2019

# HIROSAKI UNIVERSITY RESEARCH HIGHLIGHTS

Communicating to the World

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HIROSAKI UNIVERSITY

# The elucidation of the human effects of low-dose chronic radiation exposure utilizing a global network

## Purpose and Background of the Research

We have no answer to the question of low-dose chronic radiation exposure in humans. In this project, we aim to reach an answer to this long-standing issue. Recently, the National Nuclear Energy Agency of Indonesia (BATAN) discovered a high natural background radiation area in Sulawesi, Indonesia. In this research project, we are carrying out radiation dosimetry from internal and external exposure, as well as blood sampling from the residents of this area, to determine the relationship between total radiation exposure and biological effects. Furthermore, we aim to identify the biomarkers for lung cancer risk at a high lung cancer incidence area in Chiang Mai, Thailand. We are collaborating with African countries like Kenya and Cameroon for radiation dosimetry from natural radioisotopes from the viewpoint of radiation protection for the general public.

## Research Results

Our research project consists of a radiation dosimetry group and a radiation biology group. In Sulawesi, Indonesia, the radiation dosimetry group was used to determine the external doses from terrestrial gamma rays and internal doses from radon inhalation in a high natural background radiation area and a controlled area. Additionally, the radiation biology group was used to carry out comprehensive protein expression analysis using the blood samples taken from the residents in a high natural background radiation area and controlled area in Sulawesi. In Chiang Mai, Thailand, we measured indoor radon concentrations to estimate the annual effective dose. In this study, some specific proteins were observed in both the lung cancer area and high natural background radiation area, but not in the controlled area. Furthermore, we first reported on the distribution of terrestrial gamma ray doses and indoor radon concentrations at a uranium mining area in Cameroon. We also performed a preliminary survey on internal exposure due to radon inhalation at traditional houses in Kenya. Some international collaboration papers have been published in international journals.

## Future Prospects

We will discuss the possibility of epidemiological study and further biological analysis in Sulawesi, Indonesia to understand human effects due to low-dose chronic radiation exposure. We will also perform further field surveys to understand the mechanism of the enhancement of natural radiation levels. Additionally, we will establish strong collaborations to carry out detailed field surveys of external and internal exposures in African countries.

## Funding (Direct Costs)

1) Hirosaki University Institutional Research Grant FY2018-2019 16,000,000 yen
2) JSPS KAKENHI Grant Number 18K10023 FY2018-2020 3,400,000 yen
3) Research Foundation for the Electrotechnology of Chubu FY2017 1,700,000 yen

Fig. 1 Scenes showing radon (left) and terrestrial gamma ray (right) measurements at the high natural background radiation area in Sulawesi, Indonesia.

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# Analysis of the molecular mechanisms of the regulation of viral genome functions through the biochemical purification of viral genome-protein complexes

## Purpose and Background of the Research

Viral diseases are one of the major threats to human health, and the development of effective treatments against them is urgently needed. Our research group has developed locus-specific chromatin immunoprecipitation (locus-specific ChIP) technology and identified molecules regulating gene expression through binding to the regulatory regions of genomes. Among these molecules, we have also identified suitable drug targets for intractable diseases caused by abnormal gene expression programs. In the present study, we will apply locus-specific ChIP and its related technologies to the identification and characterization of factors interacting with the viral genome to discover the first-in-class drug targets for antiviral treatments.

## Research Results

1. Purification of complexes consisting of the virus genome and1. Purification of complexes consisting of the virus genome and proteins (viral and host)

Virus-infected cells were fixed with formaldehyde. After fragmentation of the nucleic acid-protein complexes by sonication, these complexes were incubated with engineered nucleic acid-binding molecules to tag the target complexes. After affinity purification of the target nucleic acid-protein complexes and reverse crosslinking, proteins associated with the target virus genome were identified via mass spectrometry.

2. Confirmation of the binding of identified proteins to the virus genome

Next, binding of the identified proteins to the virus genome was confirmed via imaging and biochemical techniques.

