Bridging the fundamental mechanism of aging and the effective treatment of age-related disease associated with impaired functional system

Program Supervisor (PS)

Naoki Mochizuki, M.D., Ph.D.

Director, National Cerebral and Cardiovascular Center Research Institute

Program Officers (POs)

Akiyoshi Fukamizu, Ph.D.

Director, Life Science Center for Survival Dynamics,
Tsukuba Advanced Research Alliance (TARA), University of Tsukuba

Koji Yasutomo, M.D., Ph.D.

Professor, Graduate School of Biomedical Sciences, Tokushima University

Application Guidelines p.27

Program Supervisor (PS)

Naoki Mochizuki, M.D., Ph.D.
Director,
National Cerebral and Cardiovascular Center Research Institute

Profile

1984 Graduated from School of Medicine, Hokkaido University
1988 Completed Doctoral Program, Graduate School of Medicine, Hokkaido University
1993–1995 Researched at UCSD (Paul A. Insel, GTP binding protein research)
1997 Tufts New England Medical Center (Prof. Michael E. Mendelson, Research on nuclear receptors and blood vessels)
1998 Section Chief, Research Institute of International Medical Center of Japan (Director Michiyuki Matsuda)
2001 Director, Department of Structural Analysis, National Cardiovascular Center Research Institute

Recent Research Direction

Investigate the mechanisms of organ formation through analysis using visualization technologies for information signaling systems as well as ontogeny imaging. Analysis of the histories of individual specimens by imaging transparent fish from fertilization through to old age.

Program Officer (PO)

Akiyoshi Fukamizu, Ph.D.
Director, Life Science Center for Survival Dynamics,
Tsukuba Advanced Research Alliance (TARA), University of Tsukuba

Profile

1983 Graduated from Faculty of Agriculture and Forestry, Second Cluster of Colleges, University of Tsukuba
1985 Entered Graduate School of Agricultural Sciences, applied biochemistry, University of Tsukuba
1987 Research Associate, Gene Research Center (GRC), University of Tsukuba
1994 Research Associate, Salk Institute for Biological Studies, USA
1995 Associate Professor, Institute of Applied Biochemistry, University of Tsukuba
1999 Professor, Center for Tsukuba Advanced Research Alliance (TARA), University of Tsukuba
2006 Director, Center for Tsukuba Advanced Research Alliance (TARA), University of Tsukuba
2022–present Director, Life Science Center for Survival Dynamics, Tsukuba Advanced Research Alliance (TARA), University of Tsukuba

Recent Research Direction

Conduct research with the goal of understanding biological homeostasis (blood pressure, pregnancy, life spans) by identifying methyltransferases and clarifying their function and biological significance, with a focus on the posttranslation modification of methylation that occurs in DNA, RNA and proteins that carry genetic information.

Program Officer (PO)

Koji Yasutomo, M.D., Ph.D.
Professor,
Graduate School of Medicine, Tokushima University

Profile

1990 Graduated from School of Medicine, Faculty of Medicine, Tokushima University and worked as pediatrician at hospitals in Tokushima City
1997 Completed Doctoral Program at Graduate School of Medicine, Tokushima University, awarded Ph.D. (Tokushima University)
1997 Visiting Scientist, National Institute of Allergy and Infectious Diseases (NIAID), USA
Feb 2001 Research Associate, Faculty of Medicine, Tokushima University
July 2001–present Professor, Graduate School of Biomedical Sciences, Tokushima University
2013 Director, School of Medicine, Faculty of Medicine, Tokushima University (served concurrently until 2017)

Received the Japanese Society for Immunology (JSI) Award in 2014, the Novartis–Japan Rheumatism Foundation Rheumatology Prize in 2015, the Kawano Prize for Pediatrics in 2021, and the MEXT Commendation for Science and Technology in 2022. Served in roles including a Japanese team PI of a project funded by the HFSP program grants, an AMED-CREST PI, and an ASCI member.

Recent Research Direction

Understand T-cell functional differentiation and develop methods to control this differentiation.
Research ranging from identification of genes that cause hereditary inflammatory diseases to elucidating the mechanisms of chronic inflammation onset.

