

## FY2020 Plans of Activities

### I. Plans of Major Activities

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. Research Projects Examining A-bomb Survivors Health

##### 1) Radiation and Cancer:

- Papers on cancer incidence risk of the prostate (Mabuchi K, et al.), ovary (Utada M, et al.), and urinary tracts (Grant EJ, et al.), and comparison of cancer incidence and mortality (Brenner A, et al.), and also a summary paper (Brenner A, et al.) will be published. Then the series of papers on cancer incidence risk with radiation in the LSS during 1958–2009 will be completed in 2020 in collaboration with the Dept. Statistics and the US National Cancer Institute. Another project of risk analyses using mechanistic models will be continued in collaboration with the RERF Dept. Statistics and the Helmholtz Zentrum München (Sugiyama H).
- Periodical publication of mortality risks for cancer and noncancer disease due to atomic bomb radiation is the most essential work of Dept. Epidemiology and the LSS Report 15 will be the highest prioritized project in the next few years. Available data and the framework of analyses will be determined and preliminary analyses will begin in collaboration with Dept. Statistics. Dose-response shape and radiation risks at low dose levels will be investigated considering potential confounding by geospatial factors and variation in baseline rates. Those analyses will include lifestyle factors (smoking, alcohol drinking, body mass index), some indicators representing socioeconomic status, and so on.
- For this LSS report 15 the Statistics Department will be involved in determining the most appropriate components of the analysis, such as modelled vs stratified baseline, or ERR vs EAR modeling, and to help identify, and for some pursue, relevant sub analyses to be reported separately from the main analysis that will supplement or refine the interpretation of the main analytic results. These may include, for example, investigating the importance of finer resolution spatial demographic data, or examining the influence of high dose subjects on inference about low dose risk estimation in this more mature cohort.

##### 2) Radiation and Non-Cancer Effects:

- *Cardiovascular*: Complete the final confirmation of our findings on atherosclerosis and radiation described previously in our 2019 accomplishments section and submit the manuscript in early 2020.
- We will also start to analyze the data on cytokines gathered in the counterpart study (Part 2. Analysis of the cytokine network regulating differentiation of mesenchymal stem cells in artery), which aims to test the hypothesis that disturbed tissue repair is involved in the pathogenesis of radiation-induced atherosclerosis. This analysis will be conducted jointly with, or subsequently after the clonal hematopoiesis program project described below because inflammation could also be involved in the pathogenesis of radiation-induced atherosclerosis. The research protocol of the latter study will be prepared in late 2020.

### **3) Immunologic Effects of Radiation:**

- A program project will be initiated to test the hypothesis that inflammation associated clonal growth of lymphocytes in the survivors leads to the cardiovascular diseases such as arteriosclerosis. This program includes four projects: 1) To examine the relationship between clonal growth and mutations of epigenetic modifier genes; 2) examine the relationship between clonal growth and serum inflammatory phenotypes; 3) To detect clonal hematopoiesis after radiation exposure and directly test its role in the development of atherosclerosis using mouse models; 4) To further examine this hypothesis using mathematical modeling of mutant lymphocyte growth after radiation.

