The International Kick-Off Symposium for Atomic Bomb Disease Institute at Nagasaki University

28-29 November, 2013
Baudine Hall, Ryojun Kaikan
Nagasaki University
Nagasaki, Japan.
On behalf of our institute, it is my great pleasure and honor to have the International Kick-Off Symposium for Atomic Bomb Disease Institute at Nagasaki University.

This institute, founded 51 years ago in 1962 and originally attached to Nagasaki University School of Medicine (later to Graduate School of Biomedical Sciences), has been reorganized as one that is attached directly to Nagasaki University this fiscal year.

We have performed education and research activities on radiation medicine for atomic bomb survivors and the late effect of radiation during 1960s-1980s, then extended our activities to international radiation exposures in Chernobyl and Kazakhstan in 1990s and now we are heavily involved in radiation health risk management in Fukushima.

As you know, it has been 68 years after the explosion of Atomic Bomb at Hiroshima and Nagasaki in 1945, 27 years after Chernobyl Nuclear Plant Accident and importantly two and a half years since Fukushima Daiichi Nuclear Disaster.

Nearly 50,000 people are still suffering from the late effect of atomic bomb in Nagasaki, more than 5,000 people (mainly children) developed thyroid cancers and this number are still increasing in Chernobyl, and hundreds of thousands of people are being terrified by chronic exposure to low-dose radiation in Fukushima.

These incidents, particularly that in Fukushima, raise many questions about radiation research, including low-dose radiation effect, child sensitivity to radiation, the effect of internal radiation exposure, etc.

I hope that all the participants will enjoy this symposium and take some clues to solve these issues from this symposium.

Yuji Nagayama
November 28, 2013
# Schedule

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Cancer Risks and Genomic Instability in Atomic Bomb Survivors

Masahiro Nakajima

Professor of Department of Tumor and Diagnostic Pathology, Atomic Bomb Disease Institute, Nagasaki University.

Several epidemiologic reports have suggested that in atomic bomb (A-bomb) survivors an increased risk of cancer has continued for decades, and a higher risk of certain types of cancers still persists. Although a long-lasting health effect is considered to be a contributing factor in tumorigenesis in A-bomb survivors, to date, the molecular mechanisms involved are not fully understood. We are promoting molecular analyses with archival tumor tissues from the survivors and animal models to clarify the involvement of genomic instability (GIN) in the late-onset carcinogenesis which should be induced by single irradiation before decades. Radiation etiology is suggested in the occurrence of solid cancers, such as basal cell carcinoma (BCC) of the skin, thyroid cancer, and breast cancer, among A-bomb survivors. Our previous study demonstrated the endogenous activation of DNA damage response in the epidermis surrounding BCC in the proximally exposed survivors, suggesting the presence of GIN in the survivors as a late effect of A-bomb radiation, which may indicate a predisposition to cancer. In animal model, we have found an increased level of abnormal signals in the non-tumorous thyroid follicular cells surrounding nodular lesions occurred at 18 month after 8Gy irradiation to thyroid glands by interphase dual color FISH. Furthermore, our recent study with microarray-comparative genomic hybridization revealed that breast cancer in survivors harbored significant genome-wide chromosome alterations compared with non-exposed patients. These findings indicate that GIN may be induced in irradiated organs at the precancerous stage and subsequently associated with carcinogenesis as a late health effect of radiation. We are now collecting fresh-frozen cancer tissues resected from survivors to establish A-bomb survivor's tissue bank, which will enhance the global collaboration and contribute to our further understanding carcinogenesis as a late health effect of radiation at molecular level.
Influence of high- and low-dose radiation, and aging on blood cell cancers

