FY2024 Plans of Activities

I. Plans of Major Activities

The bulk of RERF's research involves long-term follow up studies of atomic bomb survivors and their children, that take significant time to design and conduct. Ongoing plans for these studies have been largely covered under research achievements. Here, we provide highlights of new research plans or selected plans of note.

1. Research Projects Examining A-bomb Survivors Health

1) Radiation and Cancer:

- Updated Life Span Study (LSS) mortality report on cancer and noncancer diseases (RP 1-75, Sakata): Analysis and publication of LSS Report 15 on mortality among atomic bomb survivors will be of high priority in the next several years. Compared to Report 14, the new report will include an additional 16 years of follow up, provide more mortality information among those who were young at the time of bombing, and will be key to understanding the nature of the curvature of the dose-response relationship shown in Report 14 and the latest comprehensive cancer incidence study. The new analysis will also provide more information for non-cancer diseases such as cardiovascular diseases for which suggestive increased risks were observed in Report 14.
- *Pathogenesis of MDS (RP1-17, Miyazaki Y and Imaizumi M):* A-bomb survivors have a high risk of hematological malignancies, but little is known about the mechanisms of radiation-induced myeloid malignancies. We will further assess differences in mutational signatures between expanding and diminishing clones to reveal effects of A-bomb radiation on their mutational process.
- *Leukemia among A-bomb survivors (RP-P1-23, Yoshida N)*: We will confirm the applicability of targeted sequencing in old formalin-fixed paraffin embedded (FFPE) samples. If these samples can be sequenced successfully, we will initiate a full-scale study "Identification of clinicopathological findings associated with radiation dose in hematological malignancies among atomic bomb survivors."
- *Hiroshima and Nagasaki tumor/tissue registries (RPs 18-61, 29-60, Sugiyama):* Regular activities in National Cancer Registry and Nagasaki tissue registry will be continued under contract with each authority. The Dept. of Epidemiology will continue to crosscheck the subjects of RERF major cohorts against newly registered data with approval from each authority. By March 2025, the resource database of LSS cancer incidence will be updated for LSS through 2020.
- *Pathology studies (RPs 5-89, 1-12, Sakata):* The indexing of FFPE tissue specimens within a new database will be continued in collaboration with RERF's Biosample Research Center. Efforts to preserve and utilize pathological materials from A-bomb survivors will be continued in collaboration with local hospitals in Hiroshima and Nagasaki.
- *Preparation for Cancer GWAS (RPs P2-22, Hayashi):* A final evaluation will be made regarding whether whole genome amplification of DNA from Adult Health Study (AHS) blood smears stored over the long term (up to 50 years) is valid for genome-wide

association study (GWAS) analysis. If the results are positive, a full-scale research plan with an initial focus on cancer outcomes will be developed.

2) Radiation and Non-Cancer Effects:

- Atherosclerosis study [RP2-11, RP 1-23-2, Nakamizo T]: To understand the potential mechanisms by which radiation may promote atherosclerosis, we will continue statistical analysis of associations between cytokines, atherosclerosis, and radiation dose. A manuscript reporting on the reliability and stability of circulating markers is currently in submission. We will prepare a second manuscript examining the association between radiation dose, stable cytokines, and atherosclerosis.
- Updated Adult Health Study (AHS) report on non-cancer disease (RP2-75, Yamada and Ohishi): Preparations are underway for the 9th report of AHS, to examine associations between various non-cancer diseases and radiation exposure. Compared to Report 8, the new report will extend follow up to 2020 (vs.1958-1998) and examine twelve additional disease outcomes including valvular heart disease, hyperparathyroidism, and benign tumors of the colon and rectum.
- Evaluation of radiation-associated Clonal Hematopoiesis (CH) [RP 1-23-1, K. Yoshida]: Clonal hematopoiesis, in addition to a potential link with hematological pathologies, may also be associated with cardiovascular risk. We will complete whole exome sequencing (WES) and T-Cell Receptor (TCR) deep-sequencing analysis of blood cell DNA obtained from about 150 A-bomb survivors to characterize clonal expansion of hematopoietic stem cells in high-dose exposed survivors.

