Advanced Research and Development Programs for Medical Innovation

2024 ▶ 2025

AMED-CREST　PRIME　LEAP　FORCE

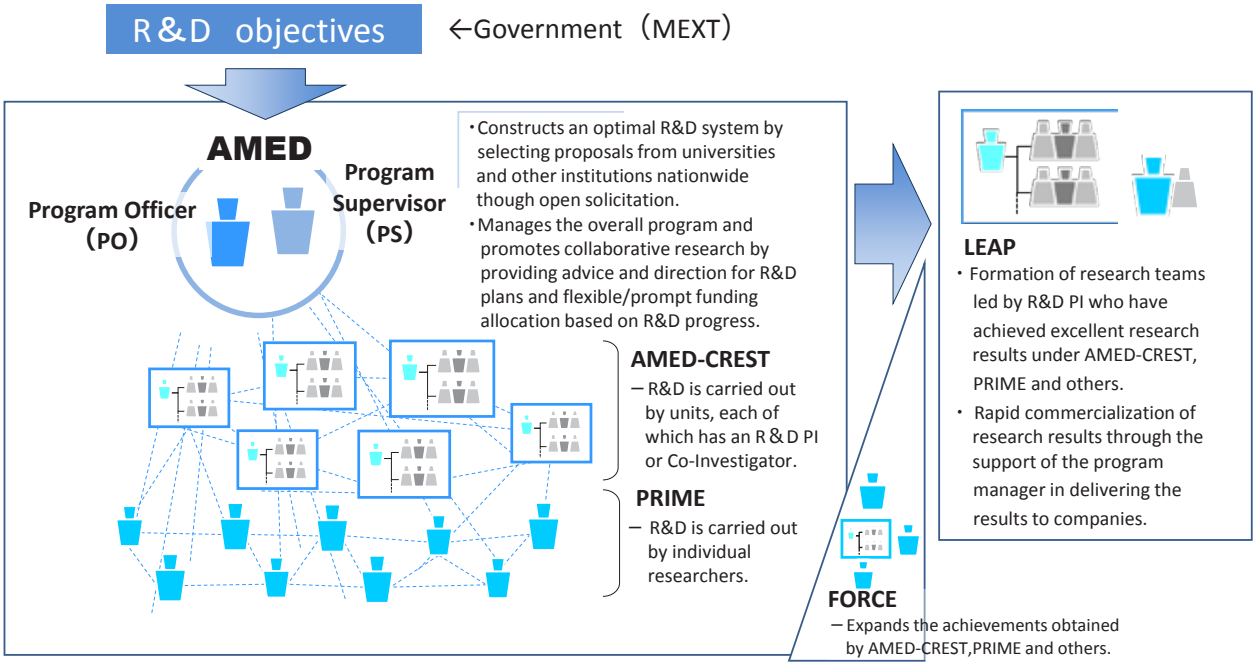
AMED
Japan Agency for Medical Research and Development

Contents

Advanced Research and Development Programs for Medical Innovation

Research and Development Objectives

With the goal of developing innovative drugs, medical devices, and medical technologies under the R&D objectives determined by the government, researchers in universities and other institutions are invited to submit R&D proposals upon which a limited-time R&D system transcending organizational frameworks for driving R&D activities are to be constructed. The program promotes advanced R&D for generating and nurturing breakthrough technologies, while also accelerating and deepening R&D that yields promising results.
The Advanced Research and Development Programs for Medical Innovation comprises four types of research: unit-type (AMED-CREST), solo-type (PRIME), step-type (FORCE) and incubation-type (LEAP).



MEXT: Ministry of Education, Culture, Sports, Science and Technology

Features of Each Research and Development Type

▬ AMED-CREST, PRIME

AMED-CREST program focuses on achieving worldclass R&D results aimed at generating innovative seeds, with the respective R&D being conducted by a unit (a group of researchers) that is led by a R&D Principal Investigator (PI). PRIME program aims to generate R&D results that will spawn innovative seeds, with the R&D being independently conducted by the individual R&D PI. In AMED-CREST and PRIME, AMED specifies the R&D pursuit areas and the Program Supervisors (PS) and Program Officers (PO) for leading the research under “Research and Development Objectives” designated by the national government.