Shigeru Chiba
Professor of Department of Hematology, University of Tsukuba

Acute radiation syndrome (ARS) is a rare but serious complication of high-dose acute radiation exposure. After the atomic bombings in Hiroshima and Nagasaki, humans have experienced over hundred of ARS cases in various accidents, such as those in the nuclear power plants, medical facilities, etc. Hematopoietic stem cell transplantation (HSCT) was attempted for a small number of victims who presented ARS. The latest experiences of HSCT for ARS were brought in the criticality accident in the nuclear fuel processing plant in Tokai-mura, Ibaraki, Japan, in 1999. As a member of the transplant team for one of the two victims who received high-dose ionizing radiation, I will briefly remind the audience of our 82-day challenge. In medical settings, autologous HSCT (autoHSCT) is among the opportunities that we observe the consequences of high-dose acute radiation exposure to the hematopoietic stem cells. I will present the clinical course of a patient who is surviving after autoHSCT and having chromosomal abnormalities. As a consequence of the Fukushima Daiichi disaster, which occurred 12 years after the Tokai-mura accident, we Japanese are now concerned about the possible increase in the frequency of cancer development in people who received low-doses radiation. With regard to this, a number of pieces of information that are not necessarily scientific are flooding the media. It is the mission by us scientists to enlighten the people on correct knowledge. Incidentally, all human beings are confronted with the damage of their cellular genome by aging, regardless of whether experiencing accidental radiation exposure. It is clear that the aging is the greatest risk of cancer development. The incidences of myelodysplastic syndrome (MDS) and many subtypes of T-cell lymphoma increase in an exponential manner along with aging. We recently found an interesting linkage between MDS and a subtype of T-cell lymphoma. I will discuss the origin of these two cancers and its genomic evolution during aging.
Some Results of Current Research on Health Effects after Low Dose Radiation Exposure

Maria Blettner

Director of Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI), Johannes Gutenberg University Mainz

Despite many epidemiological studies that investigated cancer risk after exposure to radiation, the effect of low doses such as occupational exposure or diagnostic exposure remains unclear. Some recent studies suggest that cancer risk after low exposures may be larger than assumed by ICRP in the derivation of these limits.

We are currently exploring these effects in several epidemiological studies: In two cohort studies, cancer mortality of occupational exposed persons (pilots and cabin crew; workers in nuclear power plants) is investigated. Exposure in both cohorts is low (a maximum of a few mSv per year). Methods and results of these two cohorts will be presented; for the cohort of pilots data from several European countries and the US were pooled and re-analyzed yielding a very large dataset. For both groups a very strong healthy worker effect was observed and makes the interpretation of the results difficult. Comparison of these results with current knowledge from the A-Bomb Survivors will also be presented.

We are also studying cancer risk after medical diagnostic exposures in childhood. First, a cohort of about 100,000 children with any diagnostic procedure was analyzed to see whether cancer risk increased. Currently we are investigating cancer risk after CT exposure. Some preliminary results will be reported. I will also summarize the current knowledge of cancer risk after exposure in early age in life. These studies will also include secondary cancer studies of children who were exposed due to radiotherapy for their first cancer.
Molecular cloning and characterisation of human DNA repair genes

Tomoo Ogi

Associate Professor of
Department of Molecular Medicine,
Atomic Bomb Disease Institute, Nagasaki University

Cells are continuously exposed to many types of DNA damaging activities, including ionising radiation (IR), sunlight ultraviolet (UV), environmental pollutants, and various metabolic actions. Consequently, all living organisms have developed efficient DNA repair mechanisms to warrant that the integrity of genetic information is stably maintained. Our research is focused on the molecular mechanisms of human DNA damage response (DDR) systems, especially in the DNA damage checkpoint and the damage repair pathways of UV-induced photolesion and IR-induced double strand breaks (DSB). Nucleotide excision repair (NER), is the most versatile DNA repair system, which removes the major UV-photolesions as well as bulky base adducts from cellular DNA. In mammals, compromised NER activity is the cause of several cancer predisposition diseases. We have established a rapid and efficient screening system for measuring NER related DNA repair activities; based on the system, we are running diagnostic services for DDR-deficiency related genetic disorders. Last three years of our activities, we totally diagnosed ~200 patients who displayed DDR-compromised clinical manifestations. We extracted DDR-deficient patients whose genetic causes have yet to be identified. These cases were further analysed their genomes (whole exome) to determine the disease causative mutations by next generation DNA sequencing platforms. From the cellular and the genetic combinatorial screenings, we have identified 5 new pathogenic DDR genes: UVSSA from two unrelated Japanese UV-sensitive syndrome cases; ATRIP from a Seckel syndrome family; PRKDC from a SCID patient; ERCC1 and XPF from Cockayne syndrome patients. Detailed molecular pathogenesis for the DDR diseases have been studied.
Integrating Molecular, Cellular, Tissue and Organismal Responses to Understand the Biological Effects and Consequences of Exposures to Low-Doses of Ionizing Radiation

