heavy ions of galactic cosmic-rays. But the effects and, especially risks, of such radiation, especially heavy ions, are still not fully understood.

The Space Radiation Research Unit (SRRU) in the International Open Laboratory is investigating the radiation effects and risks of space radiation for astronauts and cosmonauts and also carrying out dosimetry. Members of this unit include physicists and biologists (Fig.1). Prof. Tom K. Hei of Columbia University, USA is a Distinguished Foreign Scientist in the SRRU. Several young researchers, as appointed scientists, from Columbia University and other universities and institutes have visited NIRS. They carried out research with other young researchers using HIMAC, SPICE and other facilities in NIRS.

The main subjects in biology in SRRU are to understand low dose and low dose rate by high LET radiation and long time exposures, and to lay out a common mechanism among cells, animals and human beings. The subjects in physics are to launch our radiation detectors in order to evaluate a radiation environment in the vehicle at low earth orbit and to prepare a radiation field using particle accelerators on ground to simulate the space radiation environment.

Fig.1 The distinguished scientists, Prof. Tom Hei and members of the Space Radiation Research Unit.

Radiation-induced non-targeted effect, the so called bystander effect is a phenomenon whereby cellular damage is expressed in un-irradiated neighboring cells near an irradiated cell or cells. This bystander effect is considered to be one of the major phenomena in low dose and low dose rate environments. Also in space environment, such as in the ISS, heavy ion radiation of galactic cosmic rays is lower by several orders than low LET radiation like protons and gamma-rays but, if the bystander effect affects other cells and organs, these rare heavy ions can become a large contribution. To understand the mechanism of the bystander effect, several experiments have been performed in the microbeam facility SPICE in NIRS by appointed scientists. With HIMAC, an investigation on the heavy ion-induced p53-independent bystander effect through mitochondria malignancy was performed, and with SPICE, studies on a mechanism of the cell nucleus and cytoplasm damage-induced bystander effect, and also bystander cellular responses in CSCs and non-stem cancer cells were investigated.

Radiation dose and dose equivalent have been measured in the Russian Service Module in the ISS. These experiments were collaborative research with the Institute of Bio Medical Problems in Moscow, Russia. NIRS passive detectors were installed in several packages and launched by Russian Progress Space Rockets. These passive detectors were luminescence detectors used to measure lower LET radiation and solid state track detectors, CR-39, used to measure high LET radiation above 10 keV/μm. One of

Fig.2 Passive detectors of NIRS and IBMP, Russia, for the protective curtain project.

Fig.3 The protective curtains which were installed for our passive detector packages in the ISS.

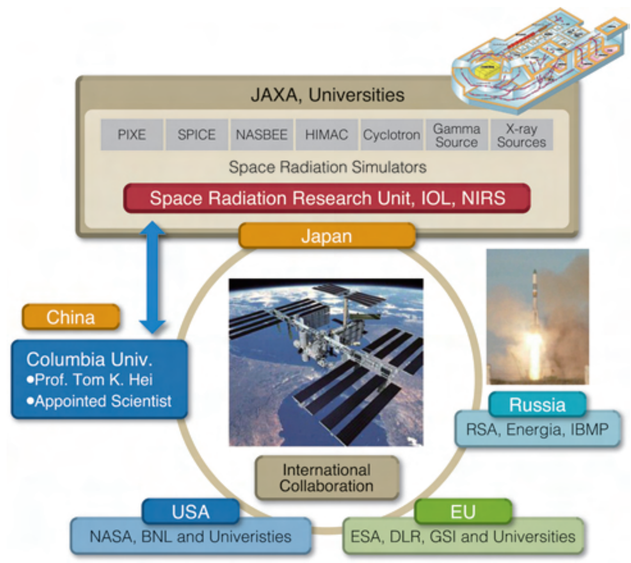


Fig.4

our space experiments was in the Water Curtain Project (Figs 2 and 3). In this project, NIRS packages were installed outside and inside water curtains. The water curtains consisted of water-saturated napkins or towels. From these experiments, we found that the water curtains could reduce radiation dose and they were useful to protect astronauts and cosmonauts from space radiation. We are continuing the project in the ISS.

The members in the SRRU prepared a new radiation field for proton beams which has a wide and uniform profile in the cyclotron facility in NIRS. The proton beam field can be used to calibrate radiation detectors and to irradiate biological samples using 30 to 80 MeV of proton beams. This work and micro beam experiments have been a bridge between physics and biology.

The SRRU has had very fruitful collaborations with Columbia University, and other international universities and institutes, e. g. Peking University, Fudan University, Key Laboratory of the Chinese Academy of Science, Hong Kong City University in China, German Aerospace Center (DRL) in Germany, and Institute of Bio Medical Problems in Russia.

Topics

Masami Torikoshi, Ph.D.

