Functional Impairment

Clarification of the Mechanisms of Individual's Functional Impairment over the Entire Life Course

Research and Development Objectives

Clarification of the mechanism of individual's functional impairment over the entire life course

With the rapid progress of aging in industrialized countries including Japan, extending healthy longevity is an issue of global importance. While treating individual diseases and improving quality of life (QOL) are important for extending healthy longevity, preemptively suppressing functional impairment at the individual level is expected to be an effective approach.

From birth to death, organisms are constantly subject to various stimuli from the environment. It is thought that the long-term effects of these external factors and internal genetic factors cause individual functional impairment. In understanding and controlling this complex phenomenon, there are limits to the conventional research approaches focusing separately on diseases and on tissues and organs. Instead, a strategic approach is necessary.

Therefore, for this R&D objective, we aim to undertake innovative interdisciplinary research across wide-ranging fields such as development, immunity, stem cells, protein quality control mechanisms, and epigenetics, over the entire life course from birth to maturity, aging, and heredity. We expect this research to identify the mechanisms involved for evaluating and controlling individual functional impairment, and to create the seeds for basic technologies.

Program Supervisor (PS)

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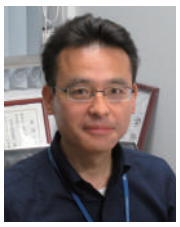
Director, RIKEN Center for Biosystems Dynamics Research



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Started in 2017 • • • 1st period

Elucidation of mechanisms underlying how nutrition history in juveniles impacts later life events (*)

UEMURA Tadashi
Professor, Graduate School of Biostudies, Kyoto University

The aim of our research is to understand how “the nutrition history” in juvenile stages impacts later life events at molecular, cellular and systemic levels, and to ameliorate the eventual deterioration of organismal functions later in life. We use the fruit fly Drosophila, a model organism that has contributed much to our understanding of evolutionarily conserved mechanisms of metabolism, epigenetics, and longevity. To accomplish our goal, we are developing a collection of "unbalanced" diets and an automated tracking system, which allows high-throughput quantification of locomotor activity and life span on an individual basis.

Started in 2017 • • • 1st period

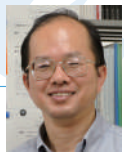
Stem cell homeostasis and functional impairment in spermatogenesis (*)

YOSHIDA Shosei
Professor, Division of Germ Cell Biology, National Institute for Basic Biology

Continual production of huge numbers of sperm for prolonged reproductive periods is essential for successful transmission of life to the next generation. This study will investigate the mechanisms with which the stem cells stably support the long-term homeostasis (steady state) of spermatogenesis, and continual support of homeostasis inevitably causes the functional impairment of the stem cells over time both quantitatively and qualitatively. These studies will lead to the comprehensive understanding of the homeostasis in adult phases and the functional impairment in aged phases as seamless and continual life-course events.

Started in 2017 • • • 1st period

Elucidation of the mechanism of functional decline of adult neural stem cells and development of technologies for reactivation of these cells (*)



KAGEYAMA Ryoichiro
Director, RIKEN Center for Brain Science

Adult neural stem cells (NSCs) gradually lose their proliferative and neurogenic activities and become dormant as they grow older. We found that in embryonic NSCs Hes1 drives Ascl1 oscillation, which activates the proliferative and neurogenic activities, whereas in adult NSCs, Ascl1 expression is repressed. We hypothesized that this repression leads to the dormancy of adult NSCs. We will examine whether induction of Ascl1 oscillation can activate adult NSCs and identify other genes responsible for such activation. These experiments will reveal the mechanism of the age-related functional declines of adult NSCs and establish the technologies to reactivate NSCs.