William F. Morgan

Director of Radiation Biology and Biophysics,
Biological Sciences Division,
Pacific Northwest National Laboratory

Understanding the potential health effects of exposures to low doses of ionizing radiation (<100 mSv) is going to require a concerted, highly integrated effort. It will require biologists, physicists, chemists, epidemiologists, computational biologists, biostaticians, lawyers and ethicists all working together, interacting and speaking a common language. It will require modern technology and individuals skilled in using this technology collaborating to dissect and tease apart the subtle effects of how, and if, a low dose of ionizing radiation might impact a biological system. Mankind has evolved in an environment rich in naturally occurring background radiation, and has added to that the significant benefits of medical and industrial irradiation. Consequently, to understand potential adverse health effects of additional radiation exposures at levels that might require evacuation to minimize further exposures, i.e., evacuation after the Fukushima accident, its justification, and potential consequences, such an integrated effort is demanded. This presentation will focus on integrating biological studies on the molecular, biochemical, cellular, tissue and organismal responses described after exposure(s) to low doses of ionizing radiation. It will focus on systems biology type approaches to understanding low dose radiation effects, how data might be integrated as a function of time after radiation exposure and radiation dose and it will attempt a rational strategy for reconciling discrepancies and uncertainties observed after low dose radiation exposures.

This perspective was supported by Battelle Memorial Institute, Pacific Northwest Division, under Contract No. DE- AC05-76RL0 1830 with the U.S. Department of Energy (DOE), Office of Biological and Environmental Research (OBER) Low Dose Radiation Science Program. It does not necessarily reflect the views of these organizations.
The DNA Damage Response in Cancer Treatment

Kiyoshi Miyagawa

Professor of Laboratory of Molecular Radiology,
Graduate School of Medicine,
The University of Tokyo

Both radiotherapy and chemotherapy play key roles in current cancer treatment. Although such treatments induce various toxicities in normal tissues, they can efficiently kill cancer cells by generating DNA damage in many cases. Nevertheless, cancer cells often become resistant to such DNA-damaging treatments. Notably, cancer stem cells have been shown to be resistant to radiation and chemotherapeutic agents. To combat genotoxic insults, cells have evolved the DNA damage response (DDR) to detect DNA damage, transmit the signals and execute DNA repair. It is therefore likely that DDR inhibition promotes the effects of radiotherapy and chemotherapy by inhibiting DNA repair in cancer cells. Indeed, various types of DDR-inhibitory drugs have been developed and investigated in preclinical studies. Furthermore, several DDR-inhibitory drugs are now under clinical investigation in single agent trials as well as in combinations with DNA-damaging agents. An alternative DDR-inhibitory approach is based on the principle of synthetic lethality, exemplified as inhibition of poly(ADP-ribose) polymerase (PARP) in BRCA1 or BRCA2 mutation-associated cancers. Cancer cells often lack components of the DDR during tumor development. BRCA1 or BRCA2 mutation-associated cancer cells are remarkably sensitive to PARP inhibition due to defective homologous recombination caused by BRCA mutations. Although this approach seems to be promising, numbers of patients are limited because BRCA mutations are found in a small fraction of tumors. Other than these mutations, alterations in molecules involved in homologous recombination are likely to exhibit the same phenotype. For instance, we have recently found that the synaptonemal complex protein SYCP3 impairs homologous recombination by interfering with BRCA2. Thus, although great progress has been made towards understanding the DDR, much remains to be clarified to apply biological findings to cancer treatment.
Development of lung adenocarcinoma (LADC), the most frequent histological type of lung cancer, depends in many cases on the activation of “driver” oncogenes such as KRAS, epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK). Recently, we and others identified the RET fusion gene as a new targetable driver gene in LADC. RET fusions occur in 1–2% of LADCs by chromosome 10 inversion. Existing FDA-approved inhibitors of RET tyrosine kinase show promising therapeutic effects both in vitro and in vivo, as well as in a few patients. Clinical trials are underway to investigate the therapeutic effects of RET tyrosine kinase inhibitors, such as vandetanib (ZD6474) and cabozantinib (XL184), in patients with RET fusion-positive lung cancer. Structural analysis of genomic DNAs containing breakpoints for RET fusion is also underway to understand underlying molecular processes.

