

Report of the 37th Scientific Council Meeting

March 3–5, 2010, Hiroshima Laboratory

Scientific Councilors

- Dr. Takashi Yanagawa (Co-chairperson)**, Professor, The Biostatistics Center, Kurume University
- Dr. John J. Mulvihill (Co-chairperson)**, Professor of Pediatrics, University of Oklahoma Health Sciences Center
- Dr. Yoshiharu Yonekura**, President, National Institute of Radiological Sciences
- Dr. Katsushi Tokunaga**, Professor, Department of Human Genetics, Division of International Health, Graduate School of Medicine, The University of Tokyo
- Dr. Kiyoshi Miyagawa**, Professor, Laboratory of Molecular Radiology, Center for Disease Biology and Medicine, Graduate School of Medicine, The University of Tokyo
- Dr. Kazuo Sakai**, Director, Research Center for Radiation Protection, National Institute of Radiological Sciences
- Dr. Marianne Berwick**, Professor and Chief, Division of Epidemiology, Associate Director, Cancer Research and Treatment Center, University of New Mexico
- Dr. David G. Hoel**, Distinguished University Professor, Department of Biostatistics, Bioinformatics and Epidemiology, Medical University of South Carolina
- Dr. Michael N. Cornforth**, Professor and Director of Biology Division, Department of Radiation Oncology, University of Texas Medical Branch
- Dr. Sally A. Amundson**, Associate Professor of Radiation Oncology, College of Physicians and Surgeons of Columbia University

Special Scientific Councilors

- Dr. David Rush**, Emeritus Professor of Nutrition, Community Health (Epidemiology) and Pediatrics, Tufts University
- Dr. Koji Maemura**, Professor, Department of Cardiovascular Medicine, Course of Medical and Dental Sciences, Graduate School of Biomedical Sciences, Nagasaki University
- Dr. Yukihito Higashi**, Associate Professor, Department of Cardiovascular Physiology and Medicine, Division of Molecular Medical Science, Programs for Biomedical Research, Graduate School of Biomedical Sciences, Hiroshima University

Introduction

The Scientific Council (SC) met from March 3 to 5, 2010, in Hiroshima, Japan. Its task, as in previous years, was to review the Radiation Effects Research Foundation's (RERF) scientific programs. This year, the SC conducted an in-depth review of the Department of Clinical Studies. With its plan of focused review, the SC had the pleasure of working with Drs. Koji Maemura, Yukihito Higashi, and David Rush, Special Scientific Councilors, each with expertise in the field reviewed in depth this year. Their addition was extremely valuable.

Dr. Toshiteru Okubo, Chairman of RERF, opened the 37th meeting of the SC in the morning of March 3, providing a warm welcome to all in attendance. He reiterated that this year's SC would be providing a focused review of the Department of Clinical Studies and how important the SC's work is to the staff of RERF. He reported that RERF must convert to an approved Public-Interest Incorporated Foundation to continue receiving funding under the A-bomb Victims Relief Law. One consequence is changing the name of Scientific Councilors to Scientific Advisors. Other major administrative activities include employee training and individualized counseling, continued implementation of Senior Panel Recommendations, hosting, for the first time, the annual meeting of the Japan Radiation Research Society, and continued meetings with the Local Liaison Council, especially about their concerns about the U.S. National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases (NIAID) contract. Throughout the 3-day

session, the SC was favorably impressed over the synergy, effectiveness, and mutual respect between the Chairman and the Chief of Research, which seems conducive of the overall performance of RERF. Following Dr. Okubo's comments, Dr. Roy Shore, Chief of Research at RERF, provided a review of the status of research at RERF and provided responses to the recommendations of the 2009 SC.

Following Dr. Shore's comments, detailed presentations by the Department of Clinical Studies were provided by the department chief and five staff members. Next, a brief overview of activities of the Departments of Genetics, of Radiobiology/Molecular Epidemiology, and of Statistics, as well as the Public Relations program, the Scientific Committees and Working Groups, and the Committees on Dosimetry, on Data Management and Documentation, and on Biological Samples. The formal presentations were followed by informal meetings between various SC members and the departments. Throughout the meeting the SC reviewed and discussed the information provided about the activities of RERF.

Overview

The SC remains convinced that RERF is the pre-eminent leader in radiation risk research in the world and has the expertise, populations, and data sets needed to conduct 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 scientific guidance

of the National Academy of Sciences, continue to be critical to the mission of RERF. Without such support and the assistance of the survivors and their families, the ability of RERF to conduct substantive research that has great impact around the world would not be possible.

The mission of RERF has recently become all the more critical with the increased international concerns over radiation health risks due to: a) the nuclear power option, b) the increased use of radiation in medical screening and treatment, and c) the threat of nuclear terrorism. The scientific opportunities for improved understanding of radiation effects on human beings continue to expand, as a result of new and exciting basic laboratory findings in radiobiology that clearly indicate the need for their integration into human risk assessment through systems and computational biology. Secondly, the statistical methods through high-speed computing allow for greater sophistication in model development including the requisite incorporation of measurement and model uncertainties. Thus RERF is well positioned to move forward by rapidly improving our knowledge of quantitative radiation risk assessment. Thus the combination of the increased needs of society and the improved scientific opportunities should justify efforts of the Japanese MHLW and the U.S. DOE to increase their support of RERF.

RERF (ABCC) has enjoyed the position of the world's top research institution of radiation risk evaluation for the past half century. During this period, the world radiation protection bodies, namely the International Commission on Radiological Protection (ICRP) and the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), relied heavily on the risk values produced by RERF, and continue to do so. With their reports, and others, risk values for radiation-induced cancer and hereditary effects produced by RERF have been implemented.

The report of the Senior Review Panel (SRP) on future planning for RERF gave valuable comments on steps toward achieving the vision of being a center of excellence and encouraged more international and domestic collaboration, excellence in research planning and its prioritization, and research infrastructure. The SC appreciates that RERF made enormous strides to take into account the SRP recommendations.

RERF research is extensively focused on showing the relationship of radiation exposure and non-cancer disease, such as stroke and cardiovascular disease. Working groups and research protocols have been established to explore causal mechanisms. These are deep, difficult and time-consuming to achieve. Patience is needed to await the results, making the present a propitious time to recruit young bright researchers for these challenging problems.