▬ FORCE

FORCE program promotes prospective R&Ds which can lead to large developments, among research accomplishments obtained from terminated AMED-CREST and PRIME R&D projects. FORCE program aims to verify correlations between their achievements and target diseases and to validate generated analytical methods, devices, and instruments, by using human clinical samples.

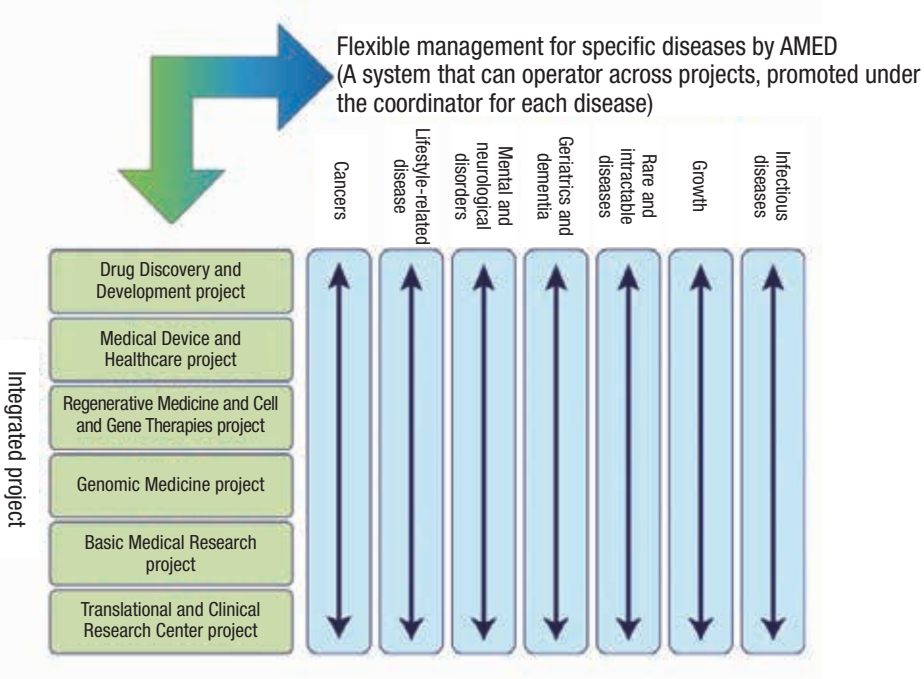
▬ LEAP

LEAP program aims to accelerate development of exceptional R&D results generated through AMED-CREST and PRIME projects implemented under the Advanced Research and Development Programs for Medical Innovation, passing on this follow of R&D to companies and venture businesses. In concrete terms, the technical feasibility of world-leading exceptional R&D results are proven and presented, and rights to these R&D results are appropriately acquired, through the innovation-orientated R&D management of the Program Manager (PM).

Six “Integrated Projects” organized and managed by AMED

This project supports basic research and international joint research to create and develop bases combining different fields, modalities and innovative seeds for creation of new modalities. It also promotes development of systems to discover/transfer seeds and conduct high-quality clinical research & trials, establishment of a base of reverse translational research & empirical research in translational research among support centers and core clinical research hospitals. With the aim of providing innovative drugs, medical devices, technologies and so on, this project promotes cutting-edge R&D, which utilizes temporary research systems beyond organizational boundaries, to create, foster, and develop the seeds of future innovation. It also advances research for the purpose of furthering promising results.

AMED promotes R&D of the six “Integrated Projects” which the 2nd Healthcare Policy and medium- to long-term plan specifies.



※ Information for October 1, 2024

Program Director

KANEDA Yasufumi, M.D., Ph.D.