3. Characterization of proteins associated with the virus genome

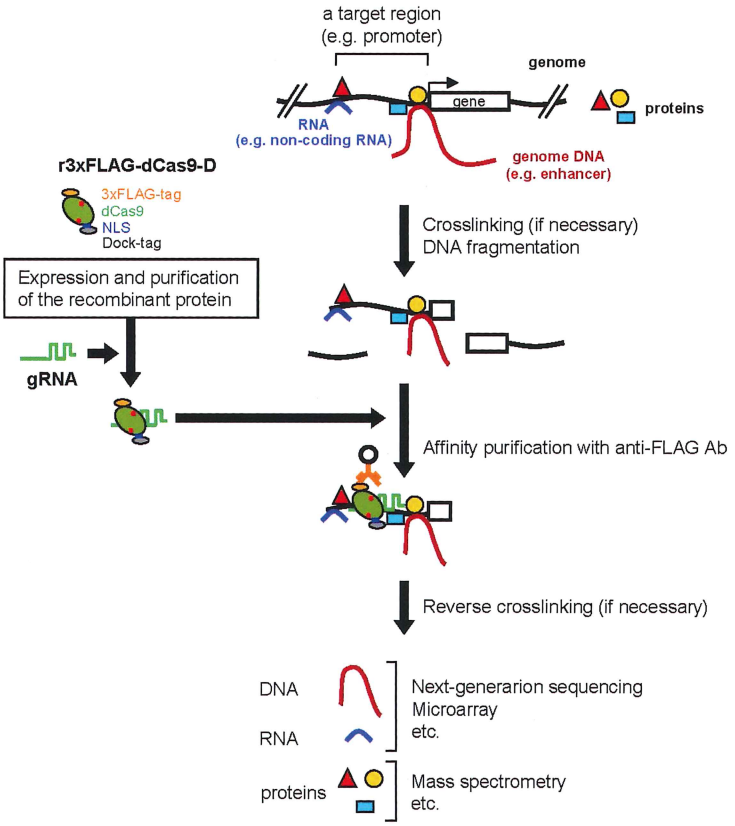
By performing loss-of-function experiments (siRNA-mediated knock-down and/or CRISPR-mediated knock-out) of the identified proteins associated with the viral genome, we elucidated their functions in the regulation of virus replication and proliferation.

## Future Prospects

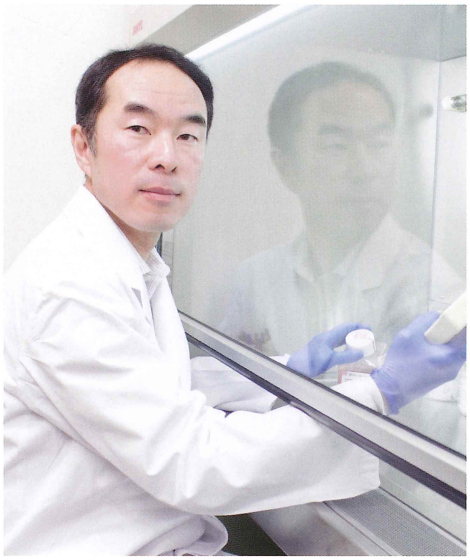
Among the identified proteins associated with the viral genome, we will select those suitable for drug targets. High-throughput screening (HTS) will be performed to find small molecular weight compounds that modulate the function of the drug target proteins. By optimizing the compounds using medical chemistry techniques, we will develop novel first-in-class drugs against viral diseases. Collaborations with pharmaceutical companies will be arranged.

## Funding (Direct Costs)

Hirosaki University Institutional Research Grant for Future Innovation
FY2018-2019, 4,000,000 yen




*In vitro* engineered DNA-binding molecule-mediated chromatin immunoprecipitation (enChIP) using recombinant CRISPR ribonucleoproteins used for purification of virus genome-protein complexes



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# Radiation dose assessment and the development of radiomitigators

## Purpose and Background of the Research

In March 2011, a serious radiological accident occurred at the Fukushima Dai-ichi Nuclear Power Station (F1-NPS) following an earthquake and tsunami. Hirosaki University sent 13 individual support teams to Fukushima and surveyed more than 5,000 people during this period. In such a nuclear accident, special attention must be paid to internal exposure to the thyroid from the inhalation of released short half-life radionuclides. We therefore also evaluated the ambient dose rate and radioactivity concentration in various environmental samples. Since Namie Town in Fukushima was heavily contaminated by the F1-NPS accident, the thyroid equivalent dose of this population was estimated.

In radiation accidents, drug therapy is the most suitable treatment; the chosen drug should already be approved domestically, stably supplied and regularly stockpiled. Our study demonstrated that a single administration of romiplostim (RP), an approved therapeutic drug for idiopathic thrombocytopenic purpura, induced a 100% survival rate in mice exposed to a lethal dose (7 Gy). We investigated the action mechanism of RP in mice models.