With the outstanding and sustained senior leadership of Drs. Okubo and Shore, the SC predicts a bright future for science at RERF. The SC continues, however, to be concerned with the retirement of several experienced and valued senior scientists.

General Recommendations

1. The SC was pleased with the development of the 5-year goals by RERF's leadership. It is the road map for

establishing research priorities, resource allocations, and research project timelines. The SC looks forward next year to hearing in some detail about the integration of project priorities within the framework of the 5-year goals.

2. The SC continues to support the recommendation of SRP that greater interdepartmental planning take place. The SC believes that the senior leadership should be highly commended for the increased collaboration among RERF researchers. The establishment of interdepartmental committees to address specific issues is a very appropriate approach, as recommended last year. The SC was pleased to see the progress of the working groups in cardiovascular disease, F₁ studies, and dosimetry. RERF is encouraged to increase the number of appropriate working groups.
3. A centralized database integrating all available information on study participants and linking these records to available samples is needed by all departments.
4. As more studies at RERF incorporate global analysis strategies and other data-intensive approaches, there will also be increasing needs for bioinformatics support, and likely for the development of novel analysis approaches. Bioinformatics support should be developed in close collaboration with the Departments of Statistics and Epidemiology, and with input from the other "end user" departments, such as Genetics and Radiobiology/Molecular Epidemiology. Bioinformatic challenges will only escalate, not diminish and are better addressed sooner rather than later.
5. The SC congratulates RERF for successfully partnering with the U.S. NIH's NIAID, and looks forward to annual reports on its progress. We appreciate the negotiations to date and the administrative challenges ahead.
6. The SC must reiterate the need for major first-authored publications, both for individual career enhancement and for the overall reputation of RERF.
7. A training pipeline is to be encouraged because of the unique experience and expertise of RERF. A happy culture of mentoring, career development, and international presentations and publications is what the trainees and RERF need and deserve.
8. One astute scientific councilor noticed differences in the meaning of "low dose" among speakers and urges some consistency in usage. In epidemiology, the term seemed to indicate a level at or below 100 mGy and, for non-cancer effects, 100 to 200 mGy.
9. To use archival tissue and blood samples, some research groups outside RERF are striving to improve techniques for extracting biomolecules from stored biospecimens. Collaboration with them may be helpful for the better use of RERF biospecimens.

Review of the Department of Clinical Studies

Overview

Dr. Fujiwara presented an overview of the activities in the Department of Clinical Studies during the past year. The department conducts two clinical programs, the Adult Health Study (AHS), a periodic examination of a subset of

the Life Span Study (LSS), and the F₁ clinical study, a subset of the F₁ mortality study population. The past year's progress in the understanding of the effects of radiation on health status among atomic-bomb survivors was presented by several departmental investigators in the SC informal break-out session. Work on cardiovascular disease was presented by Dr. Tatsukawa, on chronic kidney disease by Dr. Akahoshi, on stroke by Dr. Takahashi, on cataract by Dr. Neriishi, and on follow-up of the F₁ cohort by Dr. Ohishi. In addition, plans for future work on rheumatic and valvular heart disease were presented by Dr. Tatsukawa, on chronic kidney disease by Dr. Sera, on breast cancer by Dr. Neriishi, on hepatocellular carcinoma by Dr. Ohishi, on thyroid disease by Dr. Imaizumi, on neurocognitive function by Dr. Yamada, and on autoimmune disease by Dr. Hida.

Progress was made in the study of the relationship of radiation to the frequency of non-cancer diseases, including cataract, cardiovascular disease, stroke, hypertension, and chronic kidney disease. The most recent study of the incidence of cataract in AHS participants suggests a monotonically increasing relationship, with no threshold effect, in contrast to previous observations of a threshold. These observations raise a novel suggestion of possibly great consequence for public health and radioprotection policies: the lens may be the most radiosensitive tissue so far studied in humans. (However, we recommend that the data be further examined for possible participation- or diagnostic biases.) In addition, the mechanism of cataract induction by radiation may be different for disease soon after exposure, for which a high threshold level (5 Gy) was observed, in contrast to a monotonically increasing dose relationship with no threshold which better approximates the more recently observed data. (See below for our recommendations.)

It was interesting to see the preliminary results showing possible radiation effects on the risk of chronic kidney disease. Combined with the previous results in hypertension and cardiovascular disease, it is likely that comprehensive analysis of multiple diseases associated with vascular and endothelial dysfunction is necessary to further elucidate the biological mechanism of radiation effects on these diseases.

The publication record for 2009, as measured by the total number of publications, was more than adequate. However, on close inspection, there are suggestions that an effort needs to be made to increase scientific productivity. In 2009 there were 19 papers listed as published by the department, nine papers in press, and seven that were submitted and that are still under review, a total of 35 papers. Of the 35, 12 had primary authors who were not department members. Of the remaining 23 papers, from the titles, 20 appear not to be related directly to the mission of RERF, and, of the 18 published or in press for which the language of publication was noted, 11 are in Japanese, and thus less likely to have world-wide influence than if published in international journals.

Recommendations

1. Cataract: RERF would do well to refocus time and effort to verify and explain the association between radiation exposure and cataract. RERF has the opportunity to become the global leader in exploring

the pathophysiological and radioprotection implications of the study of radiation cataractogenesis. Further basic biological studies are recommended to elucidate the mechanism of radiation-induced cataract while taking into account possibly confounding factors.

