

Report of the 39th Scientific Advisory Committee Meeting

March 5–7, 2012, Hiroshima Laboratory

Scientific Advisors

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Special Advisors

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Introduction

The Scientific Advisory Committee (SAC), previously known as the Scientific Council (SC), met from March 5–7, 2012, in Hiroshima, Japan. Its task, as in previous years, was to review the Radiation Effects Research Foundation (RERF) scientific programs. This year, the SAC conducted an in-depth review of the Department of Radiobiology/Molecular Epidemiology (RME) and the Department of Genetics. Due to a large number of upcoming retirements in these two departments, an additional meeting was held following the regular SAC meeting to explore options for reorganization and recruitment that might be implemented to take advantage of this rare opportunity. In deference to this additional focused session, the SAC has refrained from making specific comments or recommendations related to the current and upcoming vacancies. With its plan for a detailed review of these two departments, three additional experts joined the Committee this year, Drs. William Morgan, Tetsuya Ono and Toshio Suda. Their addition was extremely valuable to the SAC and it was a great pleasure for the Council to work with these outstanding scholars. One regular member of our panel, Dr. Michael Cornforth, was unable to join us this year, and the SAC missed his presence and contributions. Dr. Shunichi Yamashita, Vice President of Fukushima Medical University, joined the Scientific Advisory Committee with the retirement from the Council of Dr. Takashi Yanagawa of Kurume University.

Dr. Toshiteru Okubo, Chairman of the RERF, opened the 39th meeting of the SAC on the morning of March 5, and provided a warm welcome to all in attendance. He explained that this year the SAC would provide a focused review of the two departments and how important the SAC's work is to the staff of the RERF. He also explained the basics of the now completed change of the Act of Endowment with RERF becoming a public interest incorporated foundation (PIIF). The Scientific Council has now become the Scientific Advisory Committee, which will continue to review the scientific programs of RERF and report its recommendations to a Board of Directors and a Board of Councilors.

Following Dr. Okubo's welcoming remarks, Dr. Roy Shore, Chief of Research at RERF, provided an overview of the status of research at RERF. He began with a detailed response to the recommendations made by the report of last year's SC, and followed with a description of RERF's major accomplishments during 2011. Among the highlights were publication of a major update of Life Span Study (LSS) cancer and noncancer mortality, update of the tumor registries through 2007, and studies of genetic risk using both F₁ data and animal models. Dr. Shore also described the crucial ongoing efforts to consolidate, integrate and support databases, sample collection and storage.

Following Dr. Shore's comments, detailed presentations by the Department of Genetics and the Department of Radiobiology/Molecular Epidemiology were given by the

department chiefs and selected staff members. Next, brief overviews of activities of the Departments of Clinical Studies, Epidemiology, and Statistics were given to the SAC. These presentations gave responses to last year's SC recommendations and reported on their major accomplishments during 2011, as well as their future plans.

Dr. Shore gave the SAC an update of the work of the scientific committees and working groups. An issue of current concern in the public media is that of residual radiation and the so-called "black rain." The subcommittee investigating these issues has been confronted with anecdotal and missing data, but has so far found no evidence of major fallout exposures based on epilation data. Further coding and analysis of the available data are still under consideration, however. Some of the issues confronting the information technology (IT) group as it begins database integration and management of datasets were also discussed. Finally, Mr. Takanobu Teramoto gave the SAC an update of the progress and accomplishments of the public relations department. Outstanding and commendable efforts were put forth in the past year to provide public access to radiation risk information in response to the Fukushima disaster.

Beginning the meeting on March 6, Dr. Okubo outlined the planning process by which future plans for RERF are being developed. He announced a fresh plan for the yearly solicitation of recommendations from intramural professionals, the SAC, and the Board of Directors in three areas, immediate implementation, longer range planning, and infrastructure. This year's intramural recommendations were distributed, but not discussed. Those who had the chance to skim the intramural comments were favorably impressed with the high level of collected wisdom. It is ALWAYS the correct time to plan ahead, so this initiative is welcomed and well begun. Without commenting on the content, we are eager to expedite the process that could include engaging specialists in corporate planning, and other stakeholders. Funds for such ambitious planning need to be identified and, with the change of the Act of Endowment, could potentially come through PIIF donations and philanthropy.

The formal program concluded with a special presentation on RERF's activities in response to the Fukushima disaster, presented by Chief Scientist Kazunori Kodama. Certain RERF members quickly responded to the crisis with scientific, design, and website information. The mission, skills, and experience of RERF are clearly directly relevant to the disaster. There are obvious areas of strength in scientific research that should continue to be helpful: the consultation and committee work by specific RERF scientists, design of epidemiologic cohort studies, the study of low-dose radiation effects, including *in vitro* and animal work, the management of biospecimens and of public relations. Such additional work in support of the Fukushima health-research activities should not be funded by the current RERF budget, but needs supplementary support.

After Dr. Kodama's special presentation on Fukushima-related activities, informal meetings were held between the SAC members and the RERF departments being reviewed. Throughout the meeting the SAC reviewed and discussed the information provided concerning the activities of the

RERF, and met with a group of junior investigators over lunch on Tuesday.

Overview

As in the past, the SAC continues in its belief that the RERF is the pre-eminent leader in radiation risk research in the world and has the expertise, populations, and datasets to conduct fruitful investigations that cannot be carried out elsewhere. The support and assistance of the Japanese Ministry of Health, Labour and Welfare (MHLW) and the United States Department of Energy (DOE) as well as the scientific guidance of the National Academy of Sciences (NAS) continue to be critical to the mission of the RERF. Without such support and the assistance of the survivors and their families, it would not be possible for the RERF to conduct substantive research that has great impact around the world.