### **2. Research Projects on the Health of A-bomb Survivors Children (F<sub>1</sub>)**

- Our previous animal model studies identified more small deletions and multisite mutations in F<sub>1</sub> mice of 4 Gy-irradiated spermatogonia and mature oocyte than in those from unexposed parents. However, larger size mutations including structural variants are not fully understood. Currently, we are developing a new pipeline to detect larger size mutations using a long-read NGS technique and a mouse mutation accumulation line. With our new pipeline we hope to uncover the spontaneous occurrence rate and characteristics of such variants (especially transposon mutations) in mice. After this, we will submit a paper demonstrating the new pipeline for detecting germline de novo large-size mutations in experimental animals.
- Since the hereditary risk of radiation exposure upon cancer or multifactorial diseases is an important issue and there are virtually no human data to address it, it is essential that the F<sub>1</sub> cohort follow-up be continued for another 30-40 years to evaluate lifetime risk. The third round of the longitudinal F<sub>1</sub> clinical study that began in November 2014 was almost completed and the next round has started. An analysis using continuous values such as blood pressure, lipid and glucose levels will be considered.
- In the F<sub>1</sub> offspring clinical study, we plan to continue our clinical studies and to integrate and coordinate with epidemiological and basic genetic studies to develop an institution of genetics program. Accordingly, the results will be combined with their epidemiological and genetics data for multidimensional analyses.
- For WGS study of the human trios including atomic bomb survivors and their offspring in FY2020, we will make a complete research plan under the review of Genetics Research Cluster and external advisors. After the reviews, we will submit the research proposal to IRB and get approval. When research environment (including financial, ethical and social issues) will have been completely prepared, we will start to access to the participants and get informed consent from them for the WGS study. After getting informed consent, we will start experiment using WGS.
- By using cultured human cell lines we will examine what method is suitable for the analysis of Atomic bomb survivors' samples. We also develop improved methodologies to detect large size mutations and structural variations in analysis of human samples using knowledge obtained from mouse genome long-read sequencing. In addition, we will develop detection method to explore epigenetic status from long read sequencing data. (Satoh, RP S3-11)
- For a GS cell study, mutations in irradiated GS cell clones will be characterized by aCGH and WGS analyses, and then the cell clones will be transplanted into Busulfan-treated testes of adult male mice. We will then examine the offspring derived from the GS cells for

heritable genetic changes. Along with this experiment, efficiency of spermatogenesis from the transplanted GS cells will be analyzed by testis tissue cross sections. As a control, GFP positive GS cells and testicular cells from GFP positive mice will be used. We plan to make artificial large scale deletions or inversions in GS cells via newly developed gene editing systems (Noda, RP-P3-17).

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

- We will complete computations for the current DS02R1 dosimetry system for subjects for whom these doses have not yet been computed, in particular for parents of F1 subjects. This is provisional on Masterfile Section's ability to complete input of revised location data for these individuals, which we anticipate will occur in FY2020, allowing us to complete this task (Funamoto, Shimizu, in consultation with H. Cullings and others). [RP18-59]
- We will continue to coordinate and participate in Phase I of the project to re-evaluate organ dosimetry based on revised phantoms to make a go/no go decision to begin formal implementation of these new doses for all survivors. In the likely event that there is a go decision, we will begin code modifications, testing, and validation for integrating the new fluence data into the existing dosimetry system (Funamoto, Shimizu, in consultation with H. Cullings and others). [RP18-59]

### **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 2020:
  - a. Partnership with the University of Washington
  - b. Partnership with Kurume University
  - c. Collaborations with the US National Cancer Institute
  - d. Collaborations with the University of Florida
  - e. Collaborations with Outside Investigators:
    - 42 Japanese Institutions
    - 10 North American Institutions
    - 8 European Institutions
    - 1 Asian, Oceanian Institutions

### **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.

Activity plans for FY2020

- i) RERF will hold an epidemiological training course for radiation biologists in Japan again in FY2020 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, funded by MHLW, for FY2020 also.

## 6. Public Information Programs

From the days of ABCC, its predecessor organization, until the present, RERF has investigated the medical effects of radiation, in atomic bomb survivors and their children (the second-generation). Because 2020 is the milestone year marking the 75th anniversary of the atomic bombing, RERF's public information programs for FY2020 are intended to reach atomic bomb survivors and second-generation atomic bomb survivors who have long understood and cooperated in RERF's research, as well as the local communities of Hiroshima and Nagasaki. We will work on public information programs, outlined below, to ensure that the general public can further understand RERF.

### i) RERF Open House event

In FY2020, RERF will hold its 26th and 24th 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 August in both Hiroshima and Nagasaki in FY2020.

