FY2018 Plans of Activities

I. Major Activity Plans

1. Research Projects Examining A-bomb Survivors Health

Because much of RERF's research involves longitudinal or large scale long-term studies that take a significant time to plan and conduct, so a number of ongoing plans for such studies have already been presented under research achievements. Here we provide highlights of new research plans or selected plans of note.

1) Radiation and Cancer Risks:

- *Updated cancer incidence:* A series of papers of cancer incidence risk of radiation for individual sites in the LSS during 1958–2009 will be published in 2018 and beyond in collaboration with US National Cancer Institute. Individual organ sites or organ systems expected to be submitted for internal review in 2018 include: upper digestive system, lower digestive system, hepato-biliary-pancreatic, uterine, prostate, and urinary tract. Other systems to follow include CNS, second cancers, and other cancers.
- *Radiation risk at low dose levels:* Current efforts on cancer incidence risk analysis at low-dose levels will be developed, in collaboration with the Statistics Department. Analyses of potential confounding by geospatial factors and variation in baseline rates, and modeling of baseline rates, will be continued. These efforts includes preparation for mortality risk in the LSS including non-cancer diseases, which are thought to be more influenced by lifestyle and socioeconomic status especially at low-dose levels as they were possibly associated with the geospatial distribution of the survivors. Dose errors as well as potential impact of exposure to residual radiation and medical radiation will also be considered.
- *Liver cancer program project:* We will initiate a multidisciplinary program project on radiation and risk of HCC proposed by involving researchers from Departments of Statistics, Molecular Biosciences, and Epidemiology within the cancer research cluster.
- *Latent factors in radiation associated liver cancer:* We will continue current collaboration with Statistics and Epidemiology Departments to investigate the contribution of the latent factors (chronic inflammation, insulin resistance, and liver fibrosis), indexed by CRP, TNF-α, IL-6, adiponectin, leptin, and type 4 collagen, etc. to HCC risk, and to assess the roles of the latent factors as possible mediators of risk for viral hepatitis and other environmental and lifestyle risk factors for HCC, particularly radiation.
- *Pathogenesis of myelodysplastic syndrome:* We will continue our collaborative program with Nagasaki University and Kyoto University to determine mutations in serially collected blood samples from individuals developing MDS using genomic analysis.

2) Radiation and Non-Cancer Risks

- *Cataract study:* We will complete ophthalmologic examinations regarding radiation effects on cataract among AHS subjects exposed after birth and start the same type of examination among in-utero subjects. We will start evaluation of collected lens images in collaboration with ophthalmologic specialists and internal investigators. We have a plan to score as many images as possible at once to prevent intra-observer bias. Evaluations will be completed in 2019.
- *Cardiovascular disease:* We will continue analyses of a CVD incidence study using consistent diagnostic criteria over the study period since AHS had started, especially for

ischemic heart disease (IHD) and stroke in the AHS.

- *Neurocognitive effects:* We will complete analysis of radiation effect on neurocognitive-deficit symptoms based on NCQ among subjects exposed at ages <13 years. Then, analyze radiation effects on NCQ and/or cognitive function based on Cognitive Abilities Screening Instrument (CASI) among subjects exposed in utero.

3) Activities to Enhance Ongoing and Future Analysis

- *Data collection and processing:*
  - *Mortality surveillance:* Mortality follow-up for all cohorts will continue and the data will be completed through 2014. Archiving early-time materials will be continued.
  - *Hiroshima and Nagasaki tumor/tissue registries:* Case collection on population-based cancer registries will be completed through 2017 in both Hiroshima and Nagasaki. Cross-check of cancer incidence information with RERF database will be biennially updated in 2018 on the LSS, *in utero*, and F_1 cohorts. Annual reports of cancer incidence in the local populations will also be released. The data will regularly be reported to the Monitoring of Cancer Incidence in Japan (MCIJ) and cooperative studies with the National Cancer Center of Japan are also being conducted. Analyses of the prefectural data of Hiroshima and Nagasaki will be conducted. RERF will continue to make efforts to adapt to the new Japanese National Cancer Registry System.
  - *Pathology studies:* The indexing of specimens of formalin-fixed paraffin-embedded tissues within a new database is continuing. We will continue to make efforts to preserve and utilize pathological materials from the A-bomb survivors in collaboration with community hospitals in Hiroshima and Nagasaki. These activities will be performed in cooperation with the RERF Biosample Center of RERF.