3) Genetic Effects of Radiation:

- *Trio Genome Study [RP 3-23, Uchimura]*: Understanding the hereditary genetic effects of A-bomb radiation has been a long-standing concern for atomic bomb survivors, their children, and the scientific community. To answer this question, we plan to analyze the whole genome of exposed parents and children ("Trios"). In FY2024, we will complete a small feasibility study of a few Trios to establish a pipeline for whole-genome sequencing (WGS) and analysis in collaboration with RIKEN and the U.S. NCI. In parallel, we will obtain consent forms (re-consent) from the remaining families and launch the full study after a public announcement.
- See Preparation for Cancer GWAS (RPs P2-22, Hayashi) in Section 1.1; Evaluation of radiation-associated Clonal Hematopoiesis in Section 1.2.
- *Clonal Hematopoiesis (CH) in Mice [RP 1-23-3, Kusunoki]:* We will evaluate the association between CH and persistent inflammation in CH mouse models, including an atherosclerosis mouse model (LDLR-KO) that will investigate the relationship between radiation-induced CH and cardiovascular disease (CVD) development.

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

- See *Trio Genome Study* in Section 1.3.
- Mortality surveillance for In Utero and F_1 cohorts (RPs 1-75, 2-61, 4-75, Sakata): Mortality follow-up for all cohorts will continue and the data will be completed through 2020. Archiving of early-period materials will continue in collaboration with the Research

Resource Center of RERF.

• *F1 Offspring Clinical Study (FOCS), (RP 4-10, Ohishi):* In collaboration with the Department of Statistics, the analysis of associations of parental radiation exposure with risk of multifactorial disease in their children using longitudinal study data (2002-2020) will be continued.

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

- *Shielding Survey and Dosimetry (RP 18-59, Sposto):* The Department of Statistics will complete work on an updated organ dosimetry system using modern, sophisticated J-45 computational phantoms.
- *Dosimetry Error (Sposto/Misumi):* The Department of Statistics will begin formal reevaluation of the currently utilized methods used to correct random dosimetry error in RERF analyses. We will investigate the importance of distinguishing between subjects with complete vs. average shielding parameters, different shielding scenarios (e.g., inside shielding or outside), and whether the assumed amount of random dosimetry error should be retained. The issue of dosimetry error is a long-standing interest of the Department of Statistics, and we will be revisiting this issue in light of the revised organ dosimetry, which will be utilized in the future.

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

- *Continuing collaboration:* RERF's long-term collaboration with numerous Japanese and international institutions is expected to continue in 2024, including:
 - a. Partnerships with the Universities of Hiroshima, Nagasaki, Tokyo, Kyoto, Kurume
 - b. Collaboration with the U.S. National Cancer Institute
 - c. Collaboration with the University of Florida
 - d. Collaboration with the University of Washington
 - e. Collaboration with Outside Investigators:
 - 47 Japanese Institutions
 - 9 North American Institutions
 - 10 European Institutions
 - 1 Asian Institution
- *Communicating Research Results:* In addition to publication of RERF research in peerreviewed academic journals, RERF will contribute to high-visibility reports by international dosimetry and radiation risk assessment groups such as the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and the International Commission of Radiation Protection (ICRP).

5. Training programs for domestic and overseas specialists

RERF will hold a training course 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. Decisions on whether these

activities could be held and how they would be held will be made considering the status of COVID-19 pandemic.

Activity plans for FY2024

- i) RERF intends to hold an online or in-person epidemiological training course for radiation biologists in Japan to enhance understanding of results from epidemiology research on A-bomb survivors.
- ii) RERF will accept overseas research trainees to support the activities of organizations such as the 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) If there are any invitations for the MHLW-sponsored FY2024 International Exchange and Research Program, RERF will consider accepting physicians and researchers from overseas to provide them with training.
- iv) The Department of Statistics will apply to the International Fellowships for Research in Japan program, sponsored by the Japan Society for the Promotion of Science (JSPS), upon application from candidate trainees, and provide research opportunities to young post-doctoral researchers from various countries.

6. Public Information Programs

From the days of its establishment until the present, RERF has investigated the medical effects of radiation on atomic bomb survivors and their children. Of utmost importance among RERF's public information programs are its efforts to feedback the results of its research projects to atomic bomb survivors and their children, both of whom have long cooperated in RERF's research, as well as to the public. To do so, RERF is considering using expert consulting services to scrutinize and revamp existing public information programs. In addition, it will plan PR activities for the 80th anniversary of the atomic bombings and RERF's 50th anniversary in 2025, and for the relocation to Hiroshima University's Kasumi Campus. In FY2024, RERF will engage in the following public information programs.