### ii) Strengthening of social media-related activities

RERF will expand its public relations activities using social media networks such as Facebook and Twitter, the latter of which was initiated in FY2019. Because the most important task facing RERF is obtaining understanding from atomic bomb survivors, second-generation, and local communities, social media will be used to achieve that goal.

### iii) Promotion of public relations activities targeting media

Aiming to allow media to accurately understand ABCC-RERF's research achievements and to report based on that clear understanding, in FY2020 we will hold lectures and study sessions for the media, in continuation from similar efforts made last year. Through such gatherings with media, we hope to increase awareness and understanding of RERF's work, as well as to foster closer ties.

### iv) Enhancement of RERF website

Following the launch of the renewed RERF website in FY2018, in FY2020 RERF will continue aiming at enhancing the homepage. Focus will be placed in particular on conveying readily understandable research and other information to the public, through the utilization of more video and other methods.

### v) Enhancement of online news-delivery system

RERF's email magazine system, which replaced the printed *Update* newsletter, will be enhanced in terms of content and used to not only distribute the latest research results

and information about RERF events and activities but also to attract readers to RERF as “members,” by offering a sense of “buy-in” with respect to RERF as an organization.

vi) School Visit Program

This program was first established in FY2016 in an attempt to convey to elementary, junior-high, and high-school students the reality of radiation health effects. Based on the program’s popularity, each year, numbers of requests for such classes increase and a now stable group of available teachers has provided RERF the opportunity to teach an increased number of classes. In FY2020, in addition to the conventional school visit program, we will also work to expand the project by not only teaching students about radiation but about how to teach the basics of radiation to their peers, in a student-led education drive.

vii) Internship (work experience) project

RERF has been accepting interns for some time now, but a college student from the United States recently requested the Public Relations and Publications Office to allow her to do an internship during FY2020. The Public Relations and Publications Office plans to have the trainee learn how to perform RERF’s facility tours, among other such work. RERF believes that the intern can enhance communication with young people.

viii) RERF public lecture series

RERF’s new public lecture series, initiated in 2019, targets peace volunteer guides among other such individuals, in partnership with external organizations such as the Hiroshima Peace Memorial Museum. In FY2020, in the same way, RERF will collaborate with external organizations and continue to hold public lectures using this new format, borrowing the organizations’ marketing resources and ability to attract attendees. Based on such efforts, RERF will be able to provide an opportunity to enhance understanding of the foundation’s research and learn more about radiation’s health effects to even greater numbers of atomic bomb survivors, second-generation, and general public.

ix) Science Club

RERF will provide a venue for science students at junior-high and senior-high schools to learn about RERF science. Creation of other such venues for learning about other RERF specialties in addition to science, such as English, is also under consideration. At the same time, this activity can be communicated widely on social media, resulting in further understanding by the public about RERF.

x) 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.
- With the aim of improving public understanding of RERF research, the Public Office initiated in FY2018 a new series of paper synopses that explain research with simpler prose and smaller word counts than used previously in our “summary explanation” series for specialists. Through continuation of this series in FY2020, the Office will aim to improve understanding by the public of RERF’s work.
- A persistent goal again in FY2020 will be the training of more RERF personnel to handle facility tours in English for overseas visitors.
- By increasing our effort at communicating RERF’s research with the aim of improved transparency related to RERF research and establishment of good communication with

the public, in particular A-bomb survivors and their children, the Public-Awareness Campaign working group was formed in January 2019. In FY2020, the PAC working group will attempt to provide information on important topics such as the human genome, genetics studies, and other such topics.

- RERF will continue to target small public groups of A-bomb survivors and their children, who will be invited to come to RERF and speak with directors and staff about ABCC/RERF history and research results, with the aim of achieving greater understanding about RERF.