Director of Research, Development and Support Center

E-mail: torikosi@nirs.go.jp

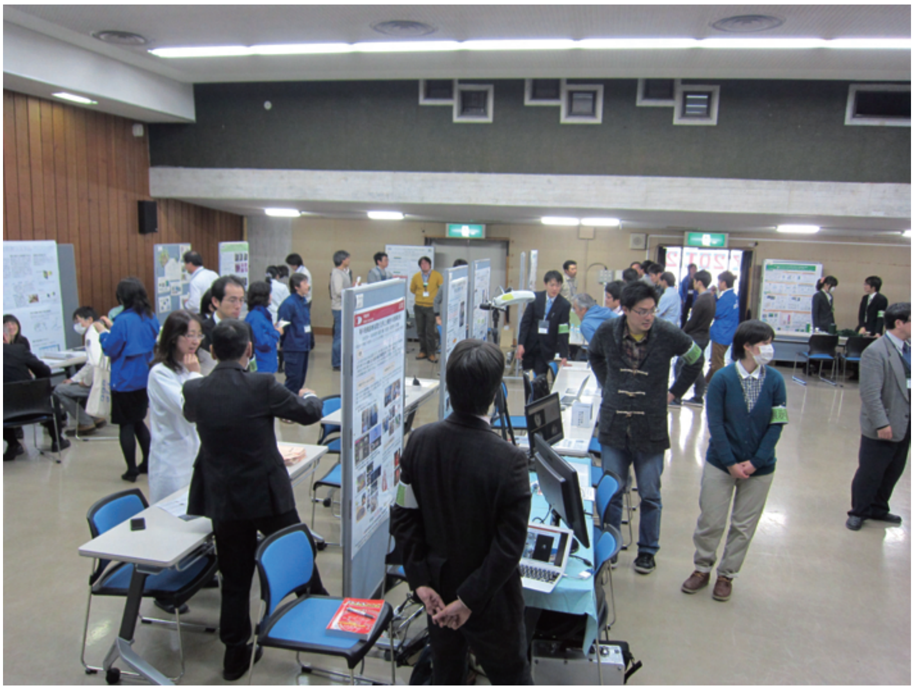
NIRS has many technologies which must be maintained and developed to support the research activities and implement the mission required of NIRS by the national government, for an instance, such as the activities as a tertiary radiation emergency medicine organization. These technologies do not stand out very much, but none the less they have an impact on various fields. Some of these technologies are introduced in this section.

NIRS sent a medical assistance team to the Fukushima Daiichi Nuclear Power Plant (NPP) Off-Site Center which was located at Okuma Town about 5 km from the plant site after the nuclear accident. At that time, since the Great East Japan Earthquake had caused major damage to the infrastructure all over the area, there was no way to communicate between the dispatched team and the headquarters at NIRS. The headquarters was very anxious about where the team was and whether it was a very high radioactivity level area, and what the team was doing. The chaos in Fukushima was so great that a member of the team was missing for a while. In order to cope with such a situation in the future, we developed a radiation monitoring system with functions of satellite communication, GPS and TV cameras as well as radiation detection. This multifunction detector enables us to know where each member is, to monitor the radiation level at which they are working and to watch views of the place they are at on a screen at the NIRS headquarters. This system can be used if the medical assistance team is dispatched both domestically and to foreign countries. It has been commercialized.

Several devices to detect radiation have been developed for the purpose of being used at high radiation level areas in Fukushima Prefecture. Many private companies, national institutions and so on have been competing with each other in developing such technologies, for an instance, a camera which visualizes the degree of radioactivity of an area while superimposing a photo taken at the same time as the radioactivity is detected. We have developed two kinds of radiation detectors; one is a gamma-ray camera which detects the radiation from only ^{137}Cs selectively and the other is a set of gamma-ray detectors installed on the detector system which can identify strong radioactive spots in a wide area. We expect that these radiation detectors will be useful in Fukushima Prefecture, especially, when people who evacuated return to their homes and begin living there again.

In NIRS many radiation detectors are used to measure and monitor the exposed dose on targets in experiments. Among doses, the most important is to measure the dose to be delivered to a patient for radiotherapy. These doses need to be very accurate and precise. Therefore, the detectors used for the above purposes need to be calibrated correctly to keep their quality high. In order to calibrate the detectors, we need standard radiation fields in which the dose rate and the field uniformity are well known. We formed a standard field of ^{60}Co gamma-rays with the cooperation of the National Institute of Advanced Industrial Science and Technology. Most of the ionization chambers used for medical purposes in Japan are being calibrated at this standard field in accordance with the protocol developed by NIRS. Until 2011, the chambers were being calibrated with reference to an air absorbed dose. However, in 2012, the new protocol was developed to calibrate an ionization chamber with reference to a water absorbed dose. The water absorbed dose is measured by an ionization chamber which is set in water. Since this measurement condition is close to the condition of the human body which is composed of more than 60 % water, we expect that the radiation dose measured by a calibrated ionization chamber in the new protocol is more accurate than that measured in the previous way.

NIRS has a facility in which a standard field of radiation emitted from radon is formed. There are only two such facilities in the world. In the facility, the radon gas concentration is accurately and stably controlled to be constant at any desired concentration value. Use of this standard field facility is being offered not only for research on dynamics of radon in the environment, but also for the calibration of radon radiation detectors. Recently, naturally occurring radon has been recognized as of the biggest source of public exposure to ionizing radiation. International organizations such



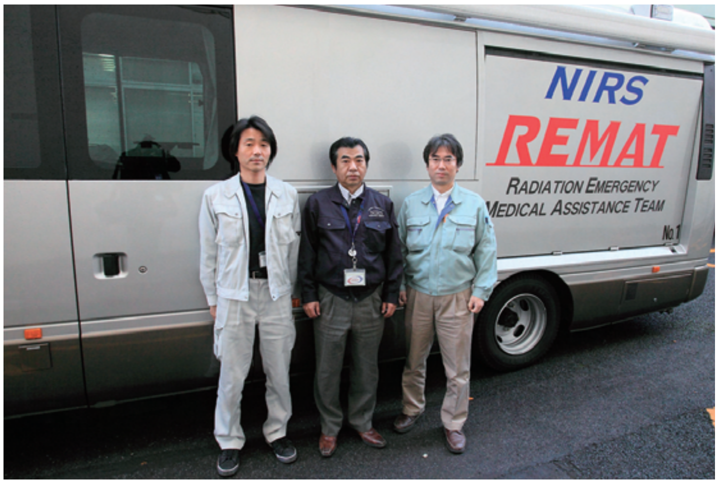
as IAEA, WHO and UNSCEAR have recommended that the reference dose levels of radon exposure in daily life and in occupational circumstances should be set. If the Japanese government adopts regulations on exposure to radon, it is obvious that the standard field of radon radiation is required as the national standard. It seems that the time has come that NIRS should make the radon field facility the national standard in cooperation with the National Institute of Technology and Evaluation.