Started in 2018 • • • 2nd period

Molecular basis of time-related deterioration of mitochondrial function by mtDNA mutation

ISHIHARA Naotada
Professor, Graduate School of Science, Osaka University

The aim of this research project is to understand the relationship between mutations of the mitochondrial genome (“mtDNA”) acquired throughout life and age-dependent whole-body dysfunction. We will analyze the molecular details of pathogenicity of various mtDNA mutations, using a unique model mice "mito-mice", having both wild-type and mutated mtDNA. We will also establish a method to measure mitochondrial malfunction in vivo. Furthermore, we will analyze mechanism of mtDNA inheritance under active mitochondrial fusion and fission. These analysis should lead to establish a novel therapeutic strategy of various mitochondria-related diseases.

Started in 2017 • • • 1st period

Strategy for extending healthy lifespan by the proteasome (*)

MURATA Shigeo
Professor, Graduate School of Pharmaceutical Sciences, The University of Tokyo

The proteasome is a supramolecular protease complex essential for intracellular protein homeostasis. It has been shown that nematodes and Drosophila is which proteasome activity is artificially enhanced extend their lifespans. However, there have been no longevity-promoting regimens by manipulating proteasome function in mammals. In this study, we will address the mechanism of decline in proteasome function accompanying aging and the process by which proteasome dysfunction leads to functional deterioration at the cellular and organismal levels. The ultimate aim of this research is to create intervention strategies for extending healthy lifespan by enhancing proteasome function in mammals.

Started in 2018 • • • 2nd period

Study on life-long and cross-generation effects of epigenetic memories

TAKEDA Hiroyuki
Professor, Faculty of Life Sciences, Kyoto Sangyo University

Epigenetic modifications to the DNA strand have been implicated in responses to environmental stimuli as memories without alternation of DNA sequence. In particular, during development and growing stages, organisms tend to retain acquired epigenetic memories for a long period of time (even across generations), after environmental stimuli have been gone. In this project, we examined the mechanisms underlying epigenetic memories by using the medaka (Japanese killifish) as a model. We will chase for long time the change in the epigenome induced by high-fat diet in medaka larvae.

Started in 2017 • • • 1st period

Manipulating cellular senescence *in vivo* to unveil its role in organismal aging, regeneration, and pathogenesis (*)

YAMADA Yasuhiro
Professor, Graduate School of Medicine, The University of Tokyo

It remains unclear how senescent cells affect organismal functions especially in mammals. The aim of this research is to uncover the effects of cellular senescence on organismal functions *in vivo*. To achieve these goals, we will employ mouse transgenic systems that can manipulate cellular senescence in a spatiotemporal manner *in vivo*. This challenging project will unveil the fundamental basis of how cellular senescence affects organismal functions and demonstrate to what extent targeting senescent cells can revert these effects in mammals. These findings may eventually contribute to a feasible strategy to control the detrimental effects associated with aging.

Started in 2018 • • • 2nd period

Individual’s functional impairment caused by changes in sleep quality: its mechanism & intervention by manipulating sleep architecture

HAYASHI Yu
Professor, Graduate School of Science, The University of Tokyo

The quality of sleep largely depends on the pattern of cycling between REM sleep and non-REM sleep, i.e. the sleep architecture. During development or aging or under various diseases, the sleep architecture changes dramatically. The physiologic significance of the sleep architecture, however, remains unclear. Here, using unique techniques to manipulate the sleep architecture, we investigate by what mechanisms the sleep architecture changes during aging or disease and what effects it has on the individual’s function. Eventually, we aim to develop novel techniques to extend our healthy life expectancy by targeting the sleep architecture.

Started in 2018 • • • 2nd period

AMED-CREST

Biological dysfunction related to T cell senescence, exhaustion, and rejuvenation

YOSHIMURA Akihiko
Professor, Keio University School of Medicine

Dysfunction of immune cells, especially T cell senescence and exhaustion is thought to play important roles in autoimmune diseases and cancer along with aging. It is also known that senescent T cells promote chronic inflammation and their own tumorigenesis. The mechanisms and environmental factors which induce T cell senescence and exhaustion are not fully elucidated. Aims of our research are elucidation of the mechanisms of T cell senescence and exhaustion by using genetically modified mice and new culture techniques, and the development of methods to reconvert senescent and exhausted T cells into good-quality memory T cells.

