Research area in Strategic Objective *"Elucidation of the mechanisms relating to changes in biological robustness associated with aging and control of age-related diseases"*

[Aging] Fundamental understanding of age-related organismal transformations

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Overview

This research area aims for elucidation of the mechanisms relating to changes in biological robustness associated with aging and control of age-related diseases. To achieve the Strategic Objective set by the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan Science and Technology Agency (JST) and Japan Agency for Medical Research and Development (AMED) have simultaneously established research areas under three different funding programs (PRESTO, AMED-CREST, and PRIME) and promote research while collaborating with each other under the initiative of Program Supervisor (PS) who is in charge of collaboration among these three programs. Please note that JST may share research proposals with AMED during the selection process.

Policy of Program Supervisor

Aging is inseparable from longevity. Organisms have biological robustness that is supported by resilience mechanisms, the ability to adapt to the environment and external stimuli, to complete their natural life. Therefore, we consider that aging could be correlated well with alteration of robustness and resilience of organisms. It is, therefore, important to promote research in order to elucidate the aging mechanism and controlling age-related diseases that are associated with life extension, by investigating the mechanism of alteration using new technologies and analytical methods. The recent advancement of analytical measurement and technologies for components that are the basis of life phenomena, such as molecules, cells, tissues, and organs making up living organisms has been remarkable. These research methods contribute to the dramatically advancing the elucidation of the mechanisms of aging. To explore the fundamental principles of aging, using these cutting-edge technologies and to elucidate the preventive/therapeutic mechanisms of age-related diseases based on these principles, the establishment of an integrated research network among researchers of the basic research and the development of research proposals for prevention and treatment, and promotion of research in a comprehensive way are expected. We tackle the basic understanding of aging by utilizing advanced analysis technologies in the human, model organisms and the organisms that show

characteristic aging phenomena. For this purpose, collaboration with researchers of aging research and the sharing of technology are essential. We thrive to make this research area where active joint investigation between researchers and exchange of samples are possible so that we can discover the universal principle among organisms.

In addition, JST and AMED manage the research areas under PRESTO, AMED-CREST, and PRIME jointly for realization of the goals, promote integrated understanding of aging research by integrating and aligning multifaceted knowledge and technologies from different fields in research promoted respectively, and address original research and development ahead of other countries. Moreover, we are planning to collaborate with Moonshot Research and Development Program (from the 2020 academic year to the 2029 academic year) Goal #7" Realization of sustainable care systems to overcome major diseases by 2040, for enjoying one's life with relief and release from health concerns until 100 years old."

Policy of Research Supervisor

As aging is recognized as a social problem globally, aging has been regarded as a drug discovery target and attention is focused on research proposals, such as searching for anti-aging drugs. However, the history of aging research is still short, and it cannot be said that basic knowledge of aging, a life phenomenon, has been sufficiently understood. Here, defining aging as "transformation of robustness and resilience of organisms over time", this research area aims for basic understanding of the transformation of biological robustness and resilience with aging using a wide range of bioscientific approaches.

Biological robustness and resilience are constantly transforming in the body from embryonic development, growth, and aging until death. Organismal transformations described here refers to the continuous changes with biological processes in living organisms, which includes epigenetic gene expression control, metabolism, redox, intracellular signal transduction, and other factors at the molecular level, and differentiation, proliferation, maintenance and dormancy of stem cells, cell senescence, cell degeneration and cell death at the cellular level. At the tissue level, this includes temporal changes in various tissues in the body, such as immune, nervus and endocrine system, tissue damage, repair, and cancer development. In addition, it is important to know how biological robustness and resilience has developed in the process of evolution and how organismal aging has been defined.

In order to understand these age-related organismal transformations, every effort should be made, utilizing all measurement and analysis technologies that have been developed in life and medical research, such as multi-omics and imaging, data analysis, simulation, and genome editing ~~technologies~~. Besides model organisms (mouse, fish, Drosophila, nematodes, yeast, and others) that have been used so far, development of novel model organisms of short-lived or long-lived species, and of organoids will be included as a research theme of this research area.

Based on the above, this research area aims to promote fundamental understanding of age-related organismal transformations by utilizing all scientific technologies that have been achieved in various research fields and promoting further technological development.

Research Supervisor's policy on call for research proposals, selection, and management of the research area

1. Background

Japan's population aging rate is 28.8%, the highest in the world, and it is projected to rise to 37.7% in 2050. The difference between the average life expectancy and healthy life expectancy is now about 8.8 years among males and about 12.3 years among females. Narrowing the difference between them is an urgent issue for improving the Quality of Life (QOL) of people and maintaining Japanese social structure.