Bridging the fundamental mechanism of aging and the effective treatment of age-related disease associated with impaired functional system

文部科学省

Research and Development Objective

Elucidation of the mechanisms relating to changes in biological robustness associated with aging and control of age-related diseases

Targets

Under this strategic objective, the aim is to conduct research to understand the principles of the biological phenomenon of aging and to build a close-knit system for research collaboration that contributes to the prevention and treatment of age-related diseases. A further aim is to combine with research in other fields to pursue new approaches to aging research that utilize the most up-to-date methods. In particular, the following three targets are to be achieved:

(1) Clarification of the mechanisms involved in age-related disease onset, prevention, and treatment

(2) Integrated understanding of the aging control mechanisms involved in the body's robustness to disease

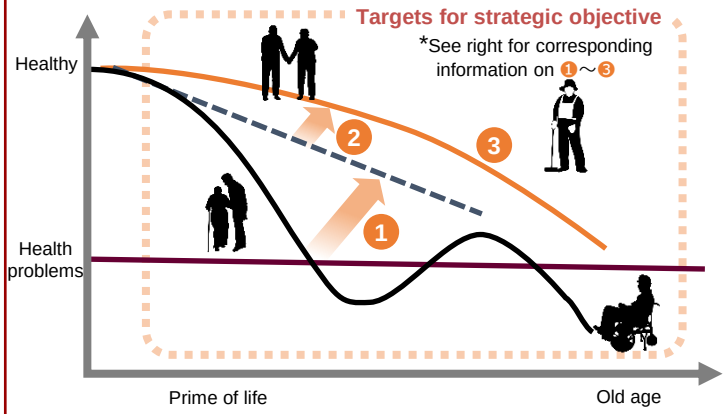
(3) Basic understanding of age-related changes in the body's robustness using the most up-to-date technologies

Image of the R&D area

Current situation, challenges

- Japan's population is aging faster than any other country in the world and Japan is becoming **a super-aged society**. The country is faced with **the urgent challenge** of how to extend healthy life years.
- Aging research is at **the frontier** of biological science and medical science research. We **need to make integrated progress** in **our understanding of the principles of aging** and applied research that clarifies mechanisms in order to prevent and treat age-related diseases.
- Dramatic progress in this research may be possible if aging research investigates biological phenomena utilizing the latest, most advanced **measuring and analytical technologies**, where significant advances have been made in recent years.

AMED-JST shared objective



❶ Clarification of the mechanisms involved in age-related disease prevention and treatment

Research examples
- Vascular disease, metabolic abnormalities, and sarcopenia and frailty

❷ Understanding of the aging control mechanisms involved in disease

Research examples
- Taking into consideration the involvement of molecules/cells (populations), organs, and the entire body
- Identification of anti-aging molecules and substances that act on factors involved in the suppression of aging

Develop integrated research

Share results

❸ **Understanding of changes in the body's robustness using the most up-to-date technologies**

Research examples
Utilizing cutting-edge technologies, such as genome omics, imaging technologies, etc. to:
- Clarify aging mechanisms
- Clarify mechanisms that are common and different in different individuals, using various model organisms

Under the joint objective, AMED and JST will conduct research in their respective areas in an integrated manner. The joint objective aims to build closely aligned research systems for research that (1) clarifies the principles of aging as a biological phenomenon and (2) contributes to the prevention and treatment of age-related diseases based on an understanding of aging mechanisms. The joint objective is also aimed at developing new aging research through interdisciplinary operations.

Expected outcomes

- Understanding of the Aging biology and advances in cutting-edge technologies
- Creation of new innovations that can lead to the prevention and treatment of age-related diseases
- Creation of low-cost, simple preventive healthcare using non-pharmaceutical modalities (e.g., medical devices)

Future vision

Through evidence-based improvements in daily lifestyle habits and the prevention, diagnosis, and treatment of disease,
- Achieve a society where people can lead active lives in good physical and mental health
- Extend healthy lifespans such that more people can expect to reach their 100th birthday

Direction and collaboration by JST and AMED

Fundamental understanding of changes in biological robustness and resilience that occur with aging, using cutting-edge technologies

- Understanding of changes over time in the body and biological phenomena
- Clarification of the basic principles of aging and factors that determine lifespans
  - Basic principles common across different species
  - Diversity, including individual variation, gender differences, differences between family lines
- Analytical technologies to accelerate aging research
  - Explore aging markers using multi-omics analysis
  - Clarification of the dynamics of aging cells using single-cell analytical technologies
  - Development of systems to predict aging using AI technologies

Clarification of basic principles
Basic and applied development of analytical technologies

Comprehensive understanding of diseases as we age, mechanisms that promote/control pathology

- Comprehensive understanding of changes during aging in the progression from physiological aging to pathological aging
- Clarification of aging control mechanisms related to disease and pathology, development of aging control methods