Estimating an exposed radiation dose on a radiation accident victim is one of the most important items in triaging in radiation emergency medicine. There are two methods for dose estimate: physical dosimetry and biological dosimetry. A typical biological dosimetry method is to search for the frequency of chromosomal abnormality appearing in blood cells. The dicentric chromosome assay is recommended by ISO as the standard method. However, this standard method takes a long time to obtain results, so that we have to develop a more practical method that can be conducted for many victims in a short period. In particular, many workers are engaging in decommissioning of the nuclear reactors at Fukushima Daiichi NPP and they could receive overdoses if an accident occurs. Therefore, establishment of a fast and automatic process for dicentric chromosome assay is very urgent.

Topic

Development of an innovative radiation monitoring system: Radi-Probe System

Norihiro Miyaushiro, Yukio Uchihori, Yoshio Takashima, Takayuki Shinomiya
E-mail: miya@nirs.go.jp



In dealing with the aftermath of the TEPCO Fukushima Daiichi Nuclear Power Plant accident that followed the Great East Japan Earthquake on March 11,2011, through December 2011, NIRS had dispatched more than 1200 experts to Fukushima Prefecture. NIRS sent the first responder team of experts on radiation emergency medicine and radiation measurement to Fukushima just 17 hours after the earthquake.

Since it was a nuclear disaster, those who were engaged in logistic support and direction from the Disaster Management Headquarters had to consider radiation risk of the dispatched workers. However, it was very difficult to ensure the safety of the dispatched persons in the situation where the infrastructure functions, such as means of communication and electricity, and the means to travel about, were lost because of serious and extensive damage from the earthquake and tsunami.

From these experiences,it was recognized that in order to ensure the safety of those who were dispatched in a nuclear disaster, it was necessary to develop a system that can monitor the location of an escape route and the dose rate in real time and can instruct personnel about these matters from a remote location.

The first prototype Radi-Probe System could record dose rate and location information on a hard disk every second. It was a simple system that is configured with a camera, GPS unit and a computer. The first test of this prototype around the Fukushima Daiichi Nuclear Power Plant was successfully carried out in early April 2011. Following this success, the system has been improved using the advice of staff who actually worked at the disaster site and other personnel. As a result, the system has been completed, which can be remotely monitored in real time and provides a local dispatcher with information on the local status and on activities to assess exposure risk when a radiation disaster has occurred.

The Radi-Probe System is composed of a radiation detector, a transmitting terminal, a communication server, an information display terminal, and data communication services (Figs.1 and 2).

1) Radiation detector

A scintillation detector can be used to measure the dose rate and obtain the energy spectrum of gamma-rays.This is called the ‘probe’ for the radiation detector and several kinds of probes can be used for this system simultaneously.

2) Transmitting terminal

This terminal is installed in an emergency vehicle which can go to the disaster site.It sends data such as dose rate, gamma-ray energy spectrum, position information and sequences of pictures in real time.

3) Communication server

This server is installed in the server room at NIRS, and it saves the information sent from the transmitting terminal and sends these data to the information display terminal. This server can have multiple connections from the terminals.

4) Information display terminal

This terminal displays information sent from the transmitting terminal via the communication server. Persons who are in charge of logistic support can check the status of the disaster site from various locations because any general-purpose terminal with a WEB browser can be used as this terminal (Fig.3).

5) Data communication services

Communication between the communication server and the transmitting terminal uses commercial data communication services, such as mobile phones provided by telecoms operators. When a major disaster occurs, terrestrial communication networks such as a mobile phone may not work or be overwhelmed. Therefore this system also can use a satellite communication network as well.

By integrating the Radi-Probe System into the emergency vehicle that can go to the nuclear disaster site, the dispatched workers can report the situation in real time to the logistics department. In addition, this system has a function to display emergency messages from the commander on the Transmitting terminal at the disaster site. If dispatched workers are in imminent danger, such as an increase in dose rate and spatial changes in the surrounding environment, the commander can issue orders for an emergency

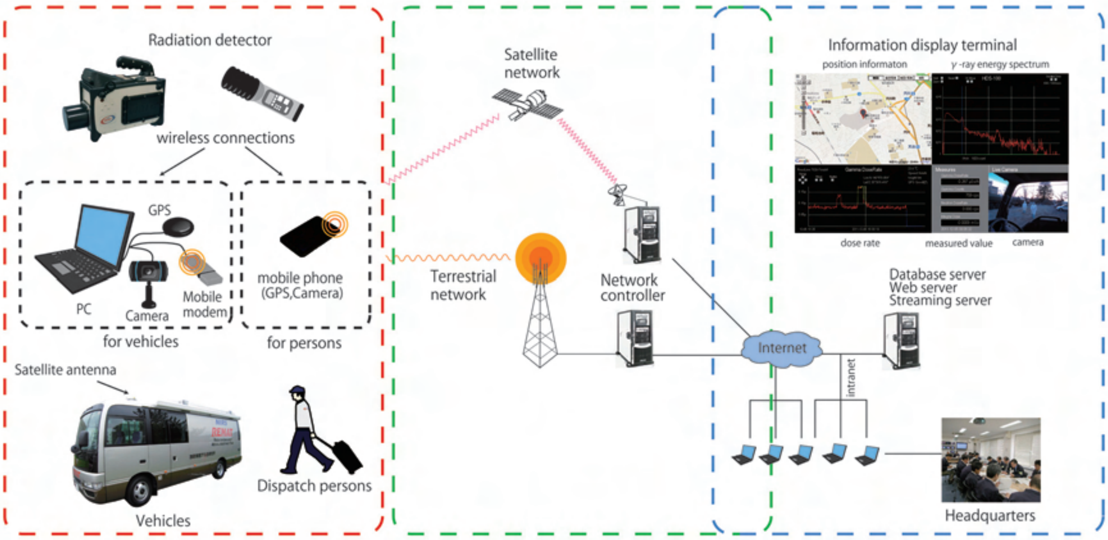


Fig. 1 Summary of Radi-Probe System

Fig. 2 Photo of the Radi-Probe System

Fig. 3 Information display terminal

evacuation.