Started in 2017 • • • 1st period

PRIME

Role of cardiomyocyte turnover in the onset of age-related heart failure (*)

KIMURA Wataru
Team Leader, RIKEN Center for Biosystems Dynamics Research

Aging is one of the major risk factors for heart failure. Mechanisms underlying the progression of heart failure in the aging heart remain elusive. Our recent data suggest that oxidative stress from oxygen metabolism causes age-associated deprivation of cardiomyocyte turnover in the mammalian heart. We therefore will explore how diminished cardiomyocyte turnover contributes to the onset of age-associated heart failure, and also the possibility of oxidative stress prevention as a potential therapeutic strategy for reduction in pathological phenotype in the aging heart.

Started in 2019 • • • 3rd period

AMED-CREST

Study of the aged ribosome and reinforcing ribosome function for the extension of a healthy life

INADA Toshifumi
Professor, The Institute of Medical Science, The University of Tokyo

Abnormal protein accumulation with aging disrupts protein homeostasis and causes various cellular dysfunctions. Therefore, improving translation accuracy and suppressing abnormal protein synthesis is an effective means of inhibiting aging. In this study, we will accurately evaluate changes in ribosome function with aging and develop a method to control the quality of ribosomes. Furthermore, we aim to identify molecular targets responsible for extending the life span of mammals by enhancing ribosome function.

Started in 2017 • • • 1st period

PRIME

Identification of novel macrophage subtypes that change with age and elucidation of its regulatory mechanism (*)

SATOH Takashi
Professor, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University

Aging is associated with development of various diseases, such as cancer, metabolic syndrome, infectious diseases, and so on. "Aging of the immune system" may influence onset and exacerbations of disease. Thus, research on the relationship between immune cell changes and disease during aging may lead to elucidation of pathological conditions and discovery of disease-specific medications. In the above-mentioned "Immune aging" study, I would aim to advance research by focusing on novel macrophages subset, which affected by aging, as target cells.

Started in 2019 • • • 3rd period

AMED-CREST

Research on altered tissue functions caused by clonal expansion and remodeling of apparently normal tissues related to normal aging or exposure to chronic inflammation and other lifestyles

OGAWA Seishi
Professor, Graduate School of Medicine, Kyoto University

Clonal selection/expansion of cells carrying common cancer mutations has recently been reported in apparently normal tissues, drawing an increasing attention with its relation to cancer. We will investigate the frequency and the degree of clonal expansion in a number of tissues. Our goal is to understand how our body undergoes expansion of clones and remodeling through our life course and how it affects homeostasis and organ dysfunction in aged individuals or people who have long-standing inflammation and exposure to various lifestyle stimuli, which we believe contribute to better living and even management of various diathesis caused by ageing and other life styles.

Started in 2017 • • • 1st period

PRIME

Molecular mechanisms of longevity via activation of autophagy by gonadal signals (*)

NAKAMURA Shuhei
Professor, Department of Biochemistry, Nara Medical University

Gonads are reproductive organs that produce eggs and sperm. In addition, it has been suggested that signals emanating from gonads affect animal lifespan, although the underlying mechanisms remain unclear. Recent evidence indicates that an intracellular degradation process, autophagy is essential for the longevity conferred by gonadal signals. In this research program, I will focus and study the candidate key factor working in this signaling cascades over the entire life course and aim to understand the molecular mechanism of longevity via activation of autophagy by gonadal signals.

Started in 2019 • • • 3rd period

AMED-CREST

Investigation of the mechanisms underlying age-associated accumulation of senescent cells

MINAMINO Tohru
Professor, Juntendo University Graduate School of Medicine

Our previous studies have suggested that stimuli such as metabolic stress accelerate age-associated accumulation of senescent cells in various organs/tissues, thereby promoting pathological aging that leads to age-associated diseases. This study will investigate the molecular mechanisms underlying age-associated accumulation of senescent cells based on the following three experimental approaches: 1) investigation of how senescent cells escape immune surveillance; 2) identification and characterization of senescent cell-specific antigens (seno-antigens) and metabolites (seno-metabolites); and 3) establishment of a genetic mouse model in which expression of seno-antigens/seno-metabolites can be manipulated in a senescent cell-specific manner for further investigation of their roles.