Vice President, Osaka University
Executive Vice President,
National University
Corporation Osaka University

Throughout the 1st Medium- to Long-Term plan since AMED's inception in 2015, the division of Innovative Research and Development (former name: division of Emerging Research) has promoted the program for the purpose of creating and fostering the seeds of further practical application under the policy goals determined by MEXT (the Ministry of Education, Culture, Sports, Science and Technology). This has resulted in numerous positive outcomes becoming a reality. Some promising results also have been expanded into both the business of private enterprises and other programs of AMED itself. In the 2nd Medium- to Long-Term Plan, we will establish six "Integrated Projects" centered on modalities and the project of related ministries and agencies will be coordinated under the Program Director (PD). Accordingly, the projects will be centrally promoted from basic to practical application. The advanced Research and Development Programs for Medical Innovation, as one of the component elements of the Project for Seeds Development and Research Base, will not only continue to provide valuable global basic research results, but will also establish the foundation for discovering the future research programs successively and cultivate the next generation of researchers. It will achieve this by further promoting both interface between basic R&D and practical clinical use, and an alliance between two programs utilizing the expanded and strengthen function of Translational & Clinical Research Core Centers. In the pursuit of these objectives, our collaboration with the other 5 integrated projects will be driven and we will plant the seeds of global-valued medical results from innovative research and they will develop into international collaborative research, translation of novel technologies, international clinical trials, and so on.