The Radi-Probe System can indicate radiation dose rate on an electrical map using a color scale. The map is seen on the emergency vehicle on the site. This function allows the dispatched workers to determine driving routes on site and an evacuation route in the worst case.

Some NIRS members have participated in radiation measurement surveys using this system. The first trial was done on main roads of Chiba Prefecture in cooperation with the Chiba Prefectural Government.This system measured radiation dose while traveling by car for a total of 1,000 km on main roads for 4 days; the car was equipped with other instruments as well. It was successfully demonstrated that the Radi-Probe System can be used as a radiation measurement system with a mapping function.

In order to participate in a survey requested by MEXT, not only a CsI scintillation detector (Mirion Technologies HDS-100GN) but also a portable germanium detector (Canberra Falcon5000) were used in the Radi-Probe System. Estimation of surface contamination density of radio nuclides was made possible by getting accurate gamma-ray energy spectra using the Falcon5000 germanium detector.

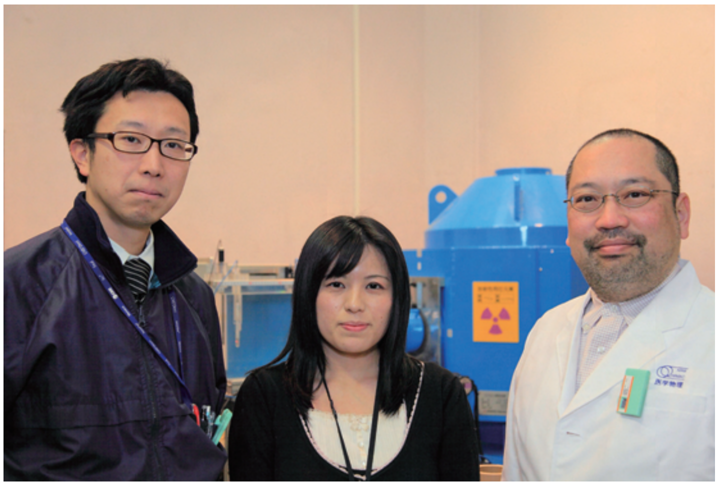
The Radi-Probe System was developed with feedback from dispatched workers who responded to the power plant accident and the system secures the safety of their activities in the field. Trial and error also contributed to the development. Lessons learned from this experience will be kept in mind,as NIRS researchers strive to ensure safety for unexpected disasters in the future.

2011/4/10	Successful testing of the prototype
2011/7/11-7/14	Participation in the survey in Chiba Prefecture
2011/10/18	Press release
2011/12/12-12/23	Participation in the second survey
2012/4/1	Radi-Probe Systems were installed on three vehicles that were newly developed for the purpose of the strengthening radiation emergency medical system at NIRS
2012/9/25-10/7	Participation in the third survey
Various times	Participation in nuclear disaster prevention and training sessions of national and local governments

Topic

Development of the ^{60}Co gamma-ray standard field for therapy-level dosimeter calibration in terms of absorbed dose to water

Akifumi Fukumura, Hideyuki Mizuno, Mai Fukahori, Suoh Sakata
E-mail: fukumura@nirs.go.jp



NIRS has been the Secondary Standard Dosimetry Laboratory (SSDL) for radiotherapy in Japan. More than 600 therapy-level dosimeters from hospitals were calibrated with the NIRS ^{60}Co exposure standard field per year.

In 2011, a primary standard for the absorbed dose rate to water in a ^{60}Co gamma-ray field was established at the National Metrology Institute of Japan (NMIJ) as a primary standard dosimetry laboratory (PSDL)[1]. Then, a ^{60}Co gamma-ray standard field for therapy-level dosimeter calibration in terms of absorbed dose to water has been developed at NIRS as SSDL. The new field was designed in accordance with IAEA TRS 398[2] (Fig.1).

The results of the IAEA/WHO TLD SSDL audit with the new field at NIRS demonstrated good agreement between the IAEA TLD measurements and NIRS stated absorbed dose to water (D_{TLD}/D_{SSDL}=1.00) within the measurement uncertainty (Fig. 2). According to IAEA TECDOC-1585[3], the relative expanded uncertainty on the calibration factor for therapy-level dosimeter in terms of absorbed dose to water ($N_{D,w}$) with the new field was estimated to be 1.1 % (k=2), which corresponds to an international level such as 1.4% at ADCL in the USA and to approximately one third of the value determined in the exposure standard field previously existing at NIRS (Table 1).

The new field has been used for determination of $N_{D,w}$ for radiotherapy facilities in Japan since the beginning of October in 2012.