## **II. Operation and Management of RERF**

### **1. Research Resource Center**

With the establishment of the “Preparatory Committee for Establishment of the Research Resource Center,” four subcommittees will immediately begin their efforts. The “Data Inventory” subcommittee will be responsible for finding datasets that are not being centrally stored as well as historical datasets that have been stored but are not cataloged or available to RERF researchers. The “Scanning” subcommittee will continue to identify paper records that are in need of scanning and work with vendors to perform a pilot project to determine time and costs required to scan various types of records currently being held by RERF. The “Biosample” subcommittee will continue to work with various departments at RERF who have stored biological samples but whose samples have not been centrally inventoried. The 4<sup>th</sup> committee on “Administration” will begin making decisions on how to position the RRC in RERF’s hierarchy and determine staffing, budget, and leadership positions.

In addition to these efforts, we will endeavor to hire an intern from the University of Chicago to work over the summer on beginning to populate the Gen3 Data Commons with RERF data and build a suitable interface to the data. This is a project that will initially require outside expertise. Two new computer scientists should begin work for RERF in April. After their initial training, it is hoped that one of them will begin to work closely with the Gen3 Data Commons in an effort to continue the development work required at RERF.

The development of the “Office of Collaborative Research and Grant Support” would pay immediate dividends at RERF. The office could spearhead efforts to continue to develop institutional policies for data sharing, and develop more stream-lined and standardized procedures and approval processes for data sharing. Currently, RERF staff are responsible for handling these administrative burdens, which lowers enthusiasm for engaging in sharing research projects and reduces our researchers’ abilities to perform their own research.

It is hoped that an office for the RRC can be set up for developers and allow them to begin to field questions on data access. The top priority for the RRC is to make data access easier for RERF researchers—making initial steps to facilitate this process and understand the needs of the researchers should be made early in the development process rather than as a post hoc step.

### **2. Review on the relocation of the Hiroshima Laboratory**

For Hiroshima Laboratory’s relocation, we will clarify the function and floor space requirements of research facilities to achieve RERF’s Strategic Plans and draft specific plans.

### **3. Introduction of an attendance and work management system**

With the enforcement of a work-style reform law enacted in June 2018, RERF will continue the purchase procedures as part of the initiative launched last year. We will introduce an attendance and work management system this fiscal year to monitor employee work hours in an objective way, improving the work efficiency of attendance management duties by creating workflows for the various kinds of leave applications and the overtime report, as well as streamlining salary calculations by linking attendance information to the payroll system. After the bidding, a contract with a successful bidder will be concluded, and work to introduce the system will start immediately. After a trial operation by the Personnel Section, full-scale operation of the system is scheduled to start from July 1, 2020.

### **4. Facility upgrades**

#### **1) Facility upgrades to the Hiroshima Laboratory**

The air conditioners of Units C, D, E, H, and I (multiple packaged air conditioning unit systems and individual air conditioners) have significantly deteriorated. In addition, maintenance in the event of failure is expected to be difficult, since global warming prevention led to the end of R22 refrigerant's production at the end of December 2019. R22 is widely used for air conditioners. RERF will implement the third year of its three-year air conditioner renewal plan. The necessary expenses will be about 30 million yen.

#### **2) Facility upgrades to the Nagasaki Laboratory**

Double windows will be installed in rooms facing the national highway to reduce noise from cars and trams. Double windows have already been installed in the conference room on the 3rd floor. So windows will be installed in the offices used by the Division of Medicine, Clinical Contacting Section, Pathology Laboratory, Chief of Epidemiology, and the Tumor & Tissue Registry Office. The necessary expenses will be approximately five million yen.

### **5. Revision of the rules and regulations**

We are revising current regulations and establishing new regulations to resolve the findings of the Auditors' management letter and Deloitte Touche Tohmatsu's internal audit. Along with continuing to resolve these findings quickly and suitably in FY2020, required revisions will be made to keep this institution's management operations appropriate. Doing so will provide regulations befitting of a public interest incorporated foundation funded by Japanese and U.S. government subsidies.