Started in 2017 • • • 1st period

PRIME

Elucidation of the mechanism of B cell dysfunction with increasing age (*)

BABA Yoshihiro
Professor, Medical Institute of Bioregulation, Kyushu University

Immune function decreases with increasing age, which is closely related to increased risk of infectious diseases and severe disorder as well as the onset of autoimmune diseases caused by disruption of immune tolerance maintenance mechanism. Although these phenomena are well recognized, the mechanisms that support these events is remain unknown. The aim of this research is to clarify the changes of B cell differentiation and function accompanying aging. Furthermore, the molecular mechanism will be addressed to understand the causes of decreased humoral immune function and increased risk of autoimmune diseases in the aged.

Started in 2017 • • • 1st period

PRIME

Regulation of pathology of “immunological aging” from fibrosis-inducing pathogenic T cells and the development of new strategies for aging-related inflammatory diseases (*)

HIRAHARA Kiyoshi
Professor, Graduate School of Medicine, Chiba University

The immune system undergoes substantial transformations with aging, which cause dysregulated immune responses. This “immunological aging” triggers age-related inflammatory diseases such as lung fibrosis. However, the precise mechanisms of immunological aging remain unclear. We recently identified “fibrosis-inducing pathogenic T cells” that direct tissue fibrosis.
This proposal aims to elucidate the cellular and molecular mechanisms of induction, development and maintenance of “fibrosis-inducing pathogenic T cells” in aged individuals. We will determine the pathological roles of “fibrosis-inducing pathogenic T cells” in the age-related inflammatory diseases such as lung fibrosis. This study will define a novel strategy for the treatment, prevention, and diagnosis of age-related inflammatory diseases.

Started in 2017 • • • 1st period

PRIME

Genetic and non-genetic mechanisms of aging in Drosophila (*)

YOO Sa Kan
Chief Scientist, RIKEN

The overall goal of the proposed research is to achieve a better understanding of both genetic and non-genetic mechanisms that regulate the aging processes in whole animals using Drosophila. For this purpose, we combine the three following distinct but potentially complementary projects to achieve integrated understanding of aging: 1) Aging in intestinal stem cells, 2) Developmental origin of aging, and 3) Unbiased hunt for longevity genes.

Started in 2017 • • • 1st period

PRIME

Elucidation of individual functional deterioration provoked by secular changes of tissue macrophage (*)

FUJIU Katsuhito
Associate Professor, Graduate School of Medicine, The University of Tokyo

This research aimed to clarify the fundamental function of tissue macrophages in multiple organs. I reported that cardiac tissue macrophages are required for cardiac homeostasis, and the lack of a cardiac macrophage results in heart failure and cardiac death. Therefore, I hypothesized that a tissue macrophage is generally required for both the maintenance and development of the entire body.
In this proposal, I will identify how macrophages control the fundamental functions of multiple organs via cell-cell interaction and find therapeutic targets that will block aging. Finally, I will develop a new macrophage evaluation system to recognize their dynamism using key epigenetic changes and newly-developed cell analyzers via deep learning strategies.

Started in 2017 • • • 1st period

PRIME

Molecular analysis for circadian clock aging causing physiological dysfunction (*)

YOSHITANE Hikari
Project Leader, Tokyo Metropolitan Institute of Medical Science

Among the increasing lifestyle-related disease in modern society, shift work and jet lags perturb the circadian clock and cause various diseases such as insomnia, carcinogenesis, hypertension, and metabolic abnormalities. Here, I define the aging-dependent abnormality of circadian clock as "clock aging", and clarify the hypothesis that abnormality of circadian output accompanying clock aging is a big factor for aging-dependent decline in physiological function. "Clock aging" will be described at the molecular level in this study.