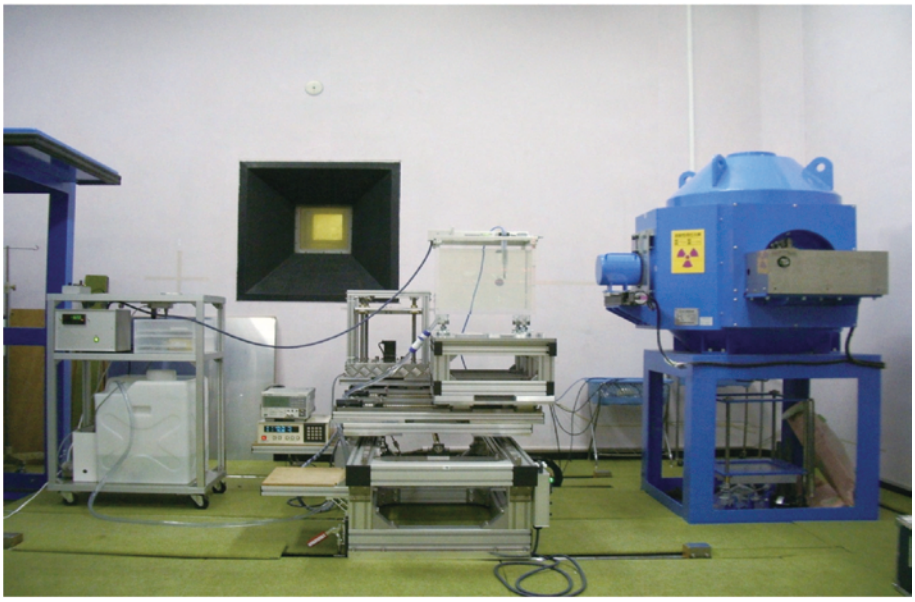


Fig. 1 NIRS ^{60}Co gamma-ray standard field for $N_{D,w}$ calibration of therapy-level dosimeter

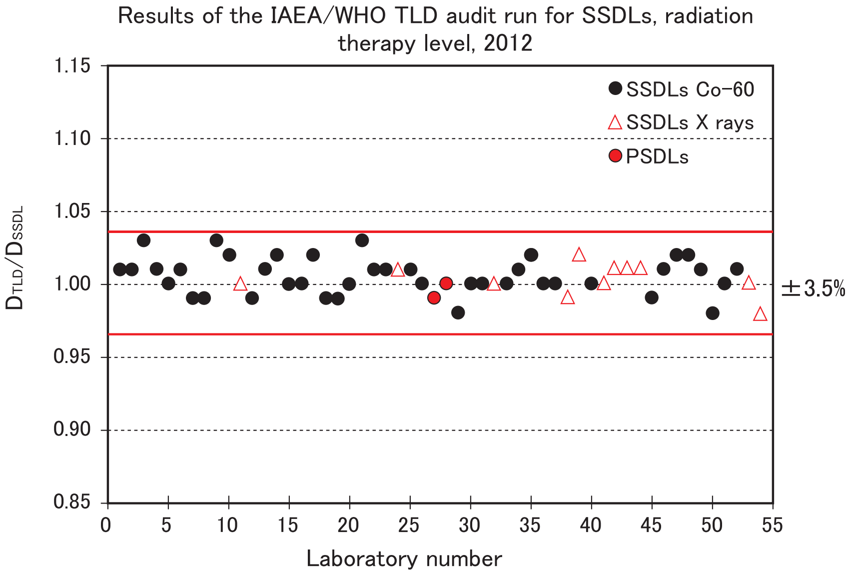


Fig. 2 Results of the IAEA/WHO TLD audit run for SSDLs radiation therapy level, 2012 (Reproduced by courtesy of IAEA, NIRS data: No.31)

Table 1 Comparison of uncertainty (k=2) of $N_{D,w}$

Institution	Relative Expanded Uncertainty(%)
NIRS (SSDL, in Japan)	1.1
NMIJ (PSDL, in Japan) [1]	0.8
ADCL (SSDL, in USA)	1.4
IAEA	1.0
NIRS (Exposure base)	3.0

At the same time Japan Society of Medical Physics (JSMP) updated its code of practice for dosimetry in external radiotherapy, in collaboration with NIRS. The dissemination of traceability of calibration factor determined in the new field is expected to diminish significantly the uncertainty of dose delivered to patients within a couple of years.

References

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[3] IAEA: Measurement uncertainty. A practical guide for secondary standards dosimetry laboratories, IAEA-TECDOC-1585, ISBN 978-92-0-104408-2, ISSN 1011-4289, 2008.

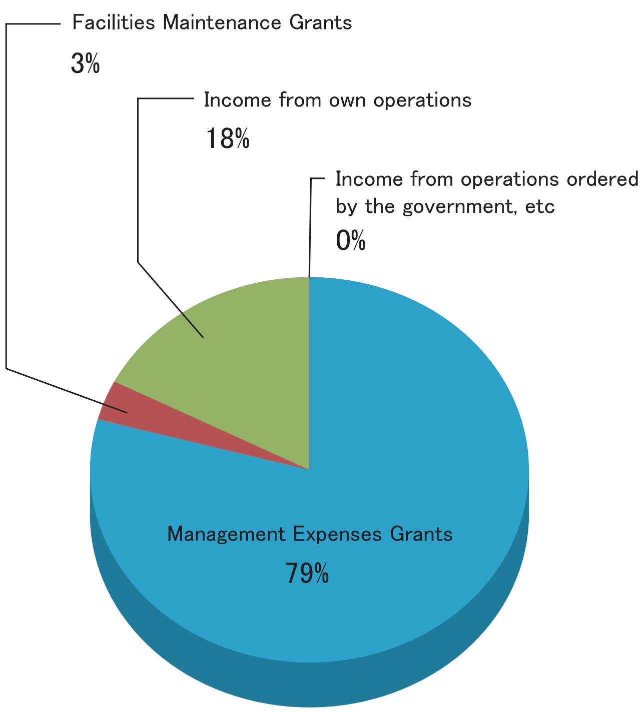
Organization Chart, Budget, Personnel, International Collaboration and Partnerships with Domestic and International Organizations and Universities

Organization Chart (FY 2011－2012)