One week after last year's SC meeting, the Great East Japan Earthquake and tsunami and the consequent radiation emergency at the Fukushima Daiichi nuclear power plant focused the world's attention on issues of radiation exposure and its health consequences. The Fukushima disaster dramatically highlights the importance of the RERF mission; a mission made only more crucial by increased worldwide power needs, increased use of medical radiation, and increased threats of radiological or nuclear terrorism. The scientific opportunities for improved understanding of radiation effects on humans are also on the increase, as development of systems and computational biology offers new opportunities for integrating basic laboratory findings into human risk assessment. Advanced statistical methods using high speed computing also allow for greater sophistication in model development including the requisite incorporation of measurement and model uncertainties. RERF is in an excellent position to make major advances in quantitative radiation risk assessment in this environment. The SAC continues to hope that the combination of increasing needs of society and increasing scientific opportunities for understanding the health effects of radiation will stimulate the Japan's MHLW and the U.S. DOE to increase or at least maintain their level of basic financial support of RERF despite the persisting environment of decreasing governmental research funds.

With the sustained and outstanding senior leadership of Drs. Okubo and Shore, the SAC looks forward to a bright future for science at RERF. In the past year, both leaders made time for writing first-authored papers about the mission. With the rapid increase in the medical use of radiation and the worldwide expansion of nuclear power generation, now is the time for the expansion of the critical radiation health research that RERF is uniquely capable of conducting. The Advisors do, however, appreciate that the continued support from the sponsoring governmental agencies has been protected during these times of budgetary contractions.

General Recommendations

The Scientific Advisors have three general recommendations, as well as seven additional specific recommenda-

tions:

- **Research Prioritization:** The justification, prioritization, and overall quality of some of the current research programs continue to be of general concern. Some progress has been made in streamlining the review of research protocols (RPs) and retiring inactive ones, but this process needs to continue.
 - As an aid to the development and prioritization of RPs, they should address clearly articulated testable hypotheses that contribute to the overall goals of RERF.
 - Adoption of new technologies (animal models, global sequencing, etc.) is applauded and encouraged, but care should be taken that such experiments are designed to address high priority questions in an appropriate way.
 - A transparent decision-making process should be in place to ensure optimal utilization of samples and to ensure they will be used to address the most important biological questions with robust experimental designs.
 - Transparent and interactive discussions on RP evaluation and selection should be used as a good opportunity for education and training for young investigators.
 - A consolidated table or spreadsheet of annual publication metrics for each RP by department would be helpful both for the SAC review and for ongoing internal assessment and prioritization of RPs. A format has been suggested to RERF leadership.
- **Fukushima:** The SAC applauds the efforts of RERF in support of activities related to Fukushima. This is an ideal example of an opportunity for delivery of the RERF “product” in that it represents transfer of RERF scientific knowledge and process knowledge (such as consideration of long term follow-up) to a new and pressing public concern. We encourage external administrative and financial support for contributions by RERF going forward. The Fukushima disaster also highlights the importance of low dose mechanistic studies and their linkage to health outcomes.
- **Biological sample storage:** One of the most important and valued scientific assets of RERF is the collection of biological samples. Space for the storage of newly collected samples will soon be filled. RERF must continue to give the highest priority to the reassignment and renovation of space for the secure and accessible storage of these samples, and to the development of a database for access to sample identification, location and other information.

Specific Recommendations

- 1) The SAC continues to strongly recommend that the many and varied databases of participant information and biological samples be integrated into a central database for the use of researchers in all departments. The complete data on every subject ever involved with ABCC-RERF research should be retrievable with ease. These efforts are crucial to RERF’s central mission. We understand that efforts at such consolidation are underway and look forward to a full report at next year’s meeting.
- 2) Principal investigators (PIs) should not depend solely

upon internal research funding, and should continue to be encouraged to obtain competitive external grants from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and other sources.

- 3) The SAC appreciates the efforts that have been made toward the resolution of the issues surrounding the potential impact of black rain on dosimetry, and linkage between black rain and health outcomes in the face of currently elevated public concern. We understand that full resolution of these questions may not be possible due to many uncertainties in the data, but we are confident that RERF is undertaking appropriate analyses where possible and encourage publication of the findings.
- 4) As high-throughput technologies are adopted in basic science and epidemiological studies, thought must be given to the future bioinformatics needs, which will exceed the capacity of the current Statistics Department. The department should explore the possibility of developing links with outside collaborators in advance of recruitment needs.
- 5) The SAC commends the ongoing efforts of seminars and interactions between and within departments. These could perhaps be leveraged into development of a smaller number of more focused research areas, such as in the example of the immunosenescence program, to help reduce the fragmentation of research effort. Establishing a professional development seminar series for young investigators may also have merit.
- 6) The ongoing collaborations with external organizations are commendable, but the SAC suggests that these and new collaborations should seek to include some level of support for RERF efforts, such as through subcontracts.
- 7) More high quality publications are essential for the continued success of RERF.

Individual Department Reviews

Department of Radiobiology/Molecular Epidemiology

Overview

The Department of Radiobiology/Molecular Epidemiology (RME) has two major laboratories performing independent but complementary research: Cell Biology Laboratory and Immunology Laboratory. The primary focus of the department is to clarify the molecular basis of radiation-induced malignant and non-malignant diseases with a focus on immunosenescence and potential epigenetic mechanisms of disease causation. Department Chief Dr. Kusunoki, is to be complimented on integrating these two areas and having investigators communicate in a productive manner. Dr. Nakachi, the PI on the National Institute of Allergy and Infectious Diseases (NIAID) project and the former department chief, retired four years ago, but was present at the informal meeting. His experience and continued interactions are viewed as important to the continued success of this department and the NIAID work. These individuals provide strong leadership and should serve to guide the department well in the future.

Much of the proposed research involves archival Adult Health Study (AHS) tissues, a resource unique to RERF. This work is important, relevant, and significant in terms of RERF. One recommendation is that the department clearly describes how the results will impact on other analyses of the AHS data.

The proposed methylation studies were vague and lacked focus and a clear hypothesis. The preliminary data presented on methylation, association with genotypes, inflammatory biomarkers, etc., need to be clearly prioritized. This department is comprised of small and relatively diverse groups with a finite number of investigators. The projects proposed are very ambitious and complex. While all are potentially interesting, the SAC again recommends that these should be related to how the data obtained in these studies will influence the AHS, and future research should be prioritized accordingly.