- *Research resource center (RRC):*
  - *RRC Development:* The RRC will see major development over 2018. First, the overall structure and reporting hierarchy will be established. Next, a new chief of the ITD will be identified and hired. RERF will re-organize the ITD to expand the Archive section with talented personnel capable of initiating the vision of the RRC. This will require specially trained workers in electronic information systems. It is anticipated that RERF's computer infrastructure is sufficient for the first several years of RRC development. It is possible that a computing infrastructure expansion may be required in the near future after the full design of the RRC has been completed.
  - The Biosample Center ("BSC", an integral part of the RRC) will welcome a new director in July 2018. This person brings significant experience in biorepositories and will embark on installing a new Laboratory Information Management System (LIMS) for QC and proper inventory tracking. Further, the BSC will employ additional personnel and design and implement a quality assurance program to systematically test the stored biosamples for usability in modern testing settings. There has been little overall QC testing over RERF's history. The BSC inventory for bloods is hoped to be completed in 2018.
  - *Data Sharing Policies:* RERF data sharing policies are often *ad hoc* and sharing requests are not necessarily always treated in an egalitarian manner. Institutional policies and procedures must be implemented to ensure collaborative research in the future is not encumbered by lack of policies and inefficient procedures.

4) Mechanistic Studies to Provide Better Understanding of Risks

- *Mechanisms of radiation-induced non-cancer disease:* As the focus of a potential new program project that is being discussed and reviewed in the Non-cancer Research Cluster, we will develop strategies for assessments of clonal hematopoiesis potentially linking to radiation-associated non-cancer diseases in the AHS. Our hypothesis in this program is that somatic mutations in epigenetic modifier genes (TET2, DNMT3A, ASXL1, etc) in hematopoietic stem cells drive clonal hematopoiesis accompanied with the myeloid bias, resulting in accumulation of pro-inflammatory monocytes and T cells. To strengthen this hypothesis, we will also develop a mouse model to evaluate clonal expansion of hematopoiesis stem cells (HSCs) and pro-inflammatory phenotypes following radiation exposure.
- *Immune cell homeostasis:* Longitudinal patterns of immune-cell homeostasis among AHS participants will be assessed for relationships with elevated risks of inflammatory diseases, such as myocardial and cerebral infarctions, liver diseases, and stroke, in A-bomb survivors. To test the hypothesis that radiation exposure may accelerate progression to hepatocellular carcinoma (HCC) through impairment and dysregulation of T-cell immunity, we will analyze longitudinal data of T-cell parameters in AHS subjects infected with HCV, in relation to radiation dose, inflammation, liver fibrosis and HCC. We will also analyze inflammatory biomarker data (e.g., WBC, CRP, IL-1β, IL-6, TNF-α, IL-8, MCP-1) in relation to arteriosclerosis indices in AHS participants, to test the hypothesis that radiation exposure may have caused persistent inflammation partly contributing to progression of arteriosclerosis and vascular calcification in A-bomb survivors.

2. Research Projects on the Health of A-bomb Survivors Children (F1)

1) Clinical

Continue to conduct health examinations among the cohort members of the F_1 follow-up clinical studies. Results will be linked into our new integrated F1 program. (see below)

2) Epidemiology

A cancer incidence paper is expected but it is difficult to estimate the migration rates of F_1 cohort members out of cancer registry areas. Effective methods of personal identification of F_1 cohort members with cancer incidence information in the national cancer registry system would be developed. Radiation effects on the F_1 generation will be investigated in an integrated program project with other departments developed in the Genetic Research Cluster. (see below)

3) Integrated Program Project

Programs examining effects of radiation in the F1 population have been ongoing separately in the Departments of Clinical Studies, Epidemiology, and Molecular Biosciences for many years. However, these programs were mostly conducted as separate entities. In 2018 a new program project will be developed as an integrated, interactive program involving interactions of Clinical Studies, Epidemiological Studies, Statistics, whole genome sequencing studies, and animal studies. This approach will provide a more in depth study of the health of the children of survivors.