2. Cardiovascular disease: Basic research programs are encouraged, particularly for cardiovascular diseases, including heart disease and stroke, to clarify the mechanism of increased risk due to radiation. It might better be achieved in collaboration with scientists at other institutions than by trying to mount a comprehensive program within RERF.
3. Endothelial dysfunction is the initial step of atherosclerosis. Proposed subclinical indicators, include the augmentation index (AI), brachial ankle pulse wave velocity (baPWV), intima medial thickness (IMT), and ankle brachial index (ABI), all of which are markers of established atherosclerosis. The measurement of endothelial function, flow-mediated vasodilation, and biomarkers of endothelial function, such as circulating levels of NADPH oxidase enzymes (NOx), cyclic guanosine monophosphate (cGMP), and von Willebrand factor (vWF) might help elucidate the relationship between radiation and atherosclerosis.
4. RERF should consider assessing lifetime risk of cardiovascular diseases among the AHS cohort associated with various factors using a protocol of the AHS stroke study.
5. Although AHS stroke studies have shown the lifetime risk of stroke by blood pressure measured at middle-age among Japanese, further studies are needed to analyze these issues in younger subjects.
6. Lifetime risks for stroke were examined by type of stroke and only cerebral hemorrhage was significantly associated with radiation and limited to males. Because atherosclerosis is related to cerebral infarction more than cerebral hemorrhage, it is advisable to investigate causal factors other than atherosclerotic markers.
7. To verify the statistically significant association between radiation and metabolic syndrome, it is recommended that knowledgeable basic research collaborators be sought with other departments of RERF and other research institutions.
8. Unfortunately, echocardiography is not available in the Department of Clinical Studies. Echocardiography devices are needed to assess cardiovascular disease, including valvular heart disease, in the unlikely case that this becomes a high priority.
9. We suggest statistical consultation to reconsider the issue of analysis of multiple dependent variables. Possible multivariate clustering techniques that address the use of simultaneous multiple dependent variables could shed light of which outcomes tend to be linked.
10. It was unclear to us how priorities are being set for research issues that the department wishes to address. Some of the projects seemed of much higher importance than others. We suggest a careful RERF-wide review of the department's research priorities.
11. One of the most compelling new projects is the study of cognitive dysfunction and dementia associated with radiation exposure before 13 years of age. We strongly

urge that collaboration be initiated with the Epidemiology Department to help increase sample size by including as many LSS subjects not in the AHS as possible.

12. We suggest collaboration with outside experts to assess the feasibility of using self-administered screening questionnaires for cognitive dysfunction. Possibly outside psychologists could be hired to administer exams in distant cities.
13. While it will be very difficult, we believe the possibility of getting autopsy material from demented subjects must be seriously evaluated.

Individual Department Mini-Reviews

Department of Genetics

In short, the SC remains optimistic about the scientific direction of Genetics, which has traditionally been a strength of RERF. We observed four presentations that essentially distilled the projects outlined in detail last year. The overall impression of the SC was that the department was on the right track, with perhaps some additional effort needed to further refine their objectives. The concern, as expressed in last year's meeting, about leadership remains an issue, although perhaps to a somewhat lesser degree.

The dose-response relationship between electron spin resonance (ESR) measurements and chromosome aberrations is an excellent example of how pragmatic interests can be served while investigating basic scientific questions, and serves as an example of how RERF should function. It is important to continue the biodosimetry work using fluorescence *in situ* hybridization (FISH) techniques with particular emphasis on lower-dose exposures. As for the dosimetry with sophisticated techniques, including FISH technique and ESR, the impact of medical exposure should be evaluated.

The prospect of genomic profiling or deep sequencing represents a logical extension of past work in which obligate copy number variants were discovered among survivors. Some members of SC encouraged the use of next generation sequencing, while expressing concern about the high level of new resources required for such an endeavor if it were to be undertaken solely at RERF. Although whole genome sequencing of a number of samples is probably not realistic at this time, the proposed comparative sequencing of specific chromosomal regions between Epstein-Barr virus (EBV)-transformed cells and untransformed cells may well provide valuable information about suitability of analyzing genomic DNA from transformed cells from the crucial victims with high exposure.

Two-color FISH following fetal irradiation of rats demonstrated that chromosomal translocation frequencies were increased in mammary epithelial cells but not in lymphocytes. To confirm the tissue-specific effect of fetal irradiation, this study is planned to be continued in collaboration with the National Institute of Radiological Sciences. The department has also carried out experimental studies using animal models. Discussion should be made on how to "translate" animal data.

A pilot study to detect unreparable radiation damage

(e.g., DNA double-strand breaks) in non-dividing cells was started this year. Recruitment of several candidate proteins at such lesion sites has been investigated. Large-sized foci of proteins involved in the DNA damage signaling pathways have been detected up to two months after radiation exposure. It is, however, difficult to conclude the nature of this unrepaired lesion. Investigation of focus formation of candidate proteins in cells deficient in downstream pathways may help to understand their roles in DNA repair. Also a new research protocol (RP) that is aimed at identifying novel proteins recruited at the sites by forming protein complexes with known proteins is underway. There was also the suggestion made to study the possible linear energy transfer (LET) dependence of this phenomenon.

Discussion of possible collaboration with the Departments of Clinical Studies, or of Epidemiology, or both is advised, to make the information more convincing about the Department of Clinical Studies' findings of increased risk of certain non-cancer diseases. Investigations of mechanisms should be considered.

The publication record of just two articles in international journals is of concern.

Department of Radiobiology/Molecular Epidemiology

Overview

The Department of Radiobiology/Molecular Epidemiology (RME) is headed by Acting Chief Dr. Kusunoki, and the department has two major laboratories. The Laboratory of Immunology has four scientists with Dr. Hayashi as Laboratory Chief. The Laboratory of Cell Biology also has four scientists with Dr. Hamatani as Laboratory Chief. Dr. Nakachi, the former Department Chief, retired two years ago and is serving as a Principal Project Scientist. Fourteen full-scale RPs and seven type-A RPs and pilot studies are in place. In response to 2009 SC recommendations, the department has promoted interactions with Clinical Studies in the form of seven collaborative studies.

The primary focus of the department is to ascertain the molecular basis of radiation-induced malignant and non-malignant diseases with a current strong focus on immunosenescence and potential epigenetic mechanisms of disease causation. The two-laboratory structure was implemented at the founding of the department. Since then, the department has worked in two complementary areas. Analyses of molecular events associated with radiation-related cancer among A-bomb survivors is the major subject for the Laboratory of Cell Biology. The Laboratory of Immunology investigates the involvement of immunological mechanisms in the development of cancer and non-cancer diseases. Both groups have functioned in a complementary, even synergistic fashion. Relevant biospecimens from exposed and unexposed individuals serve as a basis for most of their work. Overall, the department efforts are consistent with RERF's mission. New questions have been addressed and new techniques have been developed and applied.