i) Communication of Research Results

RERF will engage in a variety of strategic PR activities to broadly communicate its research results to society. In the interim, it will do its utmost to focus on PR related to spreading understanding of its genome sequencing study of genetic effects among the A-bomb survivors, their children, and the community. Some concrete initiatives include public lectures, study sessions, and information releases on RERF's official website and through the mass media. RERF is also using social media platforms and creating videos of interviews and explanations on research conducted by scientists and using digital media to perform other research-related activities. It will consider planning more effective methods of conveying information while enhancing its relationships with science reporters and other members of the media. RERF also plans to consult external PR experts to enhance its information releases related to research.

ii) Open House

The upcoming Open Houses will be RERF's first in-person events since COVID-19 was changed to category 5 under the Act on the Prevention of Infectious Diseases. RERF aims to increase opportunities for direct dialogue with local residents as much as possible. Four members of the Public Relations & Publications Office will participate in the working committee consisting of about 25 employees from Hiroshima and Nagasaki, which will enrich the popular content from past events. At the same time, they will also use videos

related to RERF's research and facilities created previously to add more content explaining RERF's research. RERF will then distribute information highlighting its research achievements to date, contributions to A-bomb survivors, and the significance of its upcoming research to develop a more positive view of RERF within the local communities.

iii) Plans for the 80th Anniversary of the Atomic Bombings and RERF's 50th Anniversary

RERF sees the 80th Anniversary of the Atomic Bombings and RERF's 50th Anniversary in 2025 as a chance to relay its research achievements up to now, its contribution to the Abomb survivors, and the significance of its upcoming research activities. It is doing so to foster trust among the A-bomb survivors, their children, and the communities so that even more individuals in Japan and around the world come to know more about it. RERF will plan a number of activities including commemorative symposiums, commemorative publications, and launch of a special website.

iv) Official Website

Through the "What's New" section of its official website, RERF will provide comprehensive information on its activities. Also, it will make the official website more accessible by adding more understandable content about its research, including videos. Hiroshima Laboratory's relocation is a chance for RERF to update its official website. So, RERF will analyze its current website and devise a plan for its redesign.

v) Facility Tours and School Visits

While noting the status of COVID-19 infections, RERF will present information on its research achievements to date, its contributions to A-bomb survivors, and the significance of its upcoming research by receiving visitors and conducting school visits. This will include more than distributing information—RERF will continue to expand its support base to ensure its research is appreciated by people from all walks of life: A-bomb survivors, their children, researchers, government personnel, peace volunteers, academics, students, members of the communities, overseas visitors, and others.

(Other public relations activities)

- Releasing accessible information about research results through press releases and conferences.
- Regularly tracking coverage in the media and planning the maintenance and enhancement of relationships with the media through close contact.
- Preparing a synopsis for each paper and communicating research results in an accessible manner.
- Regularly responding to everyday inquiries from outside parties.
- Preparing to revise its current PR materials in anticipation of Hiroshima Laboratory's relocation (handbooks, leaflets, booklets, etc.).
- Creating a digital archive of videos and still images of the historically significant structures of the current Hiroshima Laboratory.

II. Operation and Management of RERF

1. Research Resource Center

As part of its efforts to preserve RERF's research assets and historical materials, the Research Resource Section will digitize the negative films of chromosome images and their ledgers held by the Department of Molecular Biosciences, based on the specifications prepared in FY2023. In addition, the prioritization of digitization and integration of in-house data will be carried out based on the policy for digitization and integration of research resources, which was formulated by the Research Resource Center Operating Committee (RRCOC). Construction of the integrated research data source will be promoted by linking the research database currently in operation with the biosample database created by the Laboratory Information Management System (LIMS) and the consent information database being created by the Department of Clinical Studies. The Office of Research Support will be newly established and staffed with hands-on personnel, following which a digital dashboard created by Tableau Server®, a software product that extracts data from existing digital information and visualizes it for at-a-glance viewing, will be shared internally.

2. Relocation of the Hiroshima Laboratory

We will proceed with the plan to relocate the laboratory to Hiroshima University's Kasumi Campus and aim for construction work to start early by completing the demolition of the existing building on the campus and the detailed design for the new building.

3. Revision of the rules and regulations

RERF revises the current regulations and establishes new regulations based on revisions to laws and regulations and regular reevaluation by the sections in charge. In FY2024, required revisions will be made to keep the foundation's management operations appropriate. Doing so will provide RERF with regulations befitting of a public interest incorporated foundation funded by the U.S. and Japanese government subsidies.