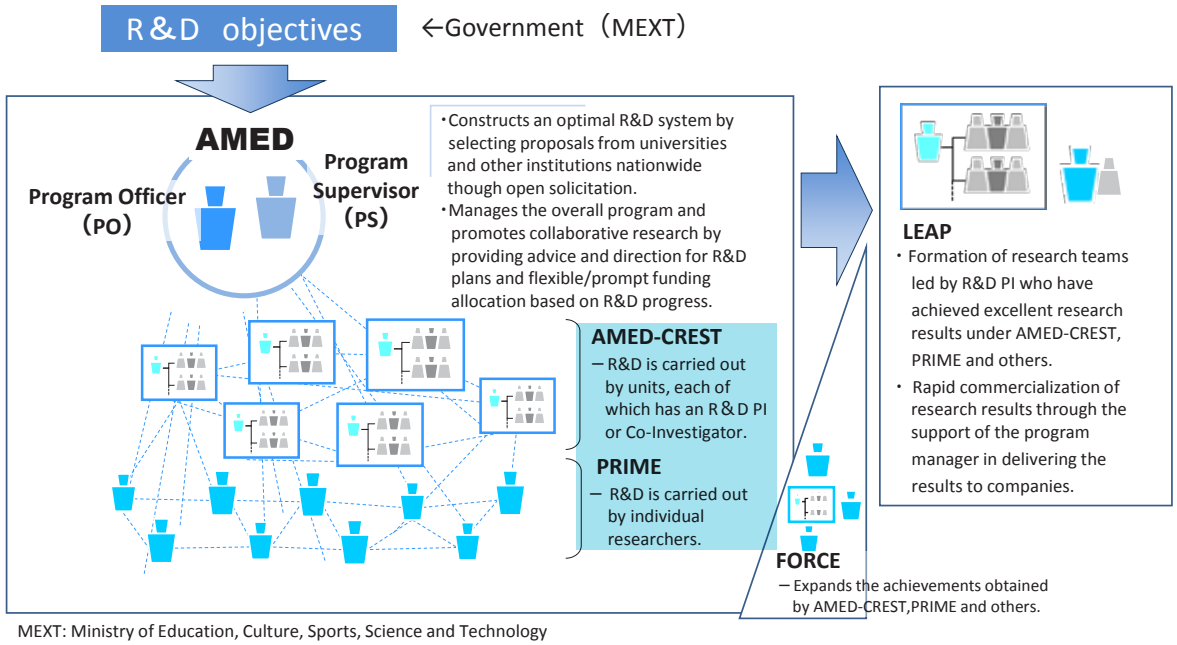
Profile

1984	Finished Doctor's Course at the Graduate School of Medicine, Osaka University Doctor of Medicine, Osaka University Assistant Professor, Institute for Molecular and Cellular Biology, Osaka University
1988	MEXT Overseas Postdoctoral Fellow (through Sep. 1990)
1992	Associate Professor, Institute for Molecular and Cellular Biology, Osaka University
1998	Professor, Faculty of Medicine, Osaka University
1999	Professor, Graduate School of Medicine, Osaka University
2013	Dean, Faculty/Graduate School of Medicine, Osaka University (through Mar. 2015) Member of Administrative Council, Osaka University (through Mar. 2015)
2017	Dean, Faculty/Graduate School of Medicine, Osaka University Executive Advisor to the President, Osaka University
2019	Vice President, Osaka University (through Aug. 2019) Senior Executive Vice President, Osaka University (from Aug. 2019 through to present)

AMED-CREST, PRIME

Program Outline

- AMED Core Research for Evolutionary medical Science and Technology (AMED-CREST) focuses on achieving world-class R&D results aimed at generating innovative seeds, with the respective R&D being conducted by a unit (a group of researchers) that is led by a R&D Principal Investigator (PI).
- Precursory Research for Innovative Medical care (PRIME) aims to generate R&D results that will spawn innovative seeds, with the R&D being independently conducted by the individual R&D PI.
- In AMED-CREST and PRIME, AMED specifies the R&D pursuit areas and the Program Supervisors (PS) and Program Officers (PO) for leading the research under "Research and Development Objectives" designated by the national government. Working together with the PO, the PS manages R&D programs by approving and revising R&D plans and overseeing R&D projects. Furthermore, this program establishes a R&D organization beyond each research institution and aims to optimally exploit R&D, through management by the PS and PO, and cooperation in each R&D Area.



MEXT: Ministry of Education, Culture, Sports, Science and Technology

R&D Period and R&D Costs

Program	R&D Period	Total R&D Costs (direct cost)
AMED-CREST	Up to 5.5 years	150 ~ 500 million yen / project
PRIME	Up to 3.5 years	30 ~ 40 million yen / project

Research and Development Areas (AMED-CREST, PRIME)

Keyword	R&D Area		
Individual Differences	Understanding the mechanisms of sex and individual differences and advancing prediction technology	CREST	PRIME
Stress	Elucidation of mechanisms for stress responses to disease development	CREST	PRIME
Aging	Bridging the fundamental mechanism of aging and the effective treatment of age-related disease associated with impaired functional system	CREST	PRIME
Immunological Memory	Immunological memory: Understanding, regulation and medical innovation	CREST	
MultiSensing	Integrated understanding of multi-sensing networks and elucidation of their control mechanisms leading to the innovation of medical technologies	CREST	PRIME
Anti-infectives	Generating research infrastructure and novel technologies for anti-infective drug and vaccine discovery	CREST	
Proteostasis	Understanding proteostasis and discovering innovative medical applications	CREST	PRIME
Early Life Stage	Understanding of the biological phenomena and responses at the early life stages to improve the quality of health and medical care	CREST	PRIME
Tissue Adaptation and Repair	Understanding of pathophysiological processes and discovery of medical technology seeds through spatiotemporal research of tissue adaptation and repair mechanisms	CREST	PRIME
Functional Impairment	Clarification of the mechanisms of individual's functional impairment over the entire life course	CREST	PRIME