As the world's population ages, anti-aging is regarded as a drug discovery target. Anti-aging research is a frontier of life and medical research which is heating up both in public and private worldwide. For example, National Institute of Health (NIH, USA) has been increasing the aging-related budget every year and Google spent huge amounts of money to establish Calico (Calico Life Sciences LLC).

Recent anti-aging research has focused on studies targeting clinical use. For instance, rapamycin and metformin were found to have life-extending effects in mice, and drug discovery research, called Senolytics, that aims to eliminate senescent cells, has attracted attention.

However, traditionally, aging-related diseases have been studied from the viewpoint of symptomatic treatment for individual diseases. It was not until recently that aging is recognized as the greatest risk of various age-related diseases or the direction of research has changed to delaying aging itself and extending healthy life expectancy. Many aspects of the principle of aging, life phenomenon, remain to be fully elucidated, which leads to the current state of discourse and publication of uncertain anti-aging claims.

Therefore, fundamental understanding of age-related organismal transformations by integrating technologies and knowledge in different fields is required in order to prevent aging and to treat age-related diseases based on evidence.

2. Expected targets to be achieved and specific examples of research and development projects

This research area aims for fundamental understanding of age-related organismal transformations by not only utilizing science and technologies that have been developed in life science research fields, but also exploiting all available engineering and information technologies. We also plan to develop new technologies, methods and materials that can contribute to future aging research. Some specific

examples of research and development projects are described below, however, research proposals other than these examples are very much welcomed.

(1) **Fundamental understanding of age-related organismal transformations, focusing on various biological phenomena**

- Development of measurement, analysis, imaging and manipulation technologies for the process of functional decline along with the life course (life history) from the developmental stage of an individual (including chemical biology)
- Elucidation of nutrition response and metabolic control, quality control mechanism of proteins and organelle, and cell-to-cell/tissue relationship in organismal transformations
- Elucidation of the mechanism of organismal transformations using stem cells, immune cells, neural cells, and others
- Search for individual aging biomarkers and quantitative evaluation of aging by multi-omics analysis
- Understanding of aging phenomena using data science, mathematical model, simulation and AI.

(2) Elucidation of common mechanisms of diversity in aging among individuals based on environment, genetic factors, stochastic fluctuations, and other factors

- Identification of the mechanism that determines individual differences in aging and longevity using model organisms and others
- Research on sex differences in aging and longevity

(3) Understanding of the basic principles of aging and longevity determination using novel model organisms with characteristic traits and organoids

- Elucidation of the mechanism of the organismal transformations in fast aging species
- Elucidation of longevity factors in organisms with long life spans
- Development of a novel organoid culture system that enables evaluation and prediction of long-term change (aging)
- Comparison of the process of organismal transformation in aging among species

3. Research period and research costs

The research period is three years and six months or less; budgets have an upper limit of a total of 40 million yen (not including indirect costs) per project.

4. Management policies for this research area

In the call for research proposals of this research area, great importance is placed on research that focuses on the nature of the age-related organismal transformations. Using or developing unique technologies and original viewpoints are also important. The uniqueness and originality of the content

based on the accurate comparison to other research works should be clearly described in research proposals. In addition, this research area emphasizes the ability to collaborate with other researchers across disciplines from the viewpoint of human resource development. In these days, scientific research requires not only the driving force of individual researchers but also the results of joint research through interdisciplinary integration that cannot be obtained by individual research, so the ability to create new technologies and ideas through collaboration with other researchers is indispensable. The applicant's opinions and achievement on this viewpoint should be also indicated in research proposals.

By making best use of collaboration opportunities with researchers inside and outside the research area, including the AMED-CREST/PRIME "Bridging the fundamental mechanism of aging and the effective treatment of age-related disease associated with impaired functional system" area set under the same Strategic Objective, we expect that PRESTO becomes a significant step for progress of the future research of each researcher. In view of the importance of innovation in current science and technology policies, this research area supports the acquisition of intellectual property rights of participating researchers.

5. Collaboration and cooperation with other research areas, etc.

Since JST and AMED established research areas under the same Strategic Objective, this research area is expected to closely collaborate with the research area of AMED-CREST/PRIME "Bridging the fundamental mechanism of aging and the effective treatment of age-related disease associated with impaired functional system." JST will jointly hold research meetings and workshops with AMED, relevant academic community, research institutions as necessary.