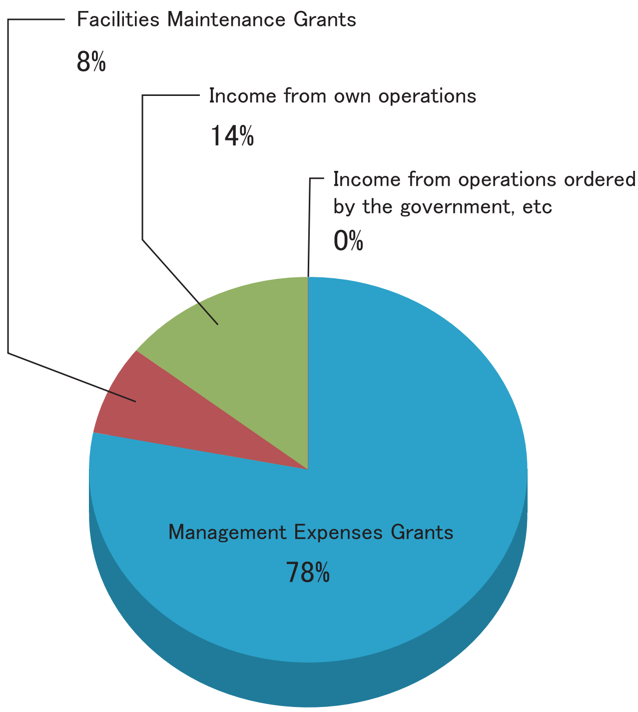
- Board of Executive Directors: President, Executive Directors, Auditors
  - Dept. of Planning and Management
  - Dept. of General Affairs
  - Auditing and Compliance Office
  - Research, Development and Support Center
    - Planning and Promotion Unit
    - Dept. of Technical Support and Development
    - Dept. of Information Technology
    - Dept. of Safety and Facility Management
  - Research Center for Charged Particle Therapy
    - Planning and Promotion Unit
    - Hospital
    - Dept. of Accelerator and Medical Physics
    - Research Program for Carbon Ion Therapy and Diagnostic Imaging
    - Medical Physics Research Program
    - Advanced Radiation Biology Research Program
    - Research Program for the Application of Heavy Ions in Medical Sciences
  - Molecular Imaging Center
    - Planning and Promotion Unit
    - Molecular Probe Program
    - Biophysics Program
    - Diagnostic Imaging Program
    - Molecular Neuroimaging Program
  - Research Center for Radiation Protection
    - Planning and Promotion Unit
    - Radiobiology for Children's Health Program
    - Radiation Risk Reduction Research Program
    - Regulatory Science Research Program
  - Research Center for Radiation Emergency Medicine
    - Planning and Promotion Unit
    - Dept. of Radiation Emergency Medicine
    - Dept. of Radiation Dosimetry
    - Research Program for Radiation Emergency Medicine
  - Fukushima Project Headquarters (FY2012–)
    - Planning and Promotion Unit (From FY2012)
    - Project for Environmental Dynamics and Radiation Effects (From FY2012)
    - Project for Human Health (From FY2012)
    - Radiation Effect Accumulation and Prevention Project (From FY2012)
  - International Open Laboratory
  - Medical Exposure Research Project

Budget

FY 2011



FY 2012



- Management Expenses Grants
- Facilities Maintenance Grants
- Income from own operations
- Income from operations ordered by the government, etc

Personnel

(FY2011)

Total 793
- Research Staff 456
  - Permanent 231
  - Fixed-term 225
- Administrative Staff 337
  - Permanent 108
  - Fixed-term 229

(FY2012)

Total 795
- Research Staff 459
  - Permanent 222
  - Fixed-term 237
- Administrative Staff 336
  - Permanent 104
  - Fixed-term 232

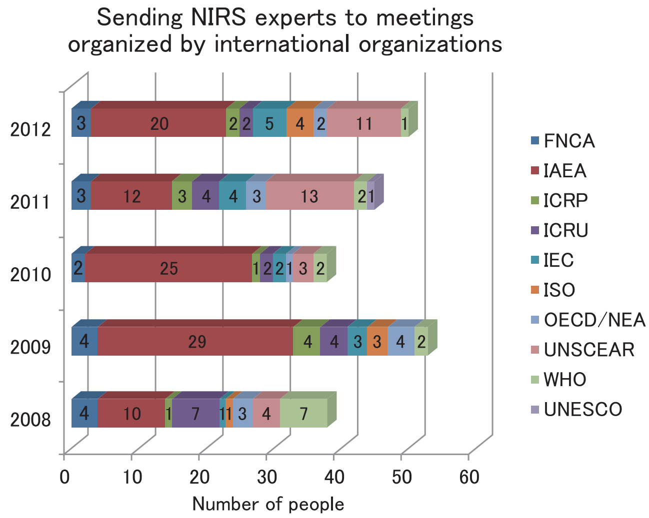
Working with international organizations

Closing working with international organizations such as UNSCEAR, IAEA, etc., NIRS has been dedicated to R&D and human resources development in radiological sciences, aiming to contribute to advances in human health and the creation of a society that enjoys better safety and peace of mind.

In FYs 2011-2012 NIRS experts took part in the meetings such as:

- 58th and 59th UNSCEAR meetings
- Expert meetings for the UNSCEAR "Fukushima assessment"
- IAEA research coordination meetings for CRPs (Tc-99m production; biodosimetry)
- IAEA Postgraduate educational course in radiation protection and the safety of radioactive sources
- IAEA consultants advice on the glass dosimetry system
- Meeting for the development of WHO guidelines on public health response to radiation emergencies

etc.