Deficiencies in SWI/SNF chromatin-remodeling genes in common cancers have attracted a great deal of interest. Deficiencies in BRG1/SMARCA4, a catalytic (ATPase) subunit for the SWI/SNF chromatin-remodeling complex, are preferentially observed in LADCs without alterations in driver oncogenes above. We propose a synthetic-lethality therapy for treating cancers deficient in BRG1/SMARCA4. The strategy relies upon the inhibition of BRM/SMARCA2, another catalytic SWI/SNF subunit with similar activity to that of BRG1.


International framework for emergency preparedness and response and IAEA RANET

Eduardo Daniel Herrera Reyes
Incident and Emergency Centre,
International Atomic Energy Agency

The role of the International Atomic Energy Agency (IAEA) in a response to nuclear and radiological incidents and emergencies has been defined and further expanded through the IAEA Statute, the Convention on Early Notification of a Nuclear Accident, the Convention on Assistance in the Case of a Nuclear Accident or Radiological Emergency, the Convention on Physical Protection of Nuclear Material, IAEA safety standards, relevant decisions by Policy Making Organs of the IAEA, inter-agency agreements and other documents such as the IAEA Action Plan on Nuclear Safety. The IAEA Secretariat fulfils its roles through the Agency's Incident and Emergency System (IES) and the Incident and Emergency Centre (IEC). The IEC is the global focal point for international preparedness and response to nuclear and radiological safety or security related incidents, emergencies, threats or events of media interest and for coordination of International assistance.

During a response the IEC performs and facilitates for Member States many specific functions which include: prompt notification and official information exchange; assessment of potential consequences and prognosis of emergency progression; provision, facilitation and coordination of international assistance; provision of timely, accurate and easily understandable public information; coordination of inter-agency response at the international level. Through officially designated contact points of Member States the IEC is able to communicate at any time with national authorities to ensure the prompt and successful sharing of information.

Some of the main activities in the preparedness area are the development of safety standards, standardized materials, guidelines and practical tools; rendering services; capacity building centre; building human capacities; conduct of training courses, workshops and exercises.

The IEC routinely performs internal exercising of all aspects of the IAEA response and in cooperation with Member States, the IAEA organizes and facilitates the conduct of large scale international exercises to practice cooperation and coordination.
The Great East Japan Earthquake on March 11th, 2011, magnitude 9 with huge tsunami, struck in the Tohoku region of Pacific Ocean coast. The meltdown and hydrogen explosion occurred in Fukushima Daiichi nuclear power plant, and resulted in massive radionuclides release into atmosphere. More than 200,000 residents have moved to emergency shelters along long evacuation route in cold weather. Various agricultural and marine products were contaminated with radioactive materials; its concentrations in some of them exceeded the provisional regulation values. It has drastically changed people’s previous life style in Fukushima from the beginning with unpredictable fear until now with anxiety of low dose radiation and tough facts of future life. Especially, mothers with small children are concerned about the health of children.

Fukushima Prefecture and Fukushima Medical University took lead in planning and implementing of the “Fukushima Health Management Survey” in response to a long-term low-dose radiation exposure caused by the accident. The purposes of the survey are; to monitor residents’ long-term health especially for children and to promote their future well-being. The survey is a cohort study of all residents in Fukushima Prefecture and consists of the Basic Survey as well as four detailed surveys. The Basic Survey is to estimate the level of external radiation exposure on first 4 months in all 2.05 million residents. Regarding the detailed surveys, we have performed thyroid ultrasound examination on all children aged 18 years and younger in Fukushima, provided a comprehensive health check and questionnaire as for mental health and lifestyle change to all residents from the evacuation zones, and monitored pregnancies and births. All data have been incorporated into a database, and will be used to support the residents and to analyze of radiation effect on health. In this paper, I would like to introduce current status of post-disaster and recent progress of the Fukushima Health Management Survey.
From Chernobyl to Fukushima

Noboru Takamura

Professor of Department of Global Health, Medicine and Welfare, Atomic Bomb Disease Institute, Nagasaki University.