Completed R&D Areas

Keyword	R&D Area		
Microbiome	Understanding the interactions and symbiosis between the microbiome and the host organism, leading to an understanding of the mechanisms of disease onset	CREST	PRIME
Mechanobiology	Elucidation of mechanobiological mechanisms and their application to the development of innovative medical instruments and technologies	CREST	PRIME
Lipid Molecules	Studies on specific activities and functions of lipid molecules to develop innovative medical technologies	CREST	PRIME
Disease-Related Metabolites	Creation of innovative technology for medical applications based on the global analyses and regulation of disease-related metabolites	CREST	
Homeostasis	Innovation for ideal medical treatment based on the understanding of maintenance, change and breakdown mechanisms of homeostasis among interacting organ systems	CREST	
Epigenomics	Development of fundamental technologies for diagnosis and therapy based upon epigenome analysis	CREST	
Chronic Inflammation	Creation of basic medical technologies to clarify and control the mechanisms underlying chronic inflammation	CREST	
Brain Neural Network	Elucidation of the principles of formation and function of the brain neural network and creation of control technologies	CREST	
iPS	Fundamental technologies for medicine concerning the generation and regulation of induced pluripotent stem (iPS) cells	CREST	
Immune Systems	Etiological basics of and techniques for treatment of allergic and autoimmune diseases	CREST	

R&D Period (FY)

P S / P O	Year Started	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	Page
PS: OKADA Mariko PO: ITO Takashi	2024																	9
PS: ISO Hiroyasu PO: ICHIJO Hidenori PO: SEKITANI Tsuyoshi	2023																	13
PS: MOCHIZUKI Naoki PO: FUKAMIZU Akiyoshi PO: YASUTOMO Koji	2022																	19
PS: TAKEDA Kiyoshi PO: KIYONO Hiroshi	2022																	27
PS: NAGAI Ryozo PO: TAKEUCHI Shoji PO: NISHIDA Kohji	2021																	31
PS: DOI Yohei PO: MATSUURA Yoshiharu	2021																	39
PS: NAGATA Kazuhiro PO: ENDO Tamao	2020																	43
PS: SASAKI Hiroyuki PO: TAKEDA Hiroyuki	2019																	51
PS: YOSHIMURA Akihiko PO: YOKOMIZO Takehiko	2018																	59
PS: NISHIDA Eisuke PO: HARA Eiji	2017																	67

	R&D Period (FY)	Page
	2016 ～ 2023	80
	2015 ～ 2022	82
	2015 ～ 2022	84
	2013 ～ 2019	86
	2012 ～ 2019	87
	2011 ～ 2018	88
	2010 ～ 2017	89
	2009 ～ 2016	90
	2008 ～ 2015	91
	2008 ～ 2015	91

Individual Differences

Understanding the mechanisms of sex and individual differences and advancing prediction technology

Research and Development Objectives

Towards elucidating and predicting sex and individual differences and intrapersonal changes — A departure from the conventional practice of medical care based on patient averages

Program Supervisor (PS)

OKADA Mariko

Professor, Institute for Protein Research, Osaka University

Program Officer (PO)

ITO Takashi

Professor, Kyushu University Graduate School of Medical Sciences

The manifestations of various symptoms of our diseases and health conditions vary not only between the sexes and between individuals, but also even within the same person at different stages of life. Significant individual differences are also sometimes observed in the effects and side effects of medicines and other drugs. Following the experience of the new coronavirus infection (COVID-19), the public interest in sex and individual differences has urgently increased. However, current medical and health research is mainly based on population averages, and the medical care that many people receive is not always optimized for the individual. The first step approaching to the issues is to understand the mechanisms of gender and individual differences in specific symptoms, diseases, and health conditions at the molecular level. Based on this information, new treatment and prevention methods need to be developed that are optimized for the individual, such as precise stratification for specific diseases and the development of predictive models at the individual level.
In this research and development area, basic and clinical medical researchers, experimental biologists, epidemiologists, computer scientists and mathematicians, as well as measurement and information technology researchers, will work closely together, combining latest knowledge and technologies from different fields to integrate and analyze multi-level data at the molecular, cellular, tissue, organ, individual and population levels.
The project aims to elucidate the mechanisms by which individual and sex differences in health and disease, as well as changes within the same individual, are generated, and to develop optimal treatment and prevention technologies for individuals by constructing accurate stratification of pathological states and predictive models at the individual level.