In the past 60 years, the central dogma of radiation carcinogenesis has been the straight-forward hypothesis that radiation-induced DNA damage causes mutations

responsible for the development and progression of cancer. However, the working hypothesis of the immunology group challenges this dogma by offering an alternate, but not necessarily mutually exclusive, hypothesis that radiation-induced immunosenescence plays a major role in the late development of both cancer and non-cancer diseases. The Laboratory of Immunology's current focus is on potentially accelerated immunosenescence in A-bomb survivors based on the hypothesis that radiation impairs T-cell mediated immunity. Relationships between radiation-damage response and T-cell functions have been investigated by analyzing T-cell subsets, radiosensitivity of T cells, and mutation frequencies of T-cell receptor (TCR) and glycoprotein A (GPA) using AHS subjects. The finding that T-cell populations with a compromised/senescent phenotype of cell surface receptors were increased in the atomic-bomb survivors will be published in an international journal. The laboratory also reported that the induction of GPA mutations is potentially associated with 53BP1 polymorphisms but not with ATM and NBS1 polymorphisms.

The Laboratory of Cell Biology is mainly focusing on the relationship between radiation exposure and carcinogenesis by analyzing epigenetic changes and genomic alterations in several types of cancers. The laboratory has contributed to the establishment of roles of RET/PTC rearrangements in radiation-induced thyroid carcinogenesis. In addition, they have found that the incidence of ALK rearrangements in thyroid cancers is high in exposed cases. These observations clearly indicate that chromosomal rearrangements play a crucial role in radiation-induced thyroid carcinogenesis.

Although it is well established that microsatellite instability plays a role in carcinogenesis in general, its role in radiation-induced carcinogenesis remains to be demonstrated. A pilot study revealed that lack of MLH-1 expression due to methylation or point mutations plays a causal role in microsatellite instability-high phenotype in five colon cancers. Despite this observation, the association of radiation exposure with epigenetic alterations remains unclear.

Evaluation and Critique

In 2009, members of the department have authored 13 publications, all in English language journals. Of these articles, only four were associated with an RERF research protocol. Eight of the 13 publications had RME staff as first or last author, and these included the four that were associated with an RP. Two additional articles, both with RME primary authors and associated RPs, were in press for 2010. Another four articles with associated RPs, three of which have RME primary authors, have been submitted for review. These efforts represent a reasonable number of publications in major journals and this effort should be praised considering the fact that the number of investigators in the department is not large. Though some concern was expressed over the proportion of listed publications that were not supported by RPs, this was mitigated by the fact that RME members were collaborating authors on those publications. Members of this department have also given a large number of presentations at domestic and international meetings, an activity that is important for both the exchange of ideas, and for maintaining a high profile for RERF and its

mission. The department should also be praised for the domestic and international collaborations they have established. Their hypotheses of immunosenescence and epigenetic alterations induced by radiation are interesting and challenging. However, stronger supporting evidence is still needed.

Recommendations

1. The Department of Radiobiology/Molecular Epidemiology has fully embraced the hypothesis of immunological senescence as a major mechanism of radiation health effects for both cancer and non-cancer diseases. With the award of the NIAID contract based on this idea, this hypothesis has now become a major driving force of this department. We recommend seeking to determine if there is a dose-response relationship for signs of immunological senescence, in order to further support the efforts ongoing in this area. This will also involve further collaborations with the Department of Clinical Studies to investigate the role of radiation-associated immunological senescence in disease risk.
2. Work on global and specific DNA methylation changes associated with squamous cell carcinoma of the lung should include additional non-exposed controls to more firmly establish the link with exposure. More non-cancer tissue should also be examined to determine if the observed changes are associated with exposure alone, or only with pre-cancerous changes. We wonder if the Genetics Department has some insights to add to the epigenetic approach.
3. A pilot genome-wide association study (GWAS) using single nucleotide polymorphism (SNP) arrays is planned in conjunction with the "immunogenome" project. This study will use 60 cancer samples and compare them with 2,000 normal samples that have been profiled by a collaborator. Great caution should be exercised in this area, as such small sample sizes are likely to result in a high number of false positive hits, which may be problematic for follow-up. The proposal to prioritize potential hits by the suggested involvement of known pathways may help in this analysis, but engaging a GWAS expert as an advisor at an early stage would be extremely beneficial, and could help ensure optimal use of precious specimens.
4. The preliminary finding of association between GPA mutation and 53BP1 polymorphisms suggests a role of the 53BP1-dependent damage response in genomic instability in A-bomb survivors. Extension of this investigation by targeting polymorphisms in genes downstream of 53BP1 will support this finding.
5. Investigation of the molecular genetic background underlying chromosomal rearrangement in thyroid cancer by systematic approaches in collaboration with other RERF groups will provide new insights into mechanisms of radiation-induced carcinogenesis and promote inter-departmental collaborations.
6. The effect of radiation on methylation status should be investigated by a large-scale study to explore the association between radiation exposure and epigenetic alterations that are responsible for genomic instability.

7. A role of ALK rearrangements in carcinogenesis is likely to be different from that of RET rearrangements. Linkage of genetic information with histopathological and clinical data will aid understanding of the significance of ALK rearrangements in thyroid carcinogenesis.
8. The Department of Clinical Studies has reported increased risk of non-cancer diseases. To make the information more convincing, mechanistic information would be useful. Discussion on possible collaborations between the Department of Clinical Studies, the Department of Genetics, and the Department of Radiobiology/Molecular Epidemiology is advised.
9. There are research groups focusing on improving techniques for extraction of biomolecules from archival blood or tissue samples. Collaboration with such groups is encouraged, as this may be helpful in optimizing current and future use of the RERF specimen archives.

Department of Epidemiology

Overview

The Department of Epidemiology is critical to the mission of RERF. It is responsible for obtaining incidence and mortality information for the survivors of the atomic-bombings in Hiroshima and Nagasaki in order to evaluate radiation effects. This work focuses on three cohorts: the Life Span Study (LSS) of approximately 120,000 survivors, the *in utero* study of 3,600 survivors, and the F₁ cohort of approximately 77,000 survivors.

The latest published data for the LSS cohort spans 1958 through 1998; a new report that covers between 1950 and 2003 has been drafted and should be published in 2010. New data are currently being collected to update and better characterize risk factors for cancer, cardiovascular and neurological outcomes, including history of medical diagnostic and therapeutic radiation. Additional papers on the modification of effects of radiation by lifestyle and on the risk for second primary cancer due to radiation are drafted and under review at RERF.