Through the promotion of comprehensive medical support and academic joint research on those exposed to low-dose radiation after the Chernobyl Nuclear Power Plant (CNPP) accident, we have conducted epidemiological studies around CNPP, such as molecular epidemiological studies on radiation-induced thyroid cancer and evaluation of internal body burden of population by whole body counter (WBC). It should be noted that our accumulated scientific results are now available for the risk communication after the accident at Fukushima Dai-ichi Nuclear Power Plant and evaluation of health effects due to this accident. Furthermore, we recently established Nagasaki University Satellite Office in Kawauchi Village, Fukushima Prefecture, those evacuees were the first to return after the accident. In this presentation, I review our ongoing projects around Chernobyl and Fukushima.
Placing Fukushima in Historical Perspective: Japan and Natural Disaster

Gregory K. Clancey
Leader of Science, Technology and Society (STS) Research Cluster, Asia Research Institute, Singapore University

It goes without saying that Japan has had long experience with Natural Disaster in many forms – earthquakes, tsunamis, typhoons, fires, floods, and volcanic eruptions, to name the most prominent examples. Historically speaking, few countries have been as susceptible to this combination of destructive events, and fewer still have flourished under such circumstances. This has led some observers outside of Japan to believe that a common social, political, psychological, and individual response to such disasters must have evolved over centuries, and is perhaps a key to understanding Japanese history. As an historian, however, I am more struck by the changes in response to disasters over time than their commonality. This is partly because no two disasters are entirely the same, but also because the social and political circumstances of the moment vary. If the historical experience of the Japanese people is reflected in disasters, it is as a series of snapshots of differing Japans – in other words, as a reflection of rapid change. I will illustrate this by concentrating on four of the largest daishinsai of the last two centuries – the Ansei, Nobi, Kanto, and Great East Japan Earthquakes – and the popular responses they occasioned. The aftermath of these great earthquakes have much to tell us about the social and political circumstances of their times. I will also argue that each earthquake also had lasting influence on the eras that followed. They were thus both mirrors, and active agents of historical change. In each instance, however, the changes they gave rise to were different. Of course it is too early to tell what long-term changes will be moulded by the event of 2011, so for the most recent of these disasters, I will simply compare the contemporary response to those which occurred earlier, starting in late Tokugawa times. I hope that by taking such a long view we can better come to terms with natural disaster as an element of historical change.
1962  The Atomic Bomb Disease Institute was established for the purpose of universal basic research with regard to radiation medicine and the late effects of radiation on the human body. New departments had been established and incorporated every year until 1967, when six departments (Departments of Pathological Biochemistry, Radiation Biophysics, Pathology, Hematology, Human Genetics and Preventive Medicine) were completed. The Institute has studied the effects of residual radiation, pathological and epidemiological approaches to various atomic bomb irradiation-related diseases, and clarification of the relationship between radiation dose and radiation-induced leukemia and other malignant diseases.

1972  The Medical Data Center for the Atomic Bomb was established with the purpose of data collection and arrangement and preservation of materials from Atomic Bomb victims to better understand the effects of the atomic bomb disaster.

1974  The Medical Data Center for the Atomic Bomb was reorganized into the Scientific Data Center for the Atomic Bomb Disaster.

1997  The Atomic Bomb Disease Institute and the Scientific Data Center for the Atomic Bomb Disaster were combined to regenerate as the new Atomic Bomb Disease Institute. Our purpose after reorganization is to clarify the molecular mechanisms underlying radiation injuries by Atomic Bomb and other radiation-related accidents, and to develop novel treatment modalities including molecular targeting therapy and gene therapy to Hibakusha. We have been pursuing epidemiological studies, clarification of the mechanisms for radiation effects from individual and cellular levels to molecular and genetic levels, development of methods for molecular diagnosis of Hibakusha, basic and translational research of molecular targeting therapy and gene therapy, and international cooperation to provide improved medical care for radiation-exposed people worldwide.

Furthermore, we have already started our work as an international research institute with an information center for medical care of late effects of radiation.

2001  The research building was renewed.

2002  The 21st century COE program "International Consortium for Medical Care of Hibakusha and Radiation Life Science" was adopted by Ministry of Education, Culture, Sports, Science and Technology.

2007  The Global COE Program of "Global Strategic Center for Radiation Health Risk Control" was adopted by Ministry of Education, Culture, Sports, Science and Technology.

2013  Reorganized into research institute affiliated to Nagasaki University.
Atomic Bomb Disease Institute,
Nagasaki University