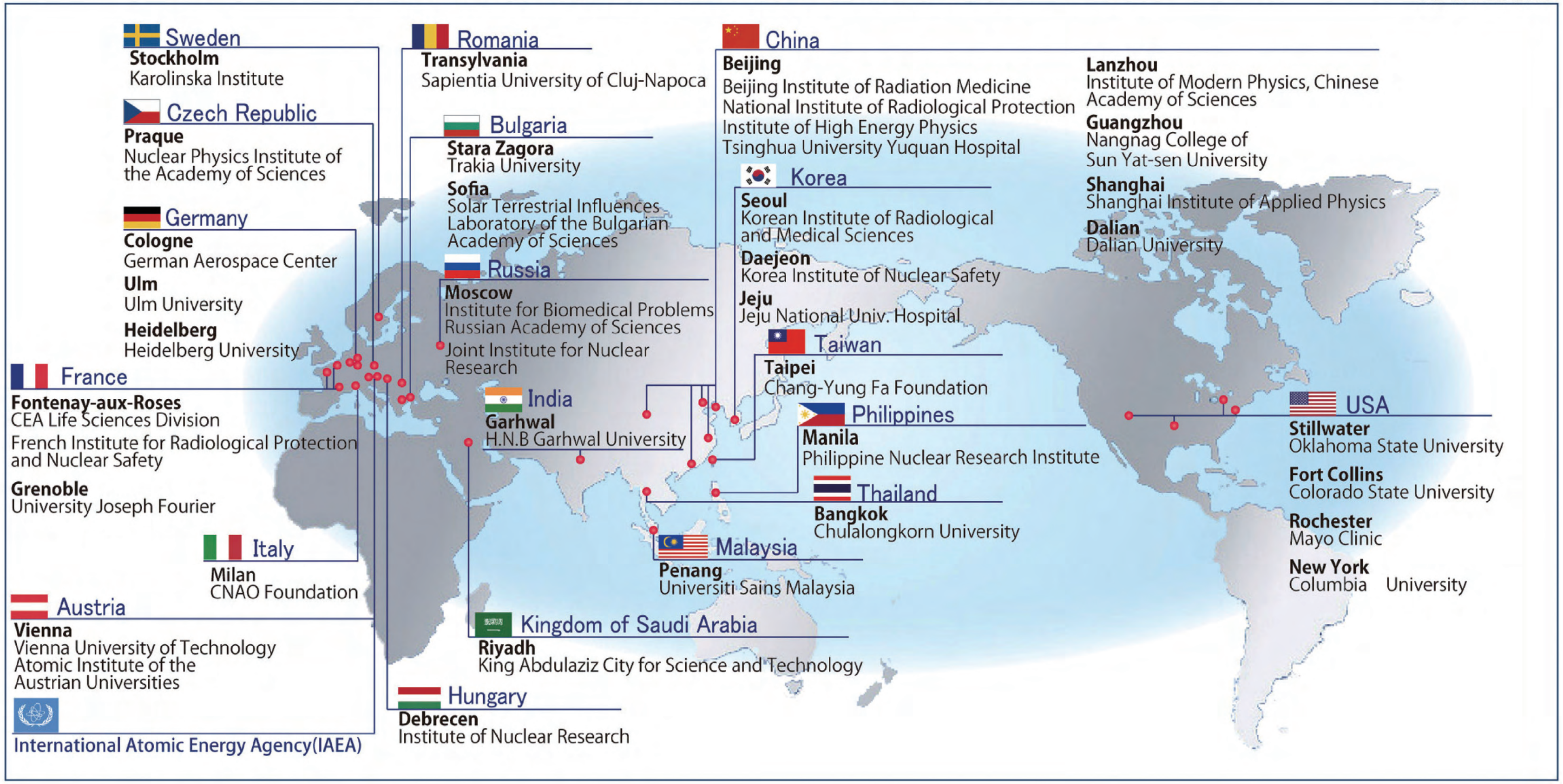
NIRS as an IAEA Collaborating Centre

NIRS held the following training courses in 2012 in the activity as an IAEA Collaborating Centre.

- IAEA-CC Molecular Imaging: "Special Training Course on Medical Physics" and Special Training Course on Radiochemistry (April 17-26)
- IAEA-CC Workshop on the Medical Physics Aspects of Heavy Ion Radiotherapy (July 3 -14)
- Short-Term Training Course on Biological Dosimetry for Radiation Exposure-with Concentration on DCA and FISH (December 10－21)

NIRS's Overseas Partners through Memorandums

As of Feb. 2013



Year in Review－international meetings and training

※ The events shown in blue were held out of Japan.

Joint Seminar with Dalian Univ. on Carbon Ion Radiotherapy (Dalian /China)

NIRS-IAEA-REAC/TS Training Course: Int'l Medical Management of Radiation Incidents

Symposium on the Accident of TEPCO Fukushima Daiichi Nuclear Power Station- What was Seen and Not Seen by Others?

International "Nano" Imaging Symposium

NIRS-ETOILE 2nd Joint Symposium 2011 on Carbon Ion Radiotherapy (Lyon/France)

Regional Meeting on Occupational Radiation Protection in Emergency Exposure Situations

Symposium of Carbon Ion Radiotherapy in Taiwan (Taipei/Taiwan)

2011

Apr.	May.	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.

2012

1st NIRS-SNU Workshop on Nuclear Medicine Imaging Science and Technology

International Symposium on the Natural Radiation Exposures and Low Dose Radiation Epidemiological Studies

NIRS-KFSHRC Joint Symposium on Carbon Ion Radiotherapy and Radiation Emergency Medicine (Riyadh/Saudi Arabia)

NIRS Workshop on Medical Response to Radiation Accidents in Asia 2012 -Lessons Learned from TEPCO Fukushima Daiichi NPP Accident-

IAEA-CC Molecular Imaging Training Courses

NIRS-Columbia Univ. Joint Workshop

NIRS-KIRAMS Joint Seminar on Radiation Emergency Medicine 2012

NIRS Workshop on Medical Response to Radiation Accidents in Asia 2013 – Interactive Training for Medical Professionals

2nd NIRS Symposium on Reconstruction of Early Internal Dose due to the TEPCO Fukushima Daiichi Nuclear Power Station Accident

2013

Apr.	May.	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.