Started in 2017 • • • 1st period

PRIME

Whole-body cell lineage tracing to understand the mammalian developmental and homeostatic systems (*)

YACHIE Nozomu
Associate Professor and Research Director, University of British Columbia, School of Biomedical Engineering

Except the early developmental stages, lineages for tens of trillions of cells forming mammalian individuals remain largely unclear. While it is extremely important to understand such complex mammalian developmental architectures, there is no technology that enables large-scale lineage tracing of whole cell divisions through the development of an individual from a single fertilized egg in high resolution. Harnessing CRISPR/Cas9 genome editing technologies, this project aims to develop “DNA Barclock” technology, which continuously records cell lineage information of somatically propagating cells in a synthetic DNA sequence and trace the whole-body cell lineage of mouse.

Started in 2018 • • • 2nd period

PRIME

Revealing and treating of stress-experience related body dysfunctions (*)

ABE Kentaro
Professor, Graduate School of Life Sciences, Tohoku University

The stressed experience causes a chronic and progressive decrement of the brain and body functions in various domains. Using the original methods, this study focuses on the changes of the activities of various transcription factors in the brain after chronic stress-experience. The aim of this study is to reveal the mechanism involved in the stress-related changes in the brain function and develop a novel method to modify or delay them.

Started in 2017 • • • 1st period

PRIME

Danger-associated molecular patterns (DAMPs)-mediated inflammatory responses that accelerate aging of the immune system and other biological systems (*)

YANAI Hideyuki
Associate Professor, Research Center for Advanced Science and Technology, The University of Tokyo

From the beginning of life, our bodies are exposed to various stresses. The immune system plays a central role in coping with these insults in order to maintain homeostasis throughout our life. Damage-associated molecular patterns (DAMPs) are self-derived molecules that are released by such stresses and alert the immune system to the presence of harmful stimuli. These molecules evoke inflammatory responses by activating innate immune receptors or through some other trigger. However, whether and how DAMPs function in the process of aging, particularly of the immune system itself, have been remained elusive. In this research project, I will elucidate DAMP-mediated inflammatory responses that accelerate aging of the immune system.

Started in 2018 • • • 2nd period

PRIME

Understanding the mechanism of maternal epigenetic inheritance of metabolic disorders (*)

INOUE Azusa
Team Leader, RIKEN Center for Integrative Medical Sciences

Given the rapid increase of the obesity population in the world, how metabolic syndromes can be intergenerationally inherited to offspring is an important question to be solved. It has recently been suggested that gametes partly mediate its inheritance, and the sperm-mediated paternal inheritance mechanisms have been intensely studied. However, the oocyte-mediated maternal inheritance mechanisms are totally unknown. In our study, we will tackle the mechanisms of maternal intergenerational inheritance of metabolic disorders by using our original mouse model, developmental engineering technologies, and low-input epigenome analysis technologies.

Started in 2018 • • • 2nd period

PRIME

Roles of mitophagy in prevention of hypofunction in whole body (*)

KANKI Tomotake

Professor, Graduate School of Medical and Dental Sciences, Niigata University

It has been proposed that mitochondrial dysfunction causes individual functional impairment during aging. Studies on mammalian cells have revealed that mitophagy, a process that selectively degrades damaged mitochondria through autophagy, contributes to the maintenance of mitochondrial function. However, it remains unclear whether mitophagy plays a role in maintaining mitochondrial function over the entire life course. In this study, we attempt to demonstrate that mitophagy prevents mitochondrial dysfunction at the individual level during aging. Furthermore, we aim to establish methodology to enhance mitophagy activity for the prevention and cure of age-related diseases.

Started in 2018 • • • 2nd period

PRIME

Study of the mechanistic contribution of defects in amino acid-response systems to aging (*)

FUKUYAMA Masamitsu

Lecturer, Graduate School of Pharmaceutical Sciences, The University of Tokyo

Human body can adapt to changes in the nutrient content of diets to maintain homeostasis. Recent studies have suggested that derangement of this ability contributes to aging. This project aims to elucidate the genetic mechanism that enables to sense dietary amino acids at the organismal level, and to assess the effects of its genetic manipulation on development and aging. These studies will help to better understand the relationship between age-related functional impairment and dietary life.