*Physiological aging: failure to maintain homeostasis in organs and tissues due to aging, resulting in changes that can lead to pathological aging
*Pathological aging: changes that occur due to acceleration of the physiological aging process and lead to disease onset and pathological conditions

Basic research through to applied research with a focus on how to move into health and medical applications

JST **AMED**

Combined approach

Prevention of age-related disease due to environmental factors (e.g., nutrition sleep), prevention of functional impairment in physical and motor functions, discovery of aging indicators for use in prevention aimed at extending healthy lifespans
=> creation of low-cost, simple preventive healthcare

Outline of the research and development area

Integrated research systems are expected to be developed to pursue comprehensive research aimed at both basic and applied research on prevention and treatment, in order to explore the fundamental principles of aging using advanced technologies and clarify the mechanisms for prevention and treatment of age-related diseases in light of these principles.

Model organisms will be used for research from genetic, biological and physical (environmental) perspectives with the aim of clarify the following. The diverse and complex linking mechanisms among molecules/cells (populations), organs, and the entire body that are induced by multi-dimensional age-related changes; age-related disease mechanisms based on an understanding of aging over time; and mechanisms to control and suppress aging.

- Based on the principles of and mechanisms involved in the body's robustness and resilience due to aging, research that contributes to understanding pathophysiology based on new concepts and ideas will be promoted.
- This research is expected to lead to aging indicators based on an integrated understanding of aging control mechanisms; the discovery of factors involved in aging control; the creation of new innovations; the prevention of age-related diseases; and breakthroughs in treatments.
- By combining technologies and diverse findings in different fields and bringing together the research themes pursued by AMED and JST, the two organizations will deepen our integrated understanding of aging research and address world-leading innovative R&D.

The Japan Agency for Medical Research and Development (AMED) and Japan Science and Technology Agency (JST) will initiate three programs simultaneously (PRESTO, AMED-CREST, and PRIME) and will work in partnership on the research, under the joint R&D objective "Elucidation of the mechanisms relating to changes in biological robustness associated with aging and control of age-related diseases."

Policy of the Program Supervisor and Program Officer on call for applications, selection, and project management

- This R&D area aims to clarify the biology of the basic mechanisms involved in aging and to develop medical approaches mediated via these mechanisms.
- The programs will include research that uses the most up-to-date analytical technologies (genetic, imaging, omics analysis) and can be progressed from analysis in model organisms through to applied research, in order to get close to the essence of how aging causes dysfunction and breakdown in molecules, cells, tissues, organs, and the entire body.
- What we recognize as being “aging” is the entire integrated progress in which dysfunction in one part of the body induces a breakdown of all bodily functions.
- Rather than research that simply clarifies the cause of dysfunction or the pathophysiology of an age-related disease in a single organ, we think it is more important to investigate the essence of aging and thereby elucidate the fundamental breakdowns and changes in complex mechanisms that result in disease onset in various organs and tissues in the body. We therefore invite research proposals that will help provide an integrated understanding of pathophysiology and will generate new concepts and ideas that contribute to the prevention and treatment of disease.
- In this R&D area, we aim to promote mutual technological guidance, experimental materials exchange, or information sharing between researchers to create a lively area that fosters joint research.

Points to note when submitting a proposal

- When submitting a proposal as a team, clearly indicate how the various research projects run by the PI and the Co-Investigators could generate **synergistic effects** and how this will contribute to the goals and objectives for the overall research proposal.
- For AMED-CREST, the proposal does not necessarily need to include actual development plans for innovative medical technology, but the research should **produce evidence that provides a pathway to applied research in the healthcare field**. However, for PRIME, there is no requirement for the proposal to produce evidence that provides a pathway to applied research in the healthcare field.
- This program **does not include development phases beyond non-clinical studies**, and we recommend out-licensing to other programs according to the status of R&D progress.
- As the goal is to create innovative medical technologies, please **consider the participation of medical science researchers with clinical experience in the relevant field**.

R&D costs and R&D period

Type of proposal	R&D funds	R&D period	No. of projects to be selected
AMED-CREST (unit-type)	250 million yen or less (entire direct costs)	Up to 5.5 years	Around 4–6 projects

Selection policy AMED-CREST PRIME

(1) We invite research proposals that use the most up-to-date analytical technologies (genetic, imaging, omics analysis) and can be progressed from analysis in model organisms through to applied research, in order to get close to the essence of how aging causes dysfunction and breakdown in molecules, cells, tissues, organs, and the entire body.
(2) We think it is important to investigate the essence of aging and thereby elucidate the fundamental breakdowns and changes in complex mechanisms that result in disease onset. We therefore invite research proposals that will help provide an understanding of pathophysiology and will generate new concepts and ideas that contribute to the prevention and treatment of disease.