It appeared that some of the research-based support was for work of specimen collection, archiving and retrieval. While such activities are critical to the RERF mission, this kind of activity could be carried out by a specialized support section rather than by a research department. It is important to stress that quality control issues with archival issues are being addressed and new techniques are being developed and applied. Another recommendation would be that a consolidated protocol for sample/specimen collection, a detailed database with information on the location of the sample storage site, the mode of storage, etc., be established as soon as possible. This is essential and would be a benefit to RERF and the worldwide research community.

Evaluation and Critique

It was very encouraging to see that most projects presented in the informal session utilized archival tissue samples. Dr. Taga's project on molecular analysis using archival formalin-fixed paraffin embedded (FFPE) tissues is state of the art and progressing well. Dr. Hamatani's project characterizing gene alterations in thyroid cancer is obviously of significant current interest and he is encouraged to focus on rearrangements of the *ALK* genes as many other investigators worldwide are working on *RET* gene alterations. Although the proposed methylation studies on papillary thyroid carcinoma (PTC)-related genes are interesting and timely, this project needs to be prioritized in terms of limited resources being applied to morphological characteristics of PTC with rearranged *ALK* genes, the tumorigenic potential of rearranged *ALK* and *RET* genes and the proposed methylation studies. Dr. Kajimura's study on DNA damage (as measured by foci formation) in circulating hematopoietic stem cells (HSCs) is hypothesis driven but needs to be considered in terms of the AHS and how the results obtained will be interpreted and its potential to the AHS. Likewise, both the influenza vaccination study of Dr. Hayashi, and the thymus study using specimens from A bomb survivors are hypothesis driven, well conceived, and interesting. But how the results generated will impact AHS is not clearly spelt out. The quality of the immunohistochemical analyses in the thymus study are impressive given these are old archival tissues and complement nicely the molecular analysis being performed by Dr. Yoshida. There was considerable enthusiasm for the studies on

cardiovascular disease (CVD) in rats proposed by Dr. N. Takahashi and colleagues. This is a potential interesting model system and relevant to studies of the AHS. It is important that the biomarkers in peripheral blood to be measured are based on past AHS data. The investigators are encouraged to go to lower radiation doses consistent with the AHS and propose mechanistic (rather than measurement) studies for the future.

In 2011, members of the department were authors on eight papers published or in press in English language journals. Of these articles, five were associated with an RERF RP. Only three of the eight publications had RME staff as first or last author, and all these were associated with an RP. Six additional articles, all with RME first or last authors, and all but one with associated RPs, were submitted for review in 2011. In absolute numbers, this bibliography represents a slight turnaround from the decrease in publication numbers noted last year, although the importance of primary authorship on papers in international journals still needs to be emphasized. The department lists 28 external collaborations, all but seven of which are associated with RPs. Members of this department have also given 12 presentations at domestic and international meetings in the past year, including presentations at a high profile American Association for Cancer Research (AACR) conference and a Keystone symposium. This activity is important for both the exchange of ideas, and for maintaining domestic and international recognition for RERF and its mission.

Specific Recommendations

1. As always, emphasis should be placed on maintaining and improving the publication record of the department, especially with respect to primary authorships in English language journals.
2. Continue to integrate the department. Communication between the active investigators within the department is essential to both productivity and synergistic interaction. Furthermore, expanding this communication to include the Statistics, Clinical, and Epidemiology Departments would be very informative and considerably strengthen RME.
3. It would be useful to see a more defined rationale for the experimental studies in terms of how these will impact the AHS.
4. Focus the proposed methylation studies in terms of the AHS, and provide a clear hypothesis on why methylation analysis will be investigated in the subset of genes selected. Epigenetic changes appear to play a role in the pathogenesis of radiation-associated diseases. However, the current measurement is not based on findings that were explored by studies of radiation biology. The link between epigenetic changes and radiation should also be investigated from the viewpoint of radiation biology.
5. Phenotype-genotype association analyses in immunogenome research mainly focus on immune- and inflammatory-related genes to investigate the effects on the immune system by radiation. The analysis of genes directly or indirectly involved in cellular functions that respond to radiation should be

- emphasized.
6. Laudably, this group has focused on archival tissue, as is appropriate. But variations in sample collection, storage, maintenance, location, etc., might well influence any results obtained, and hence their credibility. Have a subgroup, or preferably an independent support group, determine the location, quality, mode of storage, precise tissue sample, age of specimen, date of collection, etc., compile this information and make it available electronically.
 7. Some standardization of protocols should and must be developed for these archival tissues. This includes detailed protocols for preparation of samples for analysis (e.g., nucleic acid analysis and histology) as well as detailed quality control standards for sample analysis.
 8. Continue the rat CVD studies, but ensure there is a clear “control” or “baseline” established to evaluate the potential effects observed after irradiation.

Department of Genetics

Overview

This celebrated department has been a major scientific engine of the RERF, with a huge legacy and the charge of documenting the human germ cell mutation rate attributable to ionizing radiation.

The Department of Genetics is comprised of two laboratories, Cytogenetics and Biochemical Genetics. With seven professionals at year's end, the department has four members past or approaching retirement age, representing a massive loss of experience (but also, a high potential for recruitment). One scientist, Dr. Takahashi, moved from Genetics to Radiobiology/Molecular Epidemiology for reasons not detailed, but he might be in a position to improve synergy between the two departments. Publications appearing in 2011 number 5, with 6 more in press, for a total of 11. Five of these publications have department members as first authors, two are in Japanese, and nine are linked to at least one RP. Full research protocols number 18 (5 from 2010 and 2011, and 5 from the 20th century), and one type-A study. One bibliographic entry names RPs that are not on the list of active RPs for the department, and 12 RPs have no publications. The publications addressed biodosimetry with electronic spin resonance in teeth, rates of chromosomal anomalies, mutation detection in GFP-mice, and array comparative genomic hybridization abnormalities in EBV-transformed lymphocytes. Six external funding awards partially supported the work, including awards from MEXT and the Japan Chemical Industry Association. They list 11 external collaborations, all associated with at least one RP. Members of this department have also given nine presentations at domestic meetings in the past year, plus one presentation at the International Congress of Radiation Research. Such presentations are important for both the exchange of ideas, and for maintaining domestic and international recognition for RERF and its mission. The SAC continues to encourage the development of a stronger presence at international radiation meetings. One member helped in Fukushima and published the experience in the local medical journal. The dosimetry unit was prepared to

accept specimens from Fukushima, but none were sent.