The important feasibility study for mail collection of saliva is about to begin. Collaborations with outside research institutions have continued to be vibrant: the U.S. National Cancer Institute, the Partnership Program with the University of Washington and Kurume University, Oxford University and the National Cancer Center of Japan.

Evaluation and Critique

Progress is being made and focused plans are in place.

Papers have been published in international journals (eight, with one in press), which is consistent with publications during the past several years. It will be wonderful when the Epidemiology Department fulfills its promise of many high-profile papers on the important cohorts studied. A great many presentations have been made at international meetings, and this is excellent for the individual and the department. This type of publicity can only be good for RERF, and the papers that will follow from the presentations will be valuable additions to the literature.

Clear evidence of the utility of the continuing and robust

collaborations has been presented. There are papers under review in collaboration with many investigators, including those at the University of Washington, Oxford University, the U.S. National Cancer Institute, Kurume University, Kyushu University, and Nagasaki University.

Cancer and non-cancer sites currently studied include: myelodysplastic syndrome, skin cancer, thyroid cancer, breast cancer, ovarian cancer, uterine cancer, lung cancer, bladder cancer, malignant lymphoma, and soft tissue and bone sarcomas. In addition, the role of smoking is being intensively investigated in cohort specific analyses.

Recommendations

1. It is important that the core work of RERF is focused and that even more collaborations with external investigators are developed in order to optimally utilize the experience of the RERF investigators and staff.
2. It would be useful to further limit the number of RPs and to prioritize these, so that professionals can focus on writing first-author papers for international journals.
3. When updating progress reports, it would be useful to state clearly the time frame anticipated to publication.
4. The DNA collection and other biorepository items should be detailed in a central databank, real or virtual. Along these lines, it will be useful to have a clear listing of data and biospecimens available for researchers. This effort is already being developed by the Epidemiology Department for the pathology studies and is very important for future RERF studies.
5. The papers planned and in progress are all focused on the essential mission of RERF; it is anticipated that they will be published in international journals.
6. Staffing remains an issue as the Epidemiology Department has a great deal of ongoing work in following the cohorts as well as new work. One suggestion is that perhaps contractors could be used to conduct routine work for the department in following the cohorts as staffing appears to be quite minimal.

Department of Statistics

Overview

The department plays a central role: 1) in developing and implementing radiation risk estimation methodology, 2) by supporting RERF researchers regarding the design, planning, and analysis of studies related to mechanisms of radiation effects, especially in the analysis of models of casual pathways between radiation and disease with intermediate risk factors and effect modifications, 3) by understanding possible radiation effects in children of atomic-bomb survivors and general health effects research, 4) by conducting methodological research and implementing software to adopt and extend biostatistical methods for estimating risk, assessing uncertainty in dosimetry, understanding the mechanism of cancer, and performing clinical/biological data analysis, 5) by evaluating and refining the implementation of atomic-bomb dosimetry with evaluation of the size of errors in individual dose estimates, and 6) by developing expertise in statistical bioinformatics of multidimensional 'omics data.

Dr. Cullings gave responses to the recommendations of

the last year's SC and summarized recent accomplishments of the department. Consulting activities and collaborations with other RERF departments are enhanced by active participation of the staff of the Statistics Department in the projects of each RERF department. The Department of Statistics has undergone some major changes this year. Department Chief, Dr. Ross, as well as Dr. Geyer, have both resigned and Dr. Cullings has been appointed Acting Department Chief. Also, Dr. Cologne has agreed to resume full-time employment. The department has been fortunate in attracting two senior statistical researchers, Drs. Khattree and Abbott, who will join RERF this spring. The additions bring the department to eight full-time professional staff and two research assistants.

Ten papers were published in 2009, however, there was only one first-authored paper which was methodological in nature. This record unfortunately is down from eighteen papers published in 2008. Important work has been carried out on adjusting the locations of survivors, which will modify the exposure estimates for the survivors. Also hot-spot analyses using geospatial methods have been completed suggesting that there is not a serious issue with unaccounted-for fallout. In addition, the application of nested case-control studies using complex designs involving intermediate risk factors is being developed. Applications include studies such as breast cancer risk from radiation and radiation-amplified estradiol effects.

Evaluation and Critique

After the departures of the former Department Chief Dr. Ross and Dr. Geyer, the Department of Statistics is regaining its stability. There will be further adjustments to be made with the addition this spring of the two new senior statisticians, Drs. Abbott and Khattree. The department has been very successful in its efforts in establishing domestic and overseas collaborations. The pace of publishing results from these joint research efforts is varied and not directly under the control of RERF. The highest priority for the department continues to be providing consulting activities to other RERF departments at a high quality by its limited staff. That goal also requires the development of new skills and the application of newer methodologies such as the use of bioinformatics in the analysis and interpretation of genomics data to be generated by the Genetics and the Radiobiology/Molecular Epidemiology Departments.

Recommendations

1. As recommended last year, each researcher should have a goal to publish at least one first-authored paper each year. In particular, publishing in the statistical literature and presenting at statistical meetings should be priorities.
2. Preliminary analyses of the potential impact on cancer risk estimates by the revised dosimetry should be given a high priority.
3. Timelines with milestones as well as level of effort should be developed for each of the active research projects which should all be RP based.
4. It is recommended that the Department of Statistics conduct at least three methodology-oriented research projects per year to respond to the statistical needs in

rapidly-developing scientific technologies in RERF. Among them could be the methodological development for the use of individual data for assessing the relationship of radiation dose and disease, taking into account missing data and measurement errors effectively that could replace conventional Poisson regression.

5. Since the new members do not have a background in genomics it is important that this expertise be developed within the department.

Comments on Data Management and Documentation

In response to last year's SC recommendations, efforts have been launched to develop a concerted data management and documentation strategy for RERF. The importance of this effort cannot be overstated. It is central to the mission of RERF, and critical for the maintenance of its world heritage resource. To date, several subcommittees have been formed in order to define the needs and scope of this undertaking. The Data Management and Documentation Committee (DMDC) is chaired by Dr. Shore, along with Vice-Chairs Drs. Katayama and Cologne. A Steering Committee consists of those individuals plus Drs. Double, Kodama, and Ozasa, ensuring good representation of all stakeholders. Subcommittees concerned with Source Data, Data Analysis, Database Management and Maintenance, and Data Management Policies have also been defined. These committees have laid out their goals and initial scope of work.