【AMED-CREST】

- We expect **innovative research proposals that provide original perspectives and combine research in different fields** in order to elucidate the principles of and mechanisms involved in the body's robustness to aging changes and break down of resilience, control mechanisms involved in pathophysiology and disease based on aging changes over time, and mechanisms that contribute to the onset, prevention, and treatment of age-related disease. We **welcome R&D proposals that include the use of imaging and other advanced measuring technologies, database-driven omics analysis, and bioresources to develop and accelerate an integrated understanding of aging research in a wide range of fields**. Ideally, the proposals will include the formation of research units comprised of partnerships with research institutions or pharmaceutical companies in Japan and overseas, and combine various different research fields, such as molecular biology, biochemistry, cell biology, neuroscience, immunology, regenerative medicine, clinical medicine, information science, system biology, or synthetic biology.
- We also invite proposals for Projects for active resource of aging animals to allow stable distribution to R&D projects over time of standardized experimental animals such as aged mice.

【PRIME】

We welcome proposals for challenging and innovative programs that could lead to new breakthroughs through research to clarify at the molecular level the mechanisms involved in aging progression and suppression of aging by the body, and research that may lead to healthcare applications. We also invite proposals on the development of novel platform technologies to detect and control aging. Ideally, the proposals will include the formation of networks through active collaboration with other research groups in the same or different R&D areas, particularly AMED-CREST research units and researchers in JST PRESTO research areas.

Examples of R&D Proposals *Excerpt from Application Guidelines

Below we provide examples of anticipated R&D proposals, but we are looking for innovative research proposals that go beyond these examples.

- Exploration of signaling molecules involved in aging, including nutrition/metabolism immunity/inflammation, biological clocks, stem cells, autophagy, apoptosis, cell competition, mitochondria, and genetic information, and clarification of the control mechanisms for aging progression and suppression that change over time
- Understanding network mechanisms that involve molecules/cells (populations), organs, and the entire body and clarifying mechanisms of action involved in disease
- Identification of anti-aging molecules and substances that act on factors involved in the suppression/control of aging, and clarification of their mechanisms of action
- Clarification of how aging control mechanisms are involved in the body's robustness and resilience to aging that play a role in age-related disease and pathology
- Clarification of the mechanisms involved in aging in age-related diseases (e.g., sarcopenia and frailty) and pathophysiologies (e.g., vascular disease, neurological disorders, metabolic abnormalities, lipid abnormalities)
- Understanding of aging over time, development of new innovations based on pathophysiology mechanisms, exploration of aging biomarkers, and clarification of mechanisms that contribute to disease prevention and treatment

*Projects for active resource of aging animals

*Excerpt from Application Guidelines

The Call for Proposals will accept Projects for active resource of aging animals that involve the supply of standardized animal models of aging, the creation of control systems, or to complement and provide stability for R&D systems in order to build research infrastructure to support integrated basic research to achieve a healthy, long-lived society. Around one of these projects will be selected.

Specifically, Projects for active resource of aging animals include supply systems to allow the stable and cost-effective distribution to R&D projects over time of standardized experimental animals such as aged mice needed for aging research to analyze aging changes. The projects include the development of assistance systems, such as the review criteria etc. set for applications in response to the Call for Proposals in this area, in order to provide assistance in a fair and speedy manner.

When submitting an application, proposals should include specific information on the systems to be put in place to act as assistance functions. Proposals should also cover points of view on expanding assistance and effective R&D using aged mice etc. Applications that include proposals on the implementation of development research to contribute to assistance functions are also possible. Furthermore, to be selected, as well as the research proposal contents, we ask for detailed information to be provided on assistance track record, know-how, or facilities available, to allow assessment of assistance capabilities.

Message from the Program Officer Akiyoshi Fukamizu

- Aging causes the accumulation of irreversible changes over time. We hope to receive **proposals that shed a new light on aging and how it may be repaired**.
- In essence, our cells, tissues, and organs have the potential to age after receiving various stimuli emanating from our lifestyles and environment. We think that both robustness (how the body works to maintain integrated systems in the face of changes from within and without the body) and resilience (the body's repair mechanisms after systems break down) are both involved in the progression or control of aging, but numerous questions remain over how this works in practice. We hope for **research proposals that will actively engage at the frontiers of aging research**.
- When working to elucidate aging mechanisms as identified using model organisms, please submit proposals for innovative and important research that will show vital preliminary data and provide concrete explanations.