In addition to the formal overview given on the first day, seven brief presentations were given to members of the SAC in the informal session to apprise us of recent progress on current projects. Department Chief Dr. Kodama first gave an overview of the historical genetic studies that have used different approaches to try to detect genetic effects in the children of A-bomb survivors. All studies to date have been negative. Dr. Kodaira presented an update on the mouse comparative genomic hybridization (CGH) study where 9 copy number variations (CNVs) have been detected in offspring of exposed mice, and 12 in the control group. The CNVs in the exposed group may be larger than those in the controls, but the number of events is too small to determine significance. If differences in the type of events in offspring of irradiated parents do occur without concomitant increases in the frequency of events, this would be an important and interesting finding. Dr. Satoh presented a collaboration with the RIKEN group in which DNA sequences from irradiated clones will be compared with that of the un-irradiated original cell line through commercial whole genome sequencing. Data analyses will be performed at RERF with technical support by the RIKEN group, and the data will be compared with CGH data to be derived from the same clones. In a related talk, Dr. Asakawa presented a study examining the sensitivity of next generation sequencing for detecting deletions in genomic DNA. Also, Dr. Noda presented a study of persistent repair protein foci that remain unrepaired in growth-arrested cells for at least a year. The foci are thought to represent unrepaired double strand breaks, and appear to be affected by the expression levels of aging (progerin) and immortalization (hTert) related proteins, possibly presenting a link to aging or radiation-accelerated aging. Dr. Hamasaki presented a study of differential tissue sensitivity for translocations in mice irradiated *in utero*.

In the informal sessions, two talks on comparisons of biological dosimetric endpoints with the DS02 dosimetry were also presented. Dr. Kodama gave an overview of cytogenetic techniques and refinements to translocation measurements using fluorescent *in situ* hybridization (FISH), which still indicate some discrepancies with the DS02 dose estimates for some individuals. Dr. Hirai presented a similar study using electron spin resonance, which showed better agreement with the cytogenetic measurements than with the DS02 dose estimates. No additional conclusions appear to have been reached in this area since last year.

Evaluation

In short, this year has not been as productive as previous years, with work that seems fragmented and poorly focused. This was especially obvious in the seven short presentations in the informal breakout sessions. We note that the response to last year's recommendations was “brainstorming” (about leadership, prioritization, and moving into total genomic sequencing), but the results of this brainstorming never emerged. In a sense, the separate consultation about the department was a partial response from the administration. So, although the department was designated as one to be considered in depth this year, the Advisors were aware that

a more comprehensive review would occur following the SAC meeting as part of deliberations about possible changes concerning the future role of the department in the mission and structure of the RERF.

Recommendations

Genetics is the basic foundation of all biology, medicine, and biomedical research. In their role of genetic advisors for all of RERF, the geneticists should be proactive in educating other departments and bringing them the cutting edge tools of genetics. Right now, they should catalyze an early, quick, and thorough departmental discussion that then engages other departments and the administration on the RERF's commitment to genomic sequencing as a tool for the present and future.

- Those discussions and decisions could generate hypotheses that are best addressed by third generation sequencing. The form of RERF's commitment to this technology should be carefully considered.
- Topics could include addressing definitively the issue of genetic effects in the offspring of survivors, the molecular and mutational basis of radiation carcinogenesis, possible signatures of radiogenic cancers, and epigenomic contributions to radiation effects.
- Perhaps an RERF workshop could be devoted to "radiation research in the post-genomic era," or to a more focused theme, such as "germ cell mutation detected through genomic sequencing." A draft agenda was offered by one member of the SAC.
- Decisions on investing in large equipment or in bioinformatic skills or both should be made this year, lest RERF miss these genetics tools of the decade.

Similar scrutiny within the department and in concert with outside collaborators is needed in the choice and use of animal models, which are pivotal to some questions in radiation biology.

- Our puzzlement over the choice of a *rat* model for studies of female germ cell mutagenesis, and *mice* for male germ cell mutagenesis was not resolved, but may have a simple explanation.
- The images of somatic AND germ line mutations *in vivo* or in explants from the GFP-mutant mouse are stunning and spectacular. Concerns surfaced, however, about adding an autosomal gene, in addition to the X-linked marker presently used.
- The targeted issue to address with animal studies seems to be, NOT somatic cell mutation in carcinogenesis (better studied in other ways), but rather germ cell mutation, which is a neglected facet in estimating the doubling doses of radiation for germ cell mutation in humans compared to mice.

Department of Clinical Studies

Overview

With nine professionals (five in Hiroshima and four in Nagasaki), the department continues to be very productive in original research, despite enormous "routine" clinical care and infrastructure platform duties. The Hiroshima unit will be challenged by the departure of Dr. Fujiwara, a

treasured leader within the entire Foundation. One hopes her new focus on clinical care of A-bomb survivors will allow continued interactions with RERF. A suitable replacement should be able to engage quickly as a leader. Publications appearing in 2011 numbered 26, with another 6 in press, for a total of 32, 12 of which have department members as first authors, 6 in Japanese, and 20 are linked to a RP number. Full research protocols number 28 (7 from 2010 and 2011, only 6 from the 20th century), and 10 type-A and pilot studies. At least eight bibliographic entries name RPs that are not on the list of active RPs for the department, and 25 RPs have no publications. Perhaps some winnowing of RPs is in order. Of 25 presentations made by members of the department, 6 were overseas. Several publications reflect Dr. Fujiwara's roles with multi-centered studies, a sage use of her skills and experience and a favorable reflection on the RERF. Eleven awards of extramural funds have been won, mostly from MHLW and MEXT, and from the National Center for Geriatrics and Gerontology, for studies on aging.