Recommendations

1. The committee should ensure that they are making use of the experience and resources available within RERF. For instance, Mr. Eric Grant has highly relevant experience, having successfully designed and implemented a data management solution in Russia for their nuclear workers studies. He should be engaged at some level in this effort, as long as it does not impede his scientific and educational progress.
2. The planning and implementation of the data management strategy should be closely coordinated with efforts to centralize and document biospecimen banking and management. Close integration between specimen and data management in a standardized Laboratory Information Management System (LIMS) will benefit all RERF researchers and their collaborators.
3. We wonder if other large scale longitudinal cohort studies (such as the Framingham Study, Nurses Health Study, or Women's Health Study) might have insights and experience that could help speed the Committee's work.

Comments on Dosimetry

Dr. Okubo gave an excellent and detailed overview of the work of the Dosimetry Committee. There are three basic issues which will result in the adjustment of many of the dose assignments given to individuals. These include: a) precision of map coordinates, b) adjustments of the Army

map, and c) reinvestigation of individuals lacking an assigned dose. The basic information comes from the detailed shielding histories and the Master Sample Questionnaire. When these adjustments are completed it is anticipated, however, that the basic cancer risk estimates will only be subject to minor changes.

Recommendations

1. Because of the questions and concerns that will be raised over the potential impact of an adjusted dosimetry, the work should be completed as soon as possible.
2. As soon as the map coordinate precision adjustments are completed, the basic cancer risk models should be run now with the adjusted dosimetry in order to verify the assumption that the cancer risk estimates are indeed not likely to be changed appreciably. This analysis would also help to forestall questions that will be raised about the dosimetry issue.
3. Since there will be increased analyses using individual data as contrasted to grouped data, consideration should be given to the feasibility of developing individual dose uncertainty estimates. This could be as simple as classifying individuals into groups according to the estimated precision of their individual dosimetry.

Comments on Public Relations

Mr. Teramoto and his supporters are to be highly praised for achievements to date in getting out the message of the benefits of RERF's work for the public and survivors' good and making RERF visible and accessible. Exemplary are his coordination of a website for the public, survivors, and researchers with many visitors a day over the last year; the preparation of multimedia presentations of RERF in DVD and various print formats; and the coordination of open houses for the public, survivors, and school children.

Recommendations

1. Mounting key teaching slides on the public websites and monitoring their use would be an international resource for the many stakeholders in the area, especially as the world once again turns to nuclear energy for electricity generation.
2. The primer on radiation and health is superb and the well-deserved award from the Hiroshima Advertising Organization should, we hope, be a harbinger or more prominent awards, if it can still be nominated for additional national and international awards. Wide distribution is encouraged and the web linkage with the World Health Organization (WHO) is an effective start. National professional societies, such as regional Environmental Mutagen Societies, might volunteer to translate further and distribute.
3. Consultation with other Public-Interest Incorporated Foundations in Japan known for their effective public communication, or even a tour of a few American research institutions with strong public relations programs.
4. Press releases with or without press conferences, should be considered on the publication of every major

paper and initiative, like the improvements on dosimetry.

5. Perhaps the annual meeting of the Japan Radiation Research Society might be an occasion for a school outreach program by national experts with university or high school students.
6. We did not hear but assume an augmented program of interacting with cohort members and relatives of victims is underway and thriving.
7. Engaging global broadcast and print media in the mission and story of RERF must be an ongoing effort. Desirable outlets in the U.S. are National Public Radio, Public Broadcasting System (television), *The New York Times*, *The Washington Post*, etc.
8. Some milestones and evaluation criteria with agreed upon metrics might serve to strengthen and modify a 5-year plan for Public Relations, congruent with the scientific plans.

RERF International Symposium: Radiation Research Partnership

Confounding and Modification of Radiation Effects by Lifestyle and Other Factors/Utilization of Mail Survey Data

September 14–15, 2009, Hiroshima Laboratory

Kotaro Ozasa, Chief, Department of Epidemiology, Hiroshima

An international symposium based on the Radiation Research Partnership was held on September 14–15, 2009. With the objectives of encouraging radiation health effects research conducted by young researchers in the areas of epidemiology and statistics and promoting personnel exchange, the University of Washington (UW), Kurume University Biostatistics Center, and RERF have been carrying out the partnership program since 2006. The theme of this symposium was “Confounding and modification of radiation effects by lifestyle and other factors/utilization of mail survey data.” The symposium was held with the support of RERF’s International Exchange Program, and its objectives were to present summary reports of relevant studies and to review future research directions. On the morning of September 14, Kazunori Kodama (Chief Scientist, RERF), Scott Davis (Professor, UW), and Tatsuyuki Kakuma (Professor, Kurume University) presented summaries and future challenges of the partnership program from their perspectives. Their presentations were followed by keynote speeches by Dr. Davis, Kenneth Kopecky (Professor, UW), and Dr. Kakuma from their theoretical/methodological viewpoints regarding the symposium theme.

In the afternoon of the same day, symposium participants made presentations on studies of radiation-related cancer risks, as follows:

- study on bladder cancer by Eric Grant (Associate Senior Scientist, Department of Epidemiology, RERF);
- two studies on second primary cancers by Nobuo Nishi (Assistant Chief, Department of Epidemiology, RERF) and Christopher Li (Research Assistant Professor, UW);
- studies on colon cancer and breast cancer by Erin Semmens and Jean McDougall (PhD students, UW);
- study on dose-response risk model by Yoshisuke Nonaka (Visiting Research Fellow at the Department of Epidemiology from Kurume University); and
- study on causal models by Wan-Ling Hsu (Research Scientist, Department of Statistics, RERF).

Papers reporting the results of these studies are scheduled to be published in the future.