Message from the Program Officer Akiyoshi Fukamizu

- Significant advances have been made in research into the role of various organs using a wide range of new technologies, and the time is right for research to provide a better understanding of how multiple organs interact. We are therefore interested in **research proposals that will help provide an understanding of pathophysiology and will generate new concepts and ideas that contribute to the prevention and treatment of disease**, based on an understanding of networks of aging while also bearing in mind the possibility of combining research in different fields.
- This R&D area aims to understand fundamental mechanisms of aging, so we ask applicants to produce written submissions that demonstrate clearly to the reviewers, who come from a wide range of research fields, how the research will provide a pathway towards an essential understanding of aging.
- We are particularly interested in achievable **research proposals, particularly because the research will involve the formation of AMED-CREST units**.

R&D costs and R&D period

Type of proposal	R&D funds	R&D period	No. of projects to be selected
PRIME (solo-type)	40 million yen or less (entire direct costs)	Up to 3.5 years	Around 8–12 projects

Selection policy AMED-CREST PRIME

(1) We invite research proposals that use the most up-to-date analytical technologies (genetic, imaging, omics analysis) and can be progressed from analysis in model organisms through to applied research, in order to get close to the essence of how aging causes dysfunction and breakdown in molecules, cells, tissues, organs, and the entire body.
(2) We think it is important to investigate the essence of aging and thereby elucidate the fundamental breakdowns and changes in complex mechanisms that result in disease onset. We therefore invite research proposals that will help provide an understanding of pathophysiology and will generate new concepts and ideas that contribute to the prevention and treatment of disease.

【AMED-CREST】

- We expect **innovative research proposals that provide original perspectives and combine research in different fields** in order to elucidate the principles of and mechanisms involved in the body's robustness to aging changes and break down of resilience, control mechanisms involved in pathophysiology and disease based on aging changes over time, and mechanisms that contribute to the onset, prevention, and treatment of age-related disease. We **welcome R&D proposals that include the use of imaging and other advanced measuring technologies, database-driven omics analysis, and bioresources to develop and accelerate an integrated understanding of aging research in a wide range of fields**. Ideally, the proposals will include the formation of research units comprised of partnerships with research institutions or pharmaceutical companies in Japan and overseas, and combine various different research fields, such as molecular biology, biochemistry, cell biology, neuroscience, immunology, regenerative medicine, clinical medicine, information science, system biology, or synthetic biology.
- We also invite proposals for Projects for active resource of aging animals to allow stable distribution to R&D projects over time of standardized experimental animals such as aged mice.

【PRIME】

We welcome proposals for challenging and innovative programs that could lead to new breakthroughs through research to clarify at the molecular level the mechanisms involved in aging progression and suppression of aging by the body, and research that may lead to healthcare applications. We also invite proposals on the development of novel platform technologies to detect and control aging. Ideally, the proposals will include the formation of networks through active collaboration with other research groups in the same or different R&D areas, particularly AMED-CREST research units and researchers in JST PRESTO research areas.

Selection policy

The PRIME program involves research performed by an individual researcher in their specialist field. We invite proposals in the R&D areas as described in the AMED-CREST program, particularly for highly innovative research. We welcome proposals for challenging and innovative programs that could lead to new breakthroughs through research to clarify at the molecular level the mechanisms involved in aging progression and suppression of aging by the body, and research that may lead to healthcare applications. We also invite proposals on the development of novel platform technologies to detect and control aging. During the research implementation phase, rather than focusing only on the proposer's specialist field, we recommend they form networks through active collaboration with other research groups in the same or different fields, particularly AMED-CREST research units and researchers in the JST PRESTO research area "Fundamental understanding of age-related organismal transformations," with a view to future development of this research.

Given that this program is designed for proposals from individual researchers, we will give precedence in selection to proposals from younger researchers who may have innovative new research proposals but often cannot undertake challenging research because of a lack of funds and staff. We are particularly interested in how far the researchers submitting proposals can progress and expand the research in the future in the area of aging research and other research areas. We hope to receive proposals from researchers not currently involved in aging research on ideas for analytical methodologies or new concepts that fit the aims of this research area.