In good response to last year's suggestions, the main report and the five short presentations in the breakout session showed hypotheses and rationales that were better articulated than before and new crucial collaborations with clinicians have been forged. Attention has been paid to common diseases, like diabetes mellitus type 2, chronic kidney disease, and hepatitis and hepatoma, but also to conditions as rare as short QT and Brugada syndromes.

The major platforms of the AHS, the F₁ Clinical Study (FOCS), and the expanded cohort of survivors exposed in youth are going well. Participations rates of 69% in FOCS are of possible concern, but this was not explored during discussions. Single numbers of subjects refused further participation and only a few refused use of blood for genetic studies, harbingers of success.

Greater interaction with Genetics and other departments is encouraged, to explore analysis of family histories, which are finally being collected, and possible use of whole genome or exome sequencing (to replace panels of genetics markers) to improve the likelihood of fresh discoveries.

The continued collection of cataracts, a point of discussion last year, was not addressed. The same points of concern emerged this year about a new RP and strategy for collecting thyroid surgical samples, at great cost, but without firm purpose. A stronger rationale should be stated.

We sensed the young physicians were satisfied with their work, but yearn for more formal training, which might be met with some cross-institute program of professional development.

Recommendations

1. The department should maintain and improve its publication record, especially with respect to primary authorships in English language international journals.
2. More collaboration between Clinical Studies staff and the staff of other departments is urged. Additional domestic as well as international collaborative research should be considered.
3. The research on radiation and noncancer diseases should be continued and strengthened together with recruitment of young researchers.

4. The descriptive findings of negative relationship between radiation dose and body mass index (BMI) should be clarified at the standpoint of mechanism such as presence or absence of insulin resistance using various markers measured. Similar to other phenomena of aging promotion by radiation, the interaction between metabolic syndrome and negative correlation of BMI should be clarified.
5. The collaborative study with Melbourne of the decreased caliber of retinal veins with increasing radiation dose should be carefully analyzed and explained theoretically.
6. The CVD incidence study and the association between chronic kidney disease and CVD risk factors among atomic bomb survivors should be strengthened and summarized as a full paper. With small numbers of cases in some strata, it is crucial to recognize the rare disease that might be a clear etiology of a more commonly appearing phenotype, such as stroke, heart attack, or renal insufficiency, e.g., polycystic kidney disease for the latter.
7. Improvement of support system and evaluation needs to be considered for the routine work of clinical studies.
8. To further strengthen research activities, more frequent discussion and internal review should be done frequently together with interdepartmental cooperation.

Department of Epidemiology

Overview

The Epidemiology Department continues to be central to the RERF and its efforts to understand the role of radiation and subsequent health conditions. Four major cohorts are followed at RERF and the Epidemiology Department plays a crucial part in developing accurate data to understand dose response from radiation that is critical for both incidence and mortality in cancer and for noncancer endpoints, such as cardiovascular disease, myelodysplastic syndrome, liver and thyroid disease. The LSS cohort has 120,000 individuals, the AHS cohort 18,611 individuals, the *in utero* cohort 3,600 individuals as well as the F₁ cohort of children of atomic bomb survivors that consists of approximately 77,000 individuals. Follow up of over 200,000 individuals is ongoing.

The LSS cohort has followed individuals between 1950 and 2003, with 2007 follow-up data currently being analyzed. Approximately 37% of the members of this cohort were still alive at the end of 2007. Approximately 89% of the members of the *in utero* cohort and 90% of the F₁ cohort are still alive. In response to a suggestion from the SC in 2011, RERF developed and presented a chart comparing the proportion of each cohort by radiation dose. This chart is exceedingly helpful as an epidemiologic tool and clearly publications can build from this to compare dose effects.

In addition to the clear trajectory of accomplishment evidenced under the leadership of Dr. Osaza, the tragedy of Fukushima has added responsibility to the Epidemiology Department, which they have clearly carried out diplomatically and energetically. RERF can be proud of the professionalism and real utility of the Epidemiology Department.

The department has engaged in multiple activities over the last year. There has been an impressive increase in publications (30 in international journals: 14 published, 9 in press, and 7 submitted as well as contributions to international data collections, such as the International Agency for Research on Cancer (IARC) publication *Cancer Incidence in Five Continents*. Some of these publications have been in top journals, such as the *Journal of Clinical Oncology* and other journals with a wide readership. Furthermore, there have been 27 presentations at 20 meetings during the past year by members of this department, a strong record of productivity.

The department has completed the LSS Mail Survey with a 77% response rate. Vital information has been obtained. They have completed pathology reviews for soft tissue tumors and thyroid cancer. LSS mortality data up to 2007 and population-based cancer registry data up to 2007 have been completed. In addition, 250,000 documents with baseline information on the LSS between 1947 and the 1960's have been scanned.

Last year this department was intensively reviewed. Suggestions included (1) prioritization of projects, (2) more accurate characterization of the denominator for incidence studies, (3) a table detailing dose distributions for the various cohorts, (4) more first or last author publications, (5) detailed consideration of methodology, such as focus on genetic risk, comparison of incidence and mortality rates with other Japanese populations, and evaluation of exposure to medical radiation, and (6) more intensive collaborative efforts among departments. These suggestions have been carefully considered and the results are in most instances impressive. The department is currently working on 22 full-scale studies and 10 preliminary or pilot studies. These have all been thoughtfully considered and collaborators with other institutions have assisted in bringing these studies to fruition or development. In addition, there is clear evidence of more collaboration among the Epidemiology Department and other departments, such as the Statistics Department and Clinical Studies.

Other collaborations have been fruitful and include those with the University of Washington, the Asia Cohort Consortium, the U.S. National Cancer Institute (NCI), Kurume University, Kyushu University, the Japanese National Institute of Radiological Sciences, Hiroshima University, Nagasaki University and local hospitals.

Evaluation and Critique

The department has been generally impressive in responding to last year's critique. Collaborations are maturing and productivity is increasing. Database work is continuing and is clearly a priority.