## Research Results

The first team exhibited the highest external exposure dose, but the fourth team onward exhibited no significant change. Further, the internal radiation exposure measured using a whole body counter (WBC) was at undetectable levels in all participants.

The thyroid dose of residents could be estimated using 134Cs activity obtained via WBC examinations. The maximum internal exposure of the thyroid to 131I based on 134Cs accumulated in the body measured with the WBC was estimated to be 18 mSv. This value was much smaller than 50 mSv, which the International Atomic Energy Agency recommends as the dose at which exposed persons should take stable iodine tablets.

It was shown that the administration of RP led to a 100% survival rate at day 30 (Fig. 1). RP enhanced the recoveries of hematopoietic stem/progenitors, improved intestinal integrity and morphology, suppressed DNA breakage, and increased the DNA repair observed in the bone marrow cells. Further, RP may not only promote hematopoiesis in multiple organs, but also mitigate the dysfunction or regenerate the original function of organs. Our study indicates that RP is the most suitable candidate for victims exposed to high-dose ionizing radiation.

## Future Prospects

We must continue measuring the absorbed dose rate in air and radioactivity. In order to determine the long-term health effects of residents, it is necessary to continue measuring environmental radiation concentrations. In addition to the above efforts, we must consider the development of radiation/nuclear medical countermeasures. Further, precise dose estimation in each exposed individual is also critical for effective radiation emergency medicine.

## Funding (Direct Costs)

JSPS KAKENHI Grant Number 16H02667 FY2016-2019
35,500,000 yen
JSPS KAKENHI Grant Number 15K15443 FY2015-2016
2,800,000 yen
JSPS KAKENHI Grant Number 25293256 FY2013-2015
9,900,000 yen

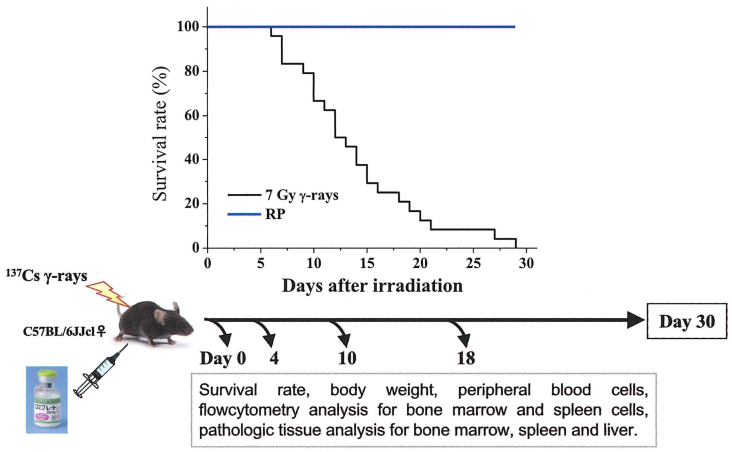


Figure 1: Radiomitigative effect of RP. Mice were exposed to 7 Gy of 137Cs γ-rays and administered once-daily doses of Nplate® (RP, 50 μg/kg of body weight) for 3 consecutive days, as illustrated in Kaplan-Meier survival curves. The first dose was administered starting within 2 hours post total body irradiation, and daily doses of RP were administered via i.p. injection. Control mice were irradiated and received injections of a vehicle.

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# Probing the large-scale structure of the universe using weak gravitational lensing

## Purpose and Background of the Research

According to general relativity, when a light ray passes near a massive object (such as galaxy or cluster of galaxies), its path is deflected due to the gravitational attractive force of the object (this phenomenon is called the gravitational lensing effect). Light rays from distant galaxies are deflected several times when they propagate in the clumpy matter distribution in the universe. As a result, distant-galaxy shapes are coherently distorted by the foreground matter distribution(called weak gravitational lensing). Therefore, we can directly map the matter distribution in the universe from the galaxy shapes. Several large-area galaxy surveys are currently measuring the weak lensing signals. Our main purpose of the research is to prepare an accurate theoretical model of large-scale matter distribution in the universe for the ongoing and forthcoming galaxy surveys.