New Frontiers in Cancer Treatment: A Focus on Photon and Carbon Ion Radiation Therapy and International Collaboration between Japan and the United States (Fort Collins/ USA)

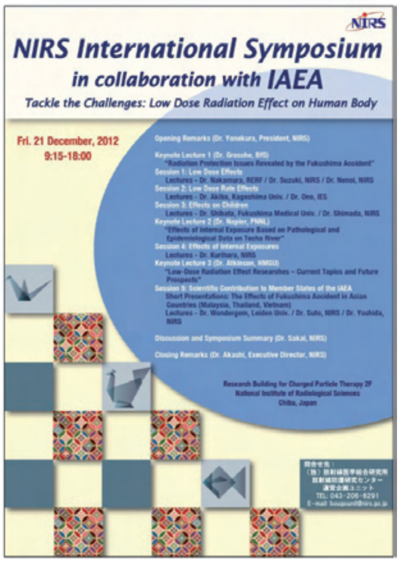
IAEA-CC Workshop on the Medical Physics Aspects of Heavy Ion Radiotherapy

International Training Course on Carbon-ion Radiotherapy (TCCIR)

1st NIRS Symposium on Reconstruction of Early Internal Dose due to the TEPCO Fukushima Daiichi Nuclear Power Station Accident

IAEA-CC Short-term Training Course on Biological Dosimetry

NIRS International Symposium “Tackle the Challenges: Low Dose Radiation Effects on Human Body



Appendix-1 (for FY 2011)
List of Original Papers

This list includes the main publications by staff members that appeared during the period from April 1, 2011 to March 31, 2012.

Research Center for Charged Particle Therapy

1. Reiko Imai, Tadashi Kamada, Shinji Sugahara, Hiroshi Tsuji, Hirohiko Tsujii: Carbon ion radiotherapy for sacral chordoma, *British Journal of Radiology*, 84, S48-S53, 2011
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12. Shinichiro Mori, Naoyoshi Yamamoto, Mio Nakajima, Masayuki Baba: Changes in chest wall thickness during four-dimensional CT in particle lung treatment planning, *British Journal of Radiology*, 84, e158-e160, 2011
13. Xing Cui, Kazuhiko Oonishi, Hirohiko Tsujii, Takeshi Yasuda, Yoshitaka Matsumoto, Yoshiya Furusawa, Makoto Akashi, Tadashi Kamada, Ryuichi Okayasu: Effects of carbon ion beam on putative colon cancer stem cells and its comparison with X-rays, *Cancer Research*, 71(10), 3676-87, 2011
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Appendix-2 (for FY 2012)
List of Original Papers

This list includes the main publications by staff members that appeared during the period from April 1, 2012 to March 31, 2013.

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Access Map

TOKYO
CHIBA
PREFECTURE
NAGOYA
KOBE
OSAKA
FUKUOKA
CENTRAL TOKYO
36km
44km
NARITA AIRPORT
36min. by Sobu Line Express
50min. by Sobu Line Express
NIRS
CHIBA
PREFECTURE

NIRS

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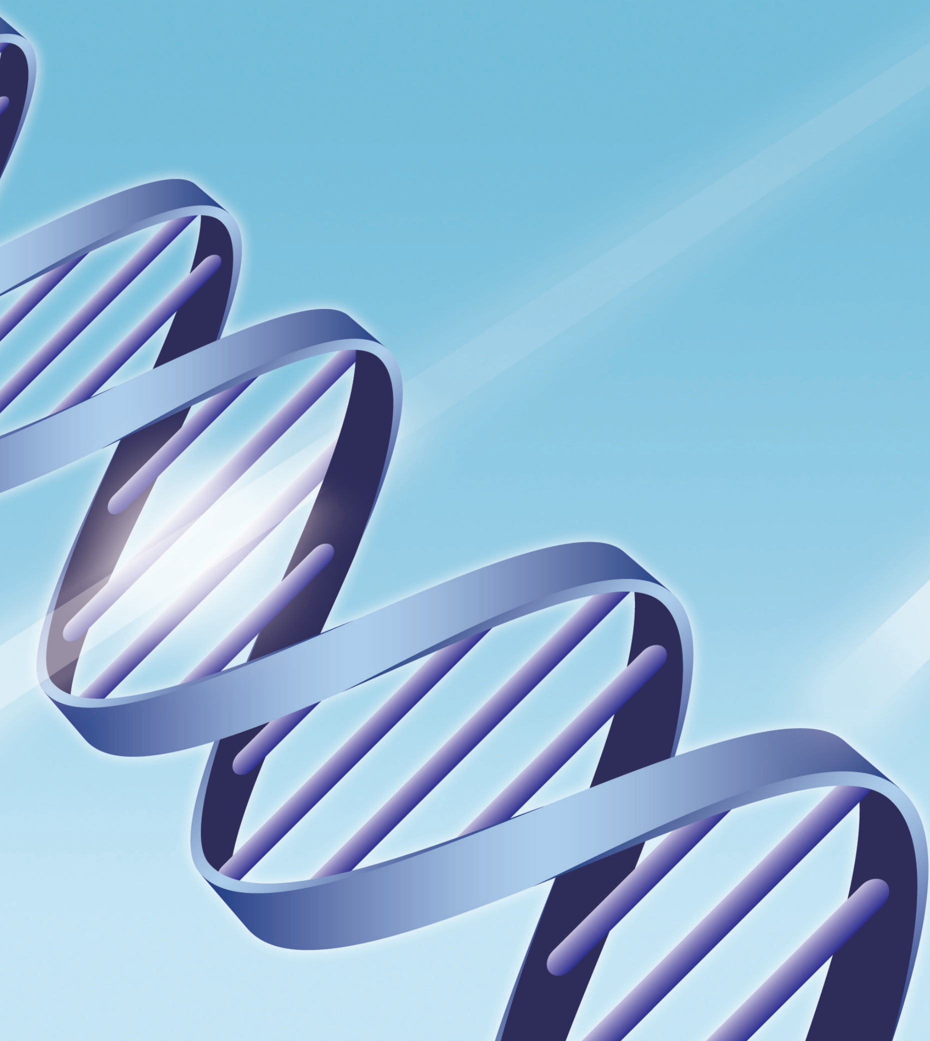

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