Recommendations

1. Based on the progress seen, it would appear that projects have been prioritized and consolidated. However, there is a great deal of work for this department and they could profit from further prioritization.
2. The Epidemiology Department is the logical place to study genetic risk. Therefore, more collaboration with other departments, such as the Genetics Department and the RME Department where genetic factors are

assessed would be useful. It would be helpful for the Epidemiology Department to conduct focus groups among the LSS to understand the barriers to collection of saliva.

3. Continue to follow up on exposures to medical imaging among cohort members. There is a great deal of such data available in the 2008 mail survey that will be highly relevant to add to the current dose estimates for that population.
4. The department is encouraged to complete, as soon as possible, the needed adjustments to LSS study subjects' location and shielding for the DS02 system based upon their re-evaluations of the original maps and aerial photographs.
5. As the younger cohorts have fewer "events" and need to be followed for a long time, efforts need to be implemented to maintain high participation and reduce loss to follow up. Also, efforts to obtain up-to-date denominators for population studies should continue.
6. There is a clear need to push studies to quicker publication. For example, the follow-up status of the LSS, *in utero*, and F₁ cohorts collected in 2007 should be published as soon as possible as well as the analysis and results on leukemia in the *in utero* cohort.

In summary, there has been an increase in productivity, fulfilling previous promise. The SAC anticipates a continued upward trajectory.

Department of Statistics

Overview

The Department of Statistics provides statistical consultation and collaboration with investigators in other departments at RERF and conducts original independent research on statistical methods to provide insight and enhancement of design and analysis of studies conducted at RERF. The department is ably led by Dr. Harry Cullings and consists of eight statisticians, one of whom left in August 2011 and a second who will leave this month. The department also has the support of two research assistants.

There is one full scale RP, as well as eight type-A research protocols and pilot studies. Seventeen papers were published in English language journals, with eight in press and eight submitted. Only one published paper was a first author publication, however. Of those in press three are first-author papers and five of the eight submitted papers are first author. Finally, of the 17 published papers, 7 are in collaboration with the Epidemiology Department and of the 8 papers in press, 7 are in collaboration with the Epidemiology Department. The high level of involvement in the RERF community noted at the last review is still clearly evident, and clearly focused attention has been given to collaboration with the Epidemiology Department.

Evaluation and Critique

Organizationally, the department appears to be functioning smoothly. Basically, the department should continue on its trajectory and continue to follow the recommendations from last year:

- Continue to emphasize statistical collaboration, especially with the Department of Epidemiology.

- Continue efforts in methodological research.
- Continue support of academic outreach. This should include collaborations with experts in other institutions and making more presentations at statistical meetings.
- Continue support for consulting, mentoring of junior investigators, and the career development of staff.

Clearly the most important departmental need is to replace the two senior statisticians who have returned to the U.S. Since only two publications have been submitted over the past two years by one of these researchers and none by the other, care should be given to continue recruiting productive researchers who publish at least at the same level as the current departmental staff.

One of the most important departmental research activities is the work on the department's RP: Shielding survey and dosimetry study. The entire RERF organization depends on having the best available dosimetry information. It is very encouraging to see the number of publications that the department has been producing in this critical area and it is important to continue giving dosimetry a high priority.

Overall the Statistics Department has been productive in both collaborative research and basic methodology development that applies to RERF research topics. Dr. Cullings has been an effective leader of the department and hopefully the department continues on its successful path.

Recommendations

Statistical methodology:

The Department of Statistics has been a global leader in the development of biostatistical research during the last several decades, including development of original models of statistical analysis for collaborative studies with other departments in the RERF. They have produced many original papers, but we urge an RP for the development of new models of statistical analysis, which could contribute to the practical evaluation of the past A-bomb exposures. Newly established statistical models could originate not only from their own RPs, but also from RPs in other departments at RERF.

Interdisciplinary collaborative research:

The Statistics Department has contributed to development of many RPs in the past, especially for the Departments of Epidemiology, Genetics, and RME. Recently more collaboration and consultation with other departments have been needed. For the Department of Clinical Studies, biodosimetric estimation of low dose radiation exposure by medical examination as well as the past A-bomb exposure could be evaluated more accurately.

Gene-environment interaction:

The department is currently carrying out important work on the appropriate design of epidemiological studies, which is well received and encouraged. The technology of genetic analysis is currently progressing rapidly and whole genome analyses will be applicable in medical research in the near future. Simultaneously with the rapid development of genomic technologies, computer technologies for biostatistics and bioinformatics are also progressing. Ordinary biostatistics and bioinformatics will also continue to play key roles in future analyses.

Inflammation:

Radiation effects on the immune system resulting in inflammation and subsequent cardiovascular effects have received considerable attention at RERF. The Statistics Department is exploring this pathway using particular statistical models for other possible radiation-related endpoints. They are encouraged to interact closely with researchers in the Clinical Studies Department.

Dosimetry:

The Statistics Department has been evaluating the basic LSS dosimetry with several publications and extensive collaborations. The department is encouraged to make, as soon as possible, the needed adjustments to the DS02 system based upon the Epidemiology Department's re-evaluation of the original maps and aerial photographs.

Bioinformatics:

As the experts in massive database management and analysis, we urge the statisticians to engage other departments, especially Genetics, to examine the needs for strengthened bioinformatics expertise.

Public Relations

The horrific Fukushima disaster presented unprecedented challenges to the public relations (PR) staff and had the beneficial consequence of illustrating the scientific and public value of the entire RERF enterprise. A new RERF website was quickly mounted to address the public and media demand for accurate information. Two million hits on the website, an avalanche of emails—all answered by professional staff members—and news coverage in *Nature* and *Science* served to enhance the already august reputation of the Foundation and its scientists.

The PR group does best when RERF scientists reveal novel findings in top peer-reviewed journals, so RERF scientists should strive for major publications every year and a comprehensive review every four years in a major biomedical journal.