4) Mechanistic Studies to Investigate Potential Transgenerational Effects

To mechanistically understand how radiation exposures induce mutations in spermatogonia

stem cells and how their mutations transmit to the next generation, we have initiated studies using a novel in vitro/in vivo approach. We first use state-of-the-art methods for the in vitro culture of mouse spermatogonia cells (hereinafter GS, germline stem cells). GS cells will be irradiated, and the genome of GS clones surviving irradiation will be fully characterized by aCGH and WGS. Then the characterized GS cell clones will be transplanted into male mice testes so that the cells can undergo meiosis for spermatogenesis to make mature sperm. Subsequently, the transplanted male mice will be mated with unexposed female mice to deliver offspring. Using the WGS of the offspring, we will determine what types of radiation-induced mutations can, or cannot pass through the process of spermatogenesis, fertilization and early development. We also plan reverse genetics; by utilizing genome editing technique, various sizes of large scale deletions or translocations will be introduced in GS cells; and a number of obtained recombinant GS clones will be assessed for their mutation transmissibility to the next generation.

3. Research to Elucidate Individual Radiation Doses and the Effects of A-bombs

- *Organ dose update:* We expect a major effort in the coming year to support and collaborate with an extramural working group that has been formed to evaluate the effect of new computational models of the human body and new radiation transport calculations on the dose estimates for specific organs and tissues of the body, both the 15 organs calculated by the current DS02 system and a larger set, as well as a pregnant-woman model and a complete pediatric series reflecting growth and development for survivors who were exposed *in utero* or at ages ranging from newborn to adult.
- *Long-term follow-up studies:* We expect to continue collaborating on studies regarding radiation-associated mortality and morbidity among major RERF cohorts, particularly in preparation for the next LSS mortality analysis, for which initial preparations have begun. A major focus of the Department over the coming year will be the use of grouped versus individual data. We perform analyses with individual-level data and binary or survival regression models, particularly in the AHS, although we rely mostly on Poisson regression models with grouped data for analyses of the LSS data. For Poisson regression models with grouped data, for example, migration adjustments are easier, but we cannot accommodate individual data such as those from mail surveys, and there is a difficult issue with size of the person-year table if more than a few covariates are used. In addition, the data used for major RERF reports are made available for download on the RERF webpage, and these data must be properly anonymized for compliance with ethical and privacy requirements. We have established a working group, which includes external collaborators, to examine the analytical challenges and tradeoffs between grouped and individual data, to include consideration of dependent and informative censoring of event-time outcomes.
- *High-dimensional data:*
  - We are preparing to deal with processing and analyzing ‘big’ data. We have already analyzed T-cell receptor sequence data (Cologne/Cordova/Misumi) and integrated expression (RNA-seq) and methylation data (Cologne/Misumi). We are now preparing to conduct future studies of SNP-array data for studying genes predisposing to radiation susceptibility in cancer (Cologne/Misumi). We will also consider what computing resources will be required for future large-scale studies involving whole-exome or whole-genome sequence data.
  - We will continue the design and implementation of a major study which is part of the integlated F1 program regarding transgenerational mutation frequency versus parental pre-conception gonadal dose in family trios; technologies and detection algorithms for

sequencing are being decided by Molecular Biosciences investigators in consultation with Statistics (Uchimura/Noda/French/Cullings). Our current focus is on sample selection, with careful matching on potential confounders such as age due to a small feasible sample size.

- *Radiation dosimetry and dose error:* We expect a major effort in the coming year to support and collaborate with an extramural working group that has been formed to evaluate the effect of new computational models of the human body and new radiation transport calculations on the dose estimates for specific organs and tissues of the body, both the 15 organs calculated by the current DS02 system and a larger set, as well as a pregnant-woman model and a complete pediatric series reflecting growth and development for survivors who were exposed *in utero* or at ages ranging from newborn to adult (Cullings/Grant). We will continue research on spatial analyses related to residual radioactivity.