On September 15, active discussions were held on future perspectives of research based on the summaries presented on day 1. As a part of a personnel exchange program with Kurume University, Ritsu Sakata was hired as a research scientist by the Department of Epidemiology in Hiroshima, and Dr. Nonaka is currently engaged in his research work as a visiting research fellow at the Department of Epidemiology in Hiroshima. Partnership activities are ongoing. From UW, the above-mentioned two PhD students and other researchers have produced research results on radiation health effects based on RERF data. The UW members also said that, in addition to using RERF data,

they had an opportunity to feel what the A-bombed city of Hiroshima has experienced through their stay at the Hiroshima Laboratory as a part of the exchange program. RERF research staff members have regularly visited UW to conduct research discussions, and Mr. Grant has had an opportunity to study epidemiology as a PhD student at UW. The three organizations agreed that it would be worthwhile to try to obtain research funding to continue the partnership program. It was noted that one example of collaborative projects to be promoted would be to analyze confounding and modification of radiation health effects by lifestyle and other factors based on information collected from past mail surveys, which was also a theme of this symposium. RERF needs to make systematic analyses in this area of research, which will be appropriate training of PhD students. Further development of the partnership program is eagerly anticipated.

— Program —

September 14, 2009

“Opening remarks”

Toshiteru Okubo (RERF)

“RERF’s Partnership perspectives”

Kazunori Kodama (RERF)

“UW’s Partnership perspectives”

Scott Davis (University of Washington)

“Kurume’s Partnership perspectives”

Tatsuyuki Kakuma (Kurume University)

Theoretical/Practical (keynote) Talks

“Functional methods to exploit biomarker data in adjustment for dose uncertainty”

Kenneth Kopecky (University of Washington)

“Methods of data collection in epidemiologic studies: Challenges and examples from ‘real-world’ field studies”

Scott Davis

“Exploring interaction: Classification and regression tree methods”

Tatsuyuki Kakuma

Presentation of Specific Projects

“Bladder cancer, radiation, and lifestyle factors”

Eric Grant (RERF)

“Risk of second primary cancers”

Nobuo Nishi (RERF)

“Relationship between radiation exposure and risk of second primary cancers among atomic-bomb survivors”

Christopher Li (University of Washington)

“Body mass index, radiation dose, and colon cancer incidence in the Life Span Study of atomic-bomb survivors”

Erin Semmens (University of Washington)

“Timing of menarche and first birth in relation to breast cancer in A-bomb survivors”

Jean McDougall (University of Washington)

“Selection of relative risk model based on information criterion and application to the Life Span Study data”

Yoshisuke Nonaka (Kurume University/RERF)

“An overview of applications for causal models”

Wan-Ling Hsu (RERF)

“Closing remarks”

Roy E. Shore (RERF)

September 15, 2009

What we've learned

Report from the students—the good, the bad, and the ugly

Prospects for further collaboration

Training grant preparedness

List of Participants

Scott Davis, Professor and Chairman, Department of Epidemiology, University of Washington School of Public Health

Kenneth J. Kopecky, Professor, Department of Biostatistics, University of Washington School of Public Health

Christopher Li, Research Assistant Professor, Department of Epidemiology, University of Washington School of Public Health

Erin O'Brien-Semmens, PhD student, Department of Epidemiology, University of Washington School of Public Health

Jean McDougall, PhD student, Department of Epidemiology, University of Washington School of Public Health

Tatsuyuki Kakuma, Director and Professor, Biostatistics Center, Kurume University Graduate School of Medicine

[RERF]

Toshiteru Okubo, Chairman

Roy E. Shore, Vice Chairman and Chief of Research

Takanobu Teramoto, Permanent Director

Evan B. Douple, Associate Chief of Research

Nori Nakamura, Chief Scientist

Kazunori Kodama, Chief Scientist

Kotaro Ozasa, Chief, Department of Epidemiology, Hiroshima

Akihiko Suyama, Chief, Department of Epidemiology, Nagasaki

N. Phillip Ross, Chief, Department of Statistics

Hiroaki Katayama, Chief, Department of Information Technology

Fumiyoshi Kasagi, Assistant Chief, Department of Epidemiology, Hiroshima

Midori Soda, Assistant Chief, Department of Epidemiology, Nagasaki

Nobuo Nishi, Assistant Chief, Department of Epidemiology, Hiroshima

Harry M. Cullings, Assistant Chief, Department of Statistics

Eric J. Grant, Associate Senior Scientist, Department of

Epidemiology, Hiroshima

Kyoji Furukawa, Associate Senior Scientist, Department of Statistics

Hiromi Sugiyama, Research Scientist, Department of Epidemiology, Hiroshima

Ritsu Sakata, Research Scientist, Department of Epidemiology, Hiroshima

Wan-Ling Hsu, Research Scientist, Department of Statistics

Yukiko Shimizu, Part-time Professional, Department of Epidemiology, Hiroshima

Yoshisuke Nonaka, Visiting Research Fellow, Department of Epidemiology, Hiroshima

International Workshop: Epigenetics in Radiation Effects among A-bomb Survivors and Their Children

March 17–18, 2010, Hiroshima Laboratory

Evan B. Douple, Associate Chief of Research

The “International Workshop on Epigenetics in Radiation Effects among A-bomb Survivors and Their Children” was held at Hiroshima Laboratory on March 17–18, 2010. The workshop included 13 invited speakers from six Japanese universities (Waseda, Hiroshima, Kumamoto, Kyushu, Tokyo Medical and Dental, and Sapporo Medical), RIKEN Kobe Institute, RERF, and two U.S. universities (Southern California and Brown). The goal of the workshop was to have experts introduce RERF scientists to the emerging frontier of epigenetics, a field which has grown exponentially in recent years, and to enable RERF speakers to introduce leading experts in the field of epigenetics to RERF’s research results, ongoing and future plans, and unique biosample resources. The workshop was dedicated to Donald G. MacPhee, former RERF Research Advisor and Chief of the Department of Radiobiology, in recognition of his active encouragement of RERF scientists to explore the field of epigenetics.