## Research Results

We have been working on the weak lensing effect in the inhomogeneous matter distribution of the universe using a theoretical approach. We ran cosmological numerical simulations to follow the non-linear gravitational evolution of matter. Cosmological matter fluctuations are usually characterized by their power spectrum (which is a square amplitude of fluctuations at a given scale). We ran several simulations for dozens of cosmological models to make an accurate fitting formula of the matter power spectrum. We also prepared mock weak-lensing maps using simulations. The figure to the right plots a projected density contrast in a mock all-sky map. These mock catalogs were prepared primarily for the Subaru HSC (Hyper Suprime-Cam) survey in Hawaii, but are currently also being used in other surveys around the world.

## Future Prospects

My collaborators and I are planning to update our theoretical model by using higher-resolution numerical simulations for upcoming large-area galaxy surveys.


## Funding (Direct Costs)

MEXT KAKENHI Grant Number 15H05893, FY2015-2019, 9,000,000 yen (Co-Investigator)

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MEXT KAKENHI Grant Number 18072004, FY2009-2011, 2,400,000 yen (Co-Investigator)

Hirosaki University Grant for Exploratory Research by Young Scientists, FY2009, 364,000 yen


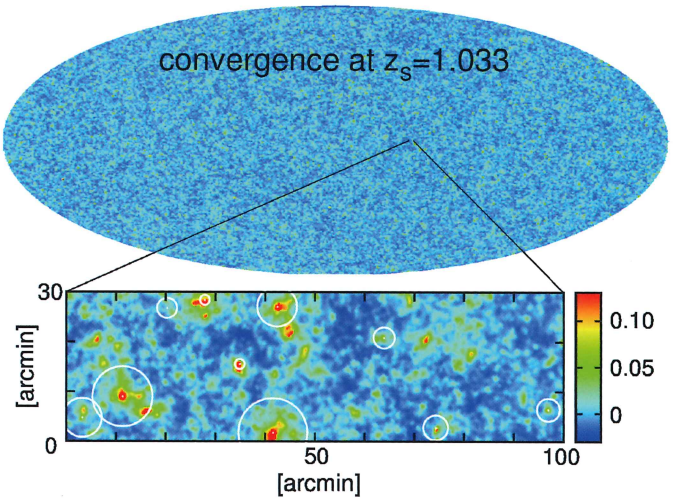


Fig caption:
A simulated all-sky map of a weak lensing signal. The red/blue regions correspond to high/low projected densities. The lower rectangular panel is a zoom-in map. The white circles denote massive foreground halos.


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# ACADEMIC ORGANIZATION of HIROSAKI UNIVERSITY

## Faculties

### Faculty of Humanities and Social Sciences
- Cultural Innovation
- Social Management

### Faculty of Education
- Teacher Training
- School Nurse Training

- Kindergarten
- Elementary School
- Junior High School
- School for Special Needs Education
- Center for Educational Research and Practice
- Center for Teacher Educational Research and Development
- Office Organizing Workshops and Courses for the Teacher Qualification Renewal System

### School of Medicine
- Medicine
- Health Sciences
- 2020 ～ Clinical Psychological Science

- University Hospital

### Faculty of Science and Technology
- Mathematics and Physics
- Frontier Materials Chemistry
- Global Environment and Disaster Prevention Sciences
- Electronics and Information Technology
- Mechanical Science and Engineering
- Sustainable Energy

### Faculty of Agriculture and Life Science
- Biology
- Biochemistry and Molecular Biology
- Applied Biology and Food Sciences
- International Agriculture and Horticulture
- Agricultural and Environmental Engineering

- Teaching and Research Center for Bio-coexistence
- Gene Research Center
- The Shirakami Research Center for Environmental Sciences

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### Humanities and Social Sciences (Master's Course)

### Education (Master's Course/Professional Degree Course)

### Medicine (Doctoral Course)
- Institute of Brain Science
- Center for Advanced Medical Research
- Institute for Animal Experimentation
- Research Center for Child Mental Development

### Health Sciences (Master's Course/Doctoral Course)

### Science and Technology (Master's Course/Doctoral Course)
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- Medical System and Healthware Innovation Frontier

### Agriculture and Life Science (Master's Course)

### Regional Studies (Doctoral Course)

### The United Graduate School of Agricultural Sciences, Iwate University (Doctoral Course)

### 2020 ～ Sustainable Community Studies (Master's Course)

## Research Institutes

### Institute of Radiation Emergency Medicine

### Institute of Regional Innovation

## Interdisciplinary Research Facilities

### Center for Education and Research of Lifelong Learning

### Health Administration Center

### Radioisotope Laboratory

### Hirosaki University Press

### Hirosaki University Museum

## University Library

Medical Branch Library

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