4. Project to Release of Research Results and to Collaborate with Other Scientific Organizations

- *Continuing collaborations:* Long term collaborations are listed below and these are expected to continue in 2018:
  a. Partnership with Kurume University
  b. University of Washington
  c. Collaborations with the US National Cancer Institute
  d. Collaborations with Outside Investigators:
     45 Japanese Institutions
     22 North American Institutions
     12 European Institutions
     6 Asian Institutions
     Nuclear Emergency Workers Study (NEWS): 10 Japanese Institutions

5. Training Programs for Domestic and Overseas Specialists

RERF will hold a training seminar for non-epidemiologist radiation researchers to learn the basics of epidemiological research and increase understanding of radiation health risks. In addition, RERF will train persons capable of working in the fields of radiation protection, radiation emergency medical care, and radiobiological research.

Activity plans for this fiscal year:

i) RERF will hold an epidemiological training seminar for radiation biologists in Japan again this year for enhanced understanding of results from epidemiology research on A-bomb survivors.

ii) RERF will accept overseas research trainees to support the activities of such organizations as the Hiroshima International Council for Health Care of the Radiation-exposed (HICARE), the Nagasaki Association for Hibakusha's Medical Care (NASHIM), and the Japan International Cooperation Agency (JICA).

iii) RERF will accept students from domestic and overseas schools/universities for facility tours, and will provide training sessions on the foundation's research activities.

iv) RERF will continue to review directions as to its training activities and publicly invite overseas trainees in the International Exchange Research Program for this fiscal year also.

6. Public Information Programs

Activity plans for this fiscal year:

i) RERF Open House event

RERF will hold its 24th and 22nd Open House events at the Hiroshima and Nagasaki RERF Laboratories, respectively. The event will feature various programs, including exhibitions as well as lectures, and is once again scheduled to be held in Hiroshima and Nagasaki in August.

ii) 70th RERF commemorative event in Nagasaki

RERF is planning to hold a public event commemorating its 70th anniversary for the Nagasaki Laboratory in June, to provide the AHS participants as well as the general public with an opportunity to enhance their understanding of the foundation's research and its contribution to global radiation protection standards.

iii) Updating of public relations materials

RERF will update its various public relations materials, including posting an online subscriber-list source of news on the new homepage—see explanation in v) below—as well as revising the pamphlets *Basic Guide to Radiation and Health Sciences* and *Radiation Effects Research Foundation*.

iv) Maintenance of new RERF website

After the new RERF website is launched at the end of FY2017, a focus will be placed on maintaining the site and improving the distribution of information to the public via this platform. With this comprehensive change to the website, some of the content will naturally change, leading to use of more video and other new methods of communication, including the aforementioned electronic subscriber-list source of RERF news—see explanation in v) below.

v) Creation of new online news-delivery system

After discontinuing the printed *Update* newsletter at the end of 2016, in conjunction with unveiling of the new website, a new subscriber-list online news-delivery system will be created and used to not only distribute the latest research results and information about RERF events and activities but also to attract subscribers to RERF as "members," by offering a sense of "buy-in" with respect to RERF as an organization.

vi) Improve introductory video and social media techniques

By joining with the independent Think Global School high school that learns in a hands-on way by traveling the world, RERF will attempt to improve our current introductory video and to attract younger people to our cause through the use of social media, such as Facebook. To attract more followers, the school will collaborate with RERF to improve our Facebook page content and to formulate project plans geared towards other social media platforms.

vii) School Visit Program

This program was first established in FY2016 in an attempt to teach young students the reality of radiation health effects. With the stable of teachers firmly established, marketing efforts have provided the opportunity to teach to an increased number of classes in elementary and middle schools compared with FY2016—at least 12 classes—during the course of FY2017. Full-scale marketing of the program will continue in FY2018.

viii) Other public relations activities

- RERF will actively promote the foundation's important scientific papers to the domestic and overseas media via press releases and press conferences.
- RERF will try to speak at a venue in Tokyo in FY2018, in a continuation from our first effort, which took place in February 2017 before the Foreign Correspondents Club of Japan, and our second effort, at the University of Tokyo jointly with ICRP in December 2017.
- RERF will seek a more efficient approach to its facility tours, reducing the times the facility is open to the public in order to attract larger groups over shorter time periods, as well as training more personnel to handle the tours in English for overseas visitors.
- A more focused effort of information distribution to A-bomb survivors and their children will be attempted to improve the transparency of RERF research and communication among those populations.
- RERF will continue to target small groups of the public, especially A-bomb survivors and their children, who will be invited to come to RERF and speak with upper-level management about ABCC/RERF, the organization's history, and research results, to achieve more personal small-scale opportunities for communication.