Advisor

ARAKAWA Kazuharu
Professor, Graduate School of Media and Governance, Keio University

UENO Hideki
Professor, Graduate School of Medicine, Kyoto University

KAMADA Mayumi
Professor, Kitasato University School of Frontier Engineering

KINOSHITA Kengo
Professor, Graduate School of Information Sciences, Tohoku University

SUSAKI A. Etsuo
Professor, Juntendo University Graduate School of Medicine

SESE Jun
CEO of Humanome Lab., Inc.

TAKAHASHI Yoriko
General Manager, Bioscience & Healthcare Engineering Division, Mitsui Knowledge Industry Co., Ltd.

NOMURA Seitaro
Specially Appointed Associate Professor, The University of Tokyo Hospital

FUJIO Keishi
Professor, Graduate School of Medicine, The University of Tokyo

AMED-CREST Started in 2024 — 1st period

Understanding the molecular basis governing individual differences of health-span and developing aging-prediction technology

ISHITANI Tohru
Professor, Research Institute for Microbial Diseases, Osaka University

There are individual and sex differences in lifespan and healthspan, making it difficult to measure the degree of aging or remaining lifespan based on age alone. In this study, we aim to understand the molecular mechanisms underlying individual and sex differences in lifespan and healthspan and to create aging prediction technology by conducting data-driven research that complements humans and ultra-rapid aging animals. In addition, by discovering quantitative aging markers and anti-aging molecules, we aim to create personalized medical technology seeds that can detect signs of aging in individual humans and extend healthspan.

Elucidation and control of the cellular microenvironment that produces sex and individual differences through deep learning

SHIMAMURA Teppei
Professor, Medical Research Laboratory, Institute of Integrated Research, Institute of Science Tokyo

This research develops an analytical platform using deep learning and next-generation small molecule inhibition technologies to analyze multi-scale, multi-modal data related to sex and individual differences. By elucidating differences in cellular states and microenvironments, their determinants, and possibilities for personalized therapies, we aim to accelerate disease research discovery and verification. We will validate the platform using osteoarthritis and intractable gastrointestinal cancers as targets, aiming to develop new treatments and prognosis prediction models that consider sex and individual differences, ultimately contributing to the realization of personalized medicine.

Multi-omics analysis for elucidating the difference between maternal and paternal genetic traits and its application to the prediction of obesity and diabetes

SUZUKI Yutaka
Professor, Graduate School of Frontier Sciences, The University of Tokyo

We aim to gain a deep understanding of the molecular mechanisms underlying sex differences, individual differences, and intra-individual changes, which will serve as the basis for future medical applications and prediction of unaffected diseases.
We will make full use of biological samples and genome data accumulated at BioBank Japan and Tohoku Medical Megabank Organization, the most representative biobanks in Japan.
We will conduct an intensive and precise multi-omics analysis of umbilical cord blood as an example of tissue in which newborns begin to express their own genes for the first time, we will attempt to elucidate the diversity of sex differences in genetic traits.

Development of predictive models and novel therapies based on sex and individual differences for cardiovascular disease

MIYAGAWA Shigeru
Professor, Graduate School of Medicine, Osaka University

Cardiovascular disease is one of the leading causes of death in Japan, with its progression being profoundly affected by sex and individual variability. Our objective is to develop predictive models for cardiovascular diseases, mainly heart failure and aortic aneurysm, through the integration of multi-omics analysis of tissue and blood samples, lifestyle data, clinical data, and the latest artificial intelligence technology, as well as a data distribution platform capable of distributed federated learning. We also aspire to develop novel therapeutic strategies by elucidating the underlying pathological mechanisms through comprehensive omics analysis.