Started in 2018 • • • 2nd period

PRIME

Elucidation of mechanisms how social environment regulates the functional impairment (*)

KOTO Akiko

Senior Research Scientist, Bioproduction Research Institute, National Institute of Advanced Industrial Science and Technology (AIST)

The social interaction with others has beneficial impact in various animals. At the same time, social deprivation has negative effect for the life of social animals, however there is little information on the mechanisms, especially how the social environment affects the functional impairment in the whole life process from birth to death. With using social insects, ants, I will address how the social environment affects their functional impairment by analyzing their longevity, behavior and physiology. Furthermore, I will conduct the omics analysis to understand the mechanisms related with the social environment-dependent dysfunction in their whole life time.

Started in 2018 • • • 2nd period

PRIME

Age-associated changes in the neural plasticity gene expression profile (*)

HONJOH Sakiko

Assistant Professor, International Institute for Integrative Sleep Medicine (WPI-IIIS), University of Tsukuba

The brain stores information as memory by changing synaptic strength (neural plasticity). One highly studied form of neural plasticity is synaptic long-term potentiation, which critically depends on de novo RNA and protein synthesis. Therefore, to understand the processes underlying age-related decline in neural plasticity and cognitive ability, we will analyze neural activity-induced transcriptional programs in young and old mice. Our project aims to contribute to the development of prevention methods or diagnostic measures for age-related cognitive decline, by identifying specific genes and/or neural processes that are susceptible to aging.

Started in 2018 • • • 2nd period

PRIME

Comprehensive analysis of ageing-related decreases in mental-body functions (*)

SASAKI Takuya

Professor, Graduate School of Pharmaceutical Sciences, Tohoku University

Recent omics-based analyses have revealed a large number of gene expressions, biochemical reactions, and organ dysfunctions related to ageing. This project aims to understand when, where, and how these biological factors contribute to decline in functions associated with ageing and how changes in these factors are accumulated in time and space. The final goal is to provide a new insight of how spatiotemporal changes in individual biological factors contribute to ageing, leading to our new knowledge about how ageing can be inhibited based on accurate evidence.

Started in 2018 • • • 2nd period

PRIME

Elucidation of mechanism of decreased brain function for regulation of social behavior caused by disturbed homeostasis of gut ecosystem (*)

MIYAJIMA Michio

Project Assistant Professor, Department of Anatomy, Keio University School of Medicine

In the intestinal tract, diverse bacteria interact with intestinal cells to form a complex ecosystem, each component dynamically contributing to the homeostasis of the entire organ. This research project aims to clarify how perturbations in the balance among the immune system and among microbiota in the gut affect brain function, particularly regulating social behavior. In addition, we hope to identify metabolites with potential as biomarkers or therapeutic targets for brain dysfunction.

Started in 2018 • • • 2nd period

PRIME

Elucidating the cellular and molecular mechanisms of epithelial stem cell aging (*)

SADA Aiko

Associate professor, International Research Center for Medical Sciences (IRCMS), Kumamoto University

A classical model predicts that tissue stem cells divide less frequently to protect themselves from accumulating genetic mutations, tumorigenesis and aging. Our recent study proposed the co-existence of two distinct stem cell populations—slow-cycling and fast-dividing stem cells—in the mouse epidermis; however, it remains unknown how aging affects these stem cell populations and how it contributes to age-associated tissue dysfunction. In our study, we aim to understand the cellular and molecular basis of stem cell aging in three epithelial tissues, skin, oral and eyes, with implications for future treatments of age-related disorders.