II. Activities necessary for the above projects

1. The Secretariat's multi-year personnel plan

The majority of management-level personnel in the Secretariat will reach mandatory retirement age within the next five years. Some sections will find it challenging to put capable successors in place due to mandatory retirements and a shrinking personnel cap. In the future, the Secretariat will select competent management-level personnel from a limited number of employees. Also, we need to establish a system in which a limited number of employees can perform current duties. We considered the merger of sections and offices within the Secretariat to cope with this situation. We will continue to deliberate and convert temporary employees to permanent staff members after carefully considering the necessity of their duties, RERF's financial situation, and our personnel cap. Also, we will consider employing fixed-term general employees based on the needs of our business and financial condition and after reviewing the specific nature of the work required.

2. Long-term leadership training

To make employees to be highly motivated to become management-level personnel, we will hold six leadership training sessions for assistant section chief or lower positions over the next three years starting from FY2017. The second and third will be held in July and November FY2018 respectively in Hiroshima and Nagasaki.

3. Continuation of internal audit process

As in FY2017, RERF will sign another contract with Deloitte Touche Tohmatsu LLC, outsourcing our internal audit process in FY2018 as well.

4. Facility upgrades

(1) Facility upgrades to the Hiroshima Laboratory

i. A new Animal Facility will be constructed and relocated to the first floor of Building B.

ii. A three-year plan to replace all the air conditioners currently in use will be implemented by FY2020, as the units are deteriorating and some contain banned fluorocarbons.

iii. A three-year plan to replace overhead lighting fixtures with LED lights will be implemented due to deterioration of the present lighting and as a measure to reduce energy costs.

iv. A five-year plan to preserve the steel sheet roofing of all buildings will be implemented through repair and painting work.

v. A three-year plan to paint the exterior walls of and restore the paths between buildings will be implemented.

5. Revision of rules and regulations

To conform to the Act on the Protection of Personal Information and the national ethical guidelines, which went into full effect in May 2017, we will amend the related internal regulations. Also, we will promptly handle any regulation-related issues if identified by the Board of Audit of Japan during its on-site inspection or by Tohmatsu during its internal audit. Furthermore, to enhance RERF's operational framework as a Public Interest Incorporated Foundation, we will amend the regulations for the handling of research funds and the administrative work for contracts by following the national guidelines.

6. Next steps in strategic planning

The 2018 informal BOC meeting reviewed the White Paper on Biosamples Usage (WP) and the first draft of the Strategic Plans (SP). The primary complaint regarding the SP was that it was not "actionable". The document needs to be re-written to include a process that can be agreed upon by the funders, the BOC and the BOD. The following four points should be the mainstays of the document:

1. Curation and action (Establish the RRC)
    a. Quality control of biosamples
    b. Integration of epidemiological, clinical, and biosample data
    c. Continue normal data and sample collection
2. Establish processes and rules for collaborative use of samples and data (Office of collaborative research)
    a. Scope of informed consent
    b. Data sharing forms and procedures for sharing of data and samples both domestically and internationally
    c. Identify trouble spots (legal and social) and implement ways to solve these issues
        i. Public buy-in
        ii. Resolve relocation questions
3. Convene scientific workshops (in Japan and around the world) to define "use cases" to identify knowledge gaps and determine which questions can be best answered by RERF resources
    a. This should include discussions on how to fund these use cases, as it is likely that some will be very expensive

   b. The world is starved for established cohort data—there should be a strong interest in our data
   c. This step should not be undertaken until #1 and #2 have been completed/demonstrated

4. Develop in-house use cases
   a. This should be started immediately and used to demonstrate our competence regarding #1 and #2

An issue that must be handled over the next few years is RERF's present inability to receive a full external accounting audit. This will be a hindrance for any outside institution to donate to or fund RERF activities. Therefore, finding a way to resolve current obstacles is necessary.

The 4-step plan above is a good short-term SP but does not address a more fundamental question (that was not tackled at the previous BOC): What does RERF plan to be after 10 years? We need an overarching theme that defines RERF's future. If this question is answered, the issue of relocation will also be solved as it will be clear what physical form RERF will take.