Integrated understanding of sex-dependent biomodulation mechanisms associated with the interaction of circadian and seasonal rhythms and application to prediction technology

YASUO Shinobu
Professor, Faculty of Agriculture, Kyushu University

Mood and physical conditions in humans are regulated by interactions between circadian rhythms, seasonal rhythms, and menstrual rhythms in menstruating women. However, the interactions among multi-scale rhythms still need to be clarified. A series of our studies, a collaborative effort between experimental and mathematical researchers, aims to elucidate the interaction mechanisms underlying sex-dependent multi-scale rhythms and search for biomarkers to evaluate the interactions. Our goal is to develop a technology that can predict multi-scale-rhythm-associated symptoms such as winter depression and premenstrual syndrome.

PRIME Started in 2024 — 1st period

The realization of preemptive medicine through the elucidation of cardiovascular complex disease systems driven by the integration of static and dynamic omics

ITO Kaoru
Team Leader, RIKEN Center for Integrative Medical Sciences

Cardiovascular complex diseases are complicated conditions that arise from intricate interactions between genetic and environmental factors, with significant influences from individual and sex differences. In this research project, we will integrate dynamic omics data with pioneering artificial intelligence, alongside genomic and clinical information, to achieve a comprehensive understanding of these individual and sex differences in disease. Simultaneously, we will establish and validate methods for stratifying disease risk in individuals who have not yet developed the disease. Ultimately, our goal is to build and implement a precision medicine system that proposes preventive measures tailored to various stages, from health to pre-disease and disease onset.

Single nucleotide resolution analysis and prediction of gene regulatory elements by saturation mutagenesis MPRA

INOUE Fumitaka
Associate Professor, WPI-ASHBi, Kyoto University

Genetic factors responsible for diseases, individual differences, and evolution are more likely to be found in gene regulatory elements in the non-coding genome, rather than in coding regions. In this project, we utilize the Massively Parallel Reporter Assay (MPRA), which enables us to characterize enhancer functions in a high-throughput manner and at single-nucleotide resolution, to predict the effects of single nucleotide variants on gene regulation. Through this approach, we aim to understand the molecular mechanisms underlying diseases and individual differences.

Space-time proteomics with single-cell resolution enabled by next-generation proteome sequencer

KANAO Eisuke
Assistant Professor, Graduate School of Pharmaceutical Sciences, Kyoto University

This research aims to completely renovate bottom-up proteomics technologies from the perspective of separation science and materials chemistry, developing a "next-generation" proteome sequencer. Furthermore, this technology will be applied for time-lapse analysis of single cells and spatial proteomics. Based on these technologies, we will capture the proteome changes during early development with unprecedented resolution as the first step toward understanding the mechanisms of sex and individual differences.

Investigating individual differences by human population-scale cell culture and time-series multi-omics

KOJIMA Shohei
Special Postdoctoral Researcher, RIKEN Center for Integrative Medical Sciences

I will employ a miniaturized human population cell culture system to conduct time-series multi-omics analyses and statistical genetics. This approach aims to unravel the complex human genetics and biology underlying the emergence of human phenotypic differences that cannot be understood by snapshot research. This work will bridge the gap between real-world studies in biobanks and laboratory-based mechanistic research, and generate basic research data that forms the foundation for improved disease prediction and precision medicine.

Study for individual differences of A-to-I RNA editing

SAKURAI Masayuki
Associate Professor, Research Institute for Biomedical Sciences,Tokyo University of Science

A-to-I RNA editing has the same effect as base substitution or mutation from A to G, but is a change in genetic information that is not described in the genomic information. It is highly possible that unexplained individual and sex differences may result from differences in editing, which in turn may include differences that affect cancer incidence, disease incidence, life span, and health. This project aims to clarify this, to accumulate information on A-to-I RNA editing sites, and to construct an editome database.