Started in 2018 • • • 2nd period

PRIME

Understanding of molecular mechanism underlying age-related changes in hematopoiesis based on biology of long-term hematopoietic stem cell (*)

MIYANISHI Masanori

Professor, Graduate School of Medicine, Kobe University

Within the hematopoietic system, the long-term hematopoietic stem cell (LT-HSC) is the only population with capacity for true self-renewal. Throughout one's lifespan, countless cycles of blood production occur and LT-HSCs inevitably accrue age-related changes which eventually lead to a functional decline in hematopoiesis. However, due in part to the rarity of LT-HSCs, the biological impact of such changes on this population and their downstream effects remain largely unknown. In this research project, using a novel LT-HSC monitoring system, we aim to elucidate the molecular mechanisms and biological changes that arise with aging in hematopoiesis.

Started in 2019 • • • 3rd period

PRIME

Comprehensive identification of enhancers in developmental and aging process of in vivo neurons (*)

KISHI Yusuke
Associate Professor, Institute for Quantitative Biosciences, The University of Tokyo

Most of neurons, essential cell type for our brain function, are generated from neural stem cells during developmental stage. During the process of neuronal maturation, they acquire neuronal plasticity for responding to external stimuli and to rewire the neuronal network. However, their neuronal plasticity declines with age and this underlying mechanism is still largely unknown. In the proposed study, we aim to elucidate the basis of neuronal plasticity by comprehensive sequencing analyses, focusing on the genetic and epigenetic changes in enhancer regions that govern the transcription of responsive genes for external stimuli.

Started in 2019 • • • 3rd period

PRIME

Investigating mechanisms of rejuvenation in basal metazoans and their potential applications (*)

NAKAJIMA Yuichiro
Lecturer, Graduate School of Pharmaceutical Sciences, The University of Tokyo

Most higher animals including humans exhibit hallmarks of senescence during ageing and experience a progressive decline of organ physiology, which lead to a limited lifespan. By contrast, some simple animals, or basal metazoans, can maintain long-term physiological functions without showing senescence and can be immortal. In this study, we aim to understand mechanisms controlling long-term healthy functions and longevity in basal metazoans, using hydrozoan jellyfish Cladonema. We further aim to improve organ functions in aged-individuals of the more complex animals by applying the knowledge obtained from basal metazoans.

Started in 2019 • • • 3rd period

PRIME

Study of age-dependent mechanosensory response decline by whole life-course, whole brain imaging technology (*)

SUGI Takuma
Associate Professor, Graduate School of Integrated Sciences for Life, Hiroshima University

Aging causes the decline of sensory response ability. Understanding its underlying mechanisms requires systems biology approach, in which stimulus parameters are controlled and neural network responses are quantified throughout life-course. Here, I aim to develop a whole life-course, whole brain imaging technology to understand a mechanism underlying the age-dependent decline of mechanosensory response. I will describe a model by clarifying transfer functions and dynamical systems. The age-dependent declines of all the sensory modalities, such as temperature sensation, are critical risk factors in clinical medicines. This study will be the first step for establishing a new research field 'sensory aging'.

Started in 2019 • • • 3rd period

PRIME

Effect of aging on time-restricted feeding in common marmoset, a non-human primate (*)

HATORI Megumi
Associate Professor, Institute of Transformative Bio-Molecules, Nagoya University

Almost all organisms on the earth show the daily behavioral and physiological rhythms, such as sleep and awake cycles, feeding behaviors, etc. These rhythms are controlled by the internal body clocks called "circadian clocks". The dysregulation of the circadian clock in the modern world is considered to be one of the causative agents of a large number of human pathologies, including cancer and diabetes. By giving mice food access only at the certain time period of a day (time-restricted feeding), their circadian and metabolic rhythms are improved, and they are protected against obesity and associated diseases. In this proposal, I aim to understand the effects of time-restricted feeding on whole body metabolism.