Specific Recommendations:

- The unique experience and practical lessons of communicating hard science during a national emergency might be reported in relevant literature.
- PR staff might productively interact with the public relations professionals of RERF's major sponsors, the U.S. NAS, DOE, NIAID, and NCI, and Japan's MHLW and major university partners in Hiroshima, Nagasaki, and Kurume.
- Model curricula, including slides for 15 minute and 50 minute lectures on the health consequences of radiation, might be prepared and mounted on the website in various languages for medical students, practicing physicians and other health care professionals, and physicians in training for radiology and radiation therapy, as well as graduate students in biomedical sciences. There might be merit in exploring the possibility of awarding continuing educational credits for self-directed tutorials for web-based instruction aimed at health professionals who need such credit.
- The museum display might be translated and sent to overseas museums (at their expense).

- Social media, such as Facebook, Twitter, and LinkedIn, might be mobilized to disseminate the message and mission of RERF. Innovative approaches like PM-codes for cell phones might also be useful.
- The annual meeting of the Japan Radiation Research Society (JRRS) might be an occasion to reach students at local universities and even secondary schools with the grandeur and excitement of radiation research. Public lectures for adult learners might be offered in other major cities beside Hiroshima and Nagasaki.
- The film, *Black Sun of Hiroshima*, might be given English or other language subtitles for regional distribution worldwide, by television, cinema, or DVD. Consider showing the French version in the background at the SAC reception in 2013.
- Advantage might be taken of the new PIIF status, to receive and even solicit philanthropic and charitable donations from personal and corporate friends, even alumni(ae), of the RERF.

RERF International Workshop: Radiation Effects on Mutation in Somatic and Germline Stem Cells

January 18–19, 2012

Asao Noda, Assistant Chief, Department of Genetics

The above workshop was held in the RERF Auditorium on January 18–19, 2012

Stem cells play a principal role in the continuous provision of new cells in the body. As long as stem cells are healthy, old cells can be replaced by new cells, whereby tissue homeostasis is maintained. Dramatic progress has been made recently in the area of research into somatic and germline stem cells, and consideration of radiation effects on such stem cells is important for investigation of radiation effects on human health. The international workshop, aiming at debate about the current status of stem cell research as well as effects of radiation on stem cells, was attended by four stem cell researchers from abroad and five from Japan (experts related to stem cells of the small intestine, skin, testis, and bone marrow).

At the workshop, lectures were provided by Catherine Booth (keynote lecturer; Epistem Ltd., UK), David T. Breault (Harvard Medical School, USA), Jolyon H. Hendry (Christie Hospital NHS Foundation Trust, UK, and member of the International Commission on Radiological Protection [ICRP]), Toshio Suda (Keio University), Takashi Shinohara (Kyoto University), Claudia E. Ruebe (Saarland University, Germany), Emi Nishimura (Tokyo Medical and Dental University), Hiroshi Mitani (The University of Tokyo), Asao Noda (Assistant Chief, RERF Department of Genetics), Nori Nakamura (RERF Chief Scientist), and Ohtsura Niwa (Professor Emeritus, Kyoto University). The workshop concluded with a comprehensive discussion regarding how data related to radiation effects on stem cells would contribute to RERF's ongoing research into cancer risk estimation.

The following questions were introduced at the workshop and identified key problems for consideration by all participants:

- (1) Where do tissue stem cells reside and function in tissues undergoing typical cell turnover? Is it possible to locate stem cells within tissue, by characterizing tissue stem cells?
- (2) What characteristics do stem cell niches maintaining tissue stem cells have?
- (3) What effects does radiation exposure have on stem cells, or, how do stem cells behave in response to radiation exposure?
- (4) What effects does radiation response of stem cells have on tissue radiosensitivity and recovery from radiation exposure?
- (5) Functional deterioration of stem cells is suggested as the cause of aging. Is it possible to successfully observe such histological (pathological) changes? Does radiation exposure affect the aging of tissues?
- (6) Is it possible to explain risks from fetal or childhood radiation exposure in terms of the behavior of tissue stem cells?

- (7) Is it possible to explain risks of radiation carcinogenesis in terms of the radiosensitivity of tissue stem cells?

The following summarizes my thoughts regarding the questions and issues listed above, after taking into account reports by workshop participants:

The small intestine is a target organ of radiation effects. In the body, the small intestine is composed of the most active tissues in terms of cell division, with digestive and absorptive cells newly born in small-intestinal villi completing their roles in approximately five days, upon which they are replaced by new cells. The intestinal basal membrane contains intestinal crypt structures, which in turn house intestinal stem cells. Dr. Booth outlined previous intestinal stem cell studies, and Dr. Breault introduced the latest findings, concluding that Tert(+) cells, which reside at the +4 crypt position from the crypt base and undergo cell division extremely slowly, are true stem cells (multi-potent intestinal stem cells: ISCs). Future tasks include determination of whether or not it is possible to explain intestinal radiosensitivity and acute radiation symptoms observed at the individual level in terms of radiosensitivity of ISCs.

The most radiosensitive stem cells are those of the bone marrow. Radiation therefore causes symptoms of anemia. Dr. Suda discussed a maintenance mechanism for bone marrow stem cell properties and concluded that hypoxia in niches and hypoxic signaling (HIF-1 α signaling) are indispensable as part of this mechanism for maintaining stem cell quiescence. Dr. Hendry stated that there was a correlation between degree of differentiation, hypoxia, and radiosensitivity of bone marrow stem cells, adding that the more undifferentiated/hypoxic cells have greater radio-resistance. Discussions engaged in by the four researchers mentioned above suggested the possibility that a hierarchical stem cell organization governing 'stemness' is present and that more primitive stem cells are more quiescent (slowly cycling) and more radio-resistant. This would represent a new development transcending the conventional wisdom that self-renewing stem cells are highly sensitive to radiation.

Spermatogonia are the original germ cells, from which spermatozoa are produced, and hence the possibility exists that radiation effects on spermatogonia are expressed as hereditary, or transgenerational, effects. Dr. Shinohara has successfully cultivated spermatogonia extracted from mice testis, while maintaining stem-cell properties. If *in vitro* reproduction of meiosis and spermatogenesis can be realized in the future, the field of radiobiology would benefit significantly. Dr. Ruebe, who investigated the recovery process (damage repair) in spermatogonia from radiation exposure, reported that the initial phase of spermatogonia radiation response was different from that of somatic cells.