Study of development of prediction platforms for progression of lung cancers based on differential omics backgrounds among sex and individual differences

SUZUKI Ayako
Associate Professor, Graduate School of Frontier Sciences, The University of Tokyo

This study aims to develop a predictive platform of lung cancer progression by integrating spatial omics techniques, human lung organoids and gene expression network analytical methods. We will measure the omics background of cells that reflect individual differences, as well as their responses to endogenous and exogenous stress stimuli. We will analyze detailed information of aberrant differentiation statuses of lung cancer cells at omics levels and utilize it for prediction of lung cancer progression.

Development of functional connectivity analysis method using deep learning and estimation of individual traits and neuropsychiatric disorders

CHIKAZOE Junichi
Team Leader, Araya Inc., R & D Department

This research aims to establish new analytical methods for resting-state fMRI data to develop objective indicators for diagnosing mental disorders. We will use multilayer perceptrons and Transformer models to examine functional connections between brain regions and construct individual characteristic estimation models. Additionally, we will create diagnostic algorithms for neuropsychiatric disorders using data from the AMED Brain/MINDS Beyond project. We particularly focus on methods for utilizing deep learning in biological data with limited sample sizes.

Mechanisms underlying heart failure pathogenesis through the lens of inter-individual variability of hematopoietic clonal divergence

NAKAYAMA Yukiteru
Assistant Professor, the University of Tokyo

Persistent inflammation following the immune response against external cardiac stress underlies incident heart failure. We have recently reported that heart failure induces the phenotypic modulation of hematopoietic stem cells, immmature cells that all types of blood cells originate from. We hypothesize that individual differences of immune response at the level of hemaotopoietic stem cells would determine inter-individual variability in risks of incident heart failure. We will analyze the differences in bone marrow niches as well.

Understanding the impact of differential sex chromosome states on cellular phenotypes

YOKOBAYASHI Shihori
RIKEN ECL Team Leader, RIKEN Center for Integrative Medical Sciences

The sex chromosome composition in the human genome is typically the XX type in females and the XY type in males, and one X chromosome in females is epigenetically silenced to compensate for the differences in gene dosage. In this study, I aim to understand sex differences at a cellular level by elucidating the impact of sex chromosome composition or conversion/instability in the X-chromosome epigenome status on cellular phenotypes and functions.

Precision stratified treatment based on individual differences due to retrotransposon-based insertion polymorphisms

YOSHIMI Akihide
Chief, Division of Cancer RNA Research, National Cancer Center Research Institute

Transpossable elements (TEs), also known as jumping genes, are known to make up about 46% of the human genome. In this project, we aim to investigate the impact of individual differences due to TE insertion polymorphisms on treatment outcomes and prognosis of cancer patients, and to refine prognosis and treatment response prediction systems by identifying new biomarkers. Additionally, by elucidating the mechanisms of expression, we aim to develop treatment methods and propose stratified treatments based on individual differences in TE insertion polymorphisms.

Stress

Elucidation of mechanisms for stress responses to disease development

Research and Development Objectives

Elucidation of stress responses and pathogenic mechanisms

Under “Stress” R&D area, the goal is to scientifically elucidate the biological responses at various different levels, from molecular/cellular levels to individual levels, caused by physical, chemical, biological, or emotional/psychological stress, and to develop an integrated understanding of stress responses and the mechanisms involved from the molecular/cellular level to the individual level.
We are surrounded by various different stressors, and new stressors have also emerged because of the changes in our lifestyles and social environments during the recent COVID-19 pandemic. Prevention of diseases triggered by such stressors is important to improve our QOL.
Specific goals of this R&D area include (1) elucidation of stress adaptation or avoidance systems in humans with a focus on applications in disease prevention, and elucidation of the mechanisms involved between the breakdown of these systems and disease onset; (2) identification of markers that allow objective evaluation of stress status in humans or prediction of disease onset due to stress, and elucidation of their pathophysiological significance; and (3) research and development of new techniques or methods, new measuring devices, or signal processing technologies that allow accurate, detailed, and long-term capture of human biological information that fluctuates subtly with exposure to stress.

Program Supervisor (PS)

ISO