Started in 2019 • • • 3rd period

PRIME

Clarification of the heterogeneity of cellular senescence in functional impairment (*)

TAKAHASHI Akiko
Chief, Cellular Senescence, Cancer Institute, Japanese Foundation for Cancer Research

Cellular senescence is the state of essentially irreversible cell cycle arrest that can be induced by various stressors. Recent studies have reported that senescent cells accumulate during the aging process in vivo and secrete many inflammatory factors. This phenotype, termed the Senescence-Associated Secretory Phenotype (SASP), contributes to numerous age-related pathologies. However, there is the phenotypic and functional heterogeneity among senescent cells in vivo. The research goal of my proposal is to innovate the quantitative analysis technology for evaluation of cellular senescence and reveal the heterogeneity of cellular senescence to understand age-associated functional impairment.

Started in 2019 • • • 3rd period

PRIME

Understanding the mechanism of individual's functional impairment mediated by age–associated changes in osteocyte–derived osteokines (*)

HAYASHI Mikihito
Associate Professor, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University

Our society is becoming increasingly sedentary, thereby exacerbating and accelerating the effects of aging. Bone is an organ actively engaged in maintaining individual's function in response to external stimuli. The hormones and cytokines involved in this process are called as "osteokine". However, it has not been possible to analyze osteocyte–specific proteome in vivo. In our study, we aim to establish method to identify and visualize osteocyte–derived osteokines spatiotemporally. The overall goal is to understand the mechanisms underlying osteokine signals to communicate and regulate the whole body system.

Started in 2019 • • • 3rd period

PRIME

Mechanism of memory impairment through age-related metabolic change (*)

TONOKI Ayako
Associate Professor, Graduate School of Pharmaceutical Sciences, Chiba University

Learning and memory decline with aging. In recent years, it has been suggested that metabolic changes associated with aging, diabetes, and obesity are one of the causes of memory impairment, however the detailed mechanism has not been understood yet. In this research, we will focus on the relationship between the brain and other organs and aim at the elucidation of the memory impairment mechanism through age-related metabolic change and the identification of the diet habits that control it, using Drosophila model that can easily evaluate age-related memory impairment and metabolic changes in a short period of time.

Started in 2019 • • • 3rd period

PRIME

ndividual's functional impairment and age-related disorders in organs by cytosolic dsDNA of mitochondrial origin (*)

MATSUI Hideaki
Professor, Brain Research Institute, Niigata University

Mitochondrial DNA can exert high toxicity when it resides in the cytosol. However, there have been little studies about such ectopic mitochondrial DNA, and the DNA sensor, downstream responses and related disorders are still not clear. We try to identify the sensor(s) of cytosolic dsDNA of mitochondrial origin, and will analyze age-related disorders in multiple organs caused by cytosolic dsDNA of mitochondrial origin.

Started in 2019 • • • 3rd period

PRIME

Elucidation of lifespan extension mechanism by S-adenosyl-L-methionine metabolism (*)

MIZUNUMA Masaki

Professor, Graduate School of Integrated Sciences for Life, Hiroshima University

Several metabolic alterations mediated by environmental factors bring about a reduction in biological fitness such as aging. In this study, we are focusing on the effect of S-adenosyl-L-methionine (SAM, methionine metabolite) on healthy aging over the entire life course. In particular, aging research focusing on yeast and nematodes has greatly advanced our understanding of the conserved mechanism of lifespan. The aim of this research is to propose a novel intervention against aging using yeast and C. elegans. Our research would not only lead the way to preventing diseases associated with aging and lifestyle, but could discover the mechanisms for extended lifespan.

Started in 2019 • • • 3rd period

PRIME

Study of age-related formation of super-enhancers and 3D genome dynamics in adaptive lymphocyte development throughout the whole life (*)

MIYAZAKI Masaki

Associate Professor, Institute for Frontier Life and Medical Sciences, Kyoto University

Among biological systems comprised with age is the decline of immune response, called immune senescence. One of the reasons for immune senescence is a decreased supply of naïve T and B lymphocytes, which results from the less growth of T- and B-precursors with age. In order to clarify the molecular mechanisms of the cell intrinsic programs throughout the whole life, we will investigate the age-related formation of Super-Enhancers and the 3D genome structures in those SE regions using T- and B-precursors from various aged mouse.

(*) indicates completed R&D projects.