The skin is composed of tissue cells that repeatedly divide over a lifetime and contains stem cells. The skin is one of the target organs of radiation disorders and is suited

for observation of the aging process. Dr. Nishimura, who analyzed radiation-accelerated senescence mechanisms in melanocyte stem cells, reported that these stem cells differentiated into pigment cells in stem cell niches, leading to the aging of such cells. This suggests that, since stem cell niches cannot maintain melanocyte stem cells as stem cells, aging of the skin may very well start at this point.

With regard to the development of model systems for research into radiation effects on stem cells, Drs. Mitani and Noda reported on *medaka* (*Oryzias latipes*)- and mice-based experimental systems, respectively. Both aimed at visualizing effects on stem cells (apoptosis and mutations) *in vivo*. Those systems are likely to make visible and observable the origins of radiation carcinogenesis in the body.

Sometimes effects of adulthood radiation exposure persist over a lifetime, while in some cases effects of fetal exposure are not detected postnatally. Dr. Nakamura reported that no effects of fetal radiation exposure observed using chromosomal aberrations as a marker were detected in adult lymphocytes.

Finally, Dr. Niwa reported on changes in tissue stem cells and stem cell niches through ontogeny, growth, and aging, adding that the relevant changes affect risk of radiation carcinogenesis.

In relation to this workshop, I would like to take this opportunity to express my deep appreciation for the support we received from the Ministry of Health, Labour and Welfare as well as the cooperation from so many people in line with the plan prepared by the RERF Department of Genetics. A more detailed account of the workshop has been published and is available at the *International Journal of Radiation Biology* 2012 (June); 88(6):501–6 (DOI: 10.3109/09553002.2012.683512)

— Program —

January 18, 2012

Opening Remarks

Toshiteru Okubo (RERF)

Introduction

Yoshiaki Kodama (RERF)

Aims of this workshop, and brief notes on genetics and somatic cell genetics study of RERF, introduction of speakers

Session#1: Stem cell research for tissue development, regeneration and recovery from radiation injury

Chair: Asao Noda (RERF)

Keynote lecture: “The role of stem cell in the response of the intestinal epithelium to radiation injury”

Catherine Booth (Epistem Ltd.)

“Role of slowly cycling telomerase-expressing intestinal stem cells in response to intestinal radiation injury”

David T. Breault (Harvard Medical School)

Session#2: Bone marrow research: tissue development, regeneration and recovery from radiation injury

Chair: Kengo Yoshida (RERF)

“Bone marrow regeneration after acute, fractionated,

and chronic radiation”

Jolyon H. Hendry (Christie Hospital NHS Foundation Trust)

“Maintenance of hematopoietic stem cells in the niche”

Toshio Suda (Keio University)

Session#3: Germ line stem cells: tissue characteristics and mechanisms of recovery from radiation injury that affect on genetic effects of radiation

Chair: Yasunari Satoh (RERF) and Kanya Hamasaki (RERF)

“Derivation of stem cell lines from the male germline”

Takashi Shinohara (Kyoto University)

“Radiation effects on tissue-specific stem cells”

Claudia E. Ruebe (Saarland University)

“Stem cell regulation and aging in hair follicles”

Emi K. Nishimura (Tokyo Medical and Dental University)

Session#4: Some data and ideas for future studies

Chair: Yoshiaki Kodama (RERF)

“The radiation-induced transdifferentiation in the adult testis of p53 deficient *medaka* (*Oryzias latipes*)”

Hiroshi Mitani (The Tokyo University)

January 19, 2012

“Development of recombinant mouse model for the study of genetic effects of radiation”

Asao Noda (RERF)

“The fate of fetal HSCs following radiation exposure”

Nori Nakamura (RERF)

“Comments for future study: How to connect stem cells to the age dependent sensitivity of radiation carcinogenesis?”

Ohtsura Niwa (Kyoto University)

Closing remarks

Roy E. Shore (RERF)

Participants

Catherine Booth: Founder and Managing Director, Contract Research Services, Epistem Ltd., UK

Claudia E. Ruebe: Professor, Department of Radiation Oncology, Saarland University School of Medicine, Germany

David T. Breault: Professor, Department of Pediatrics, Harvard Medical School

Emi K. Nishimura: Professor, Division of Stem Cell Biology, Medical Research Institute, Tokyo Medical and Dental University

Hiroshi Mitani: Professor, Department of Integrated Biosciences, Graduate School of Frontier Sciences, The University of Tokyo

Jolyon H. Hendry: Consultant, Christie Hospital NHS Foundation Trust, UK

Ohtsura Niwa: Professor Emeritus, Kyoto University

Takashi Shinohara: Professor, Department of Molecular Genetics, Graduate School of Medicine, Kyoto University

Toshio Suda: Professor, Department of Cell Differentiation, The Sakaguchi Laboratory of Developmental Biology, School of Medicine, Keio University

<RERF>

Toshiteru Okubo: Chairman
Roy E. Shore: Vice Chairman and Executive Director
Evan B. Douple: Associate Chief of Research
Nori Nakamura: Chief Scientist
Saeko Fujiwara: Chief, Department of Clinical Studies,
Hiroshima
Yoshiaki Kodama: Chief, Department of Genetics
Yoichiro Kusunoki: Chief, Department of Radiobiology/
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Kotaro Ozasa: Chief, Department of Epidemiology, Hiroshima
Harry M. Cullings: Chief, Department of Statistics
Asao Noda: Assistant Chief, Department of Genetics
Douglas C. Solvie: Associate Chief of Secretariat
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of Genetics
Kanya Hamasaki: Research Scientist, Laboratory of Cytoge-
netics, Department of Genetics
Yasunari Satoh: Research Scientist, Laboratory of Biochem-
ical Genetics, Department of Genetics
Kengo Yoshida: Research Scientist, Laboratory of Immunol-
ogy, Department of Radiobiology/Molecular Epidemiol-
ogy