The workshop keynote lecture was delivered by Peter W. Laird, a professor from the University of Southern California (USC), Keck School of Medicine who is also Director of the USC Epigenome Center. He provided an introductory overview of epigenetics—the study of inherited changes in phenotype (appearance) or gene expression caused by mechanisms other than changes in the underlying DNA sequence. The inherited changes may remain through several cell divisions or for the remainder of the cell’s life, and they may also be transmitted to multiple generations. In other words, non-genetic factors cause the organism’s genes to behave or “express themselves” differently. Dr. Laird explained that it has become clear that the origin of health and susceptibility to disease are, in part, the result of epigenetic regulation of the genetic blueprint and such effects may explain a number of human diseases including cancer. A form of epigenetics called genomic imprinting (the differential expression of a gene depending on whether it was inherited from the father or mother), may explain a number of human diseases and may be influenced by factors such as nutrition and exposure to environmental agents including low doses of ionizing radiation.

The workshop was organized into four major sessions. In the first session (Epigenetics: Overview and background of the field and of RERF and its resources), RERF’s Chief of Research, Roy E. Shore, presented “RERF: A unique laboratory for the study of human radiation epigenetic effects and disease.” A second session focused on imprinting development, and fetal origins of adult disease and a third session focused on epigenetics and carcinogenesis. The final session (Brainstorming: A role for RERF in epigenetic research) included presentations by four RERF scientists who presented their preliminary results and future research plans.

RERF scientists received valuable information,

encouragement, and advice on how best to determine whether epigenetics might have an important role in the increased health effects observed in the A-bomb survivors and how best to use RERF’s valuable databases and biosamples to address this question. The participants actively and frankly exchanged their views, and some of the invited experts expressed an interest in exploring future research collaborations with RERF scientists.

— Program —

March 17, 2010

“Opening remarks”

Toshiteru Okubo (RERF)

I. Epigenetics: Overview and background of the field and of RERF and its resources

Moderator: Peter W. Laird (University of Southern California)

“Introduction of distinguished lecturer”

Evan B. Douple (RERF)

Distinguished Lecture “The cancer epigenome: Origins and applications”

Peter W. Laird

“RERF: A unique laboratory for the study of human radiation epigenetic effects and disease”

Roy E. Shore (RERF)

“Genomic imprinting: Epigenetic programming in the germline of mammals”

Hiroyuki Sasaki (Kyushu University)

II. Imprinting, development, and fetal origins of adult disease

Moderator: Hiroyuki Sasaki

“Maternal nutrition state in Japan and one carbon metabolism”

Hideoki Fukuoka (Waseda University)

“The role of chromodomain proteins in the epigenetic gene regulation and DNA damage response”

Jun-ichi Nakayama (RIKEN)

“Is epigenetic suppression of the anti-oncogenes equivalent to genetic deletion in oncogenesis?”

Toshiya Inaba (Hiroshima University)

III. Epigenetics and carcinogenesis

Moderator: Karl T. Kelsey (Brown University)

“Epigenetic cell regulation by DNA methylation and chromatin factors”

Mitsuyoshi Nakao (Kumamoto University)

“Environmental exposures and epigenetic changes in cancer”

Karl T. Kelsey

“The origin of colorectal cancer with CpG island methylator phenotype”

Minoru Toyota (Sapporo Medical University)

“Epigenetic epidemiology of gastric cancer”
 Yasuhito Yuasa (Tokyo Medical and Dental University)
 “Summary”
 Evan B. Douple

March 18, 2010

IV. Brainstorming: A role for RERF in epigenetic research

Moderators: Peter W. Laird and Evan B. Douple
 “How can we best utilize the trio-samples in future epigenetic studies?”
 Norio Takahashi (RERF)
 “Pilot study: Epigenetic alterations in colorectal cancer among atomic-bomb survivors”
 Reiko Ito (RERF)
 “Establishment and validation of assay systems for evaluation of aging-related epigenetic alterations in blood cells”
 Yasuharu Niwa (RERF)
 “Systolic blood pressure and systolic hypertension in adolescence of atomic-bomb survivors exposed *in utero*”
 Kazuo Neriishi (RERF)
 “Closing remarks”
 Peter Laird and Evan B. Douple

List of Participants

[Distinguished Lecturer]

Peter W. Laird, Director, USC Epigenome Center, Keck School of Medicine, University of Southern California

[Speakers]

Hideoki Fukuoka, Professor, Institute of Epigenetic Regulation of Fetal Development, Waseda University
Toshiya Inaba, Professor, Department of Molecular Oncology, Division of Clinical and Experimental Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University
Karl T. Kelsey, Professor, Community Health & Pathology and Laboratory Medicine, and Director, the Center for Environmental Health and Technology, Brown University
Mitsuyoshi Nakao, Professor, Department of Medical Cell Biology, Institute of Molecular Embryology and Genetics, Kumamoto University
Jun-ichi Nakayama, Team Leader, Laboratory for Chromatin Dynamics, Center for Developmental Biology, RIKEN Kobe Institute
Hiroyuki Sasaki, Professor, Division of Molecular and Cell Therapeutics (Division of Epigenomics), Department of Molecular Genetics, Medical Institute of Bioregulation, Kyushu University
Minoru Toyota, Professor, Department of Biochemistry, Sapporo Medical University School of Medicine
Yasuhito Yuasa, Professor, Department of Molecular Oncology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University
Roy E. Shore, Vice Chairman and Chief of Research, RERF
Kazuo Neriishi, Assistant Chief, Department of Clinical Studies, Hiroshima, RERF

Norio Takahashi, Research Scientist, Laboratory of Biochemical Genetics, Department of Genetics, RERF
Reiko Ito, Research Scientist, Laboratory of Cell Biology, Department of Radiobiology/Molecular Epidemiology, RERF
Yasuharu Niwa, Research Scientist, Laboratory of Cell Biology, Department of Radiobiology/Molecular Epidemiology, RERF

[RERF]

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Evan B. Douple, Associate Chief of Research
Nori Nakamura, Chief Scientist
Kazunori Kodama, Chief Scientist
Kei Nakachi, RERF Consultant and Project Principal Scientist
Saeko Fujiwara, Chief, Department of Clinical Studies, Hiroshima
Yoshiaki Kodama, Acting Chief, Department of Genetics
Yoichiro Kusunoki, Acting Chief, Department of Radiobiology/Molecular Epidemiology
Kotaro Ozasa, Chief, Department of Epidemiology, Hiroshima
Harry M. Cullings, Acting Chief, Department of Statistics
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Akihiko Suyama, Chief, Department of Epidemiology, Nagasaki
Douglas C. Solvie, Associate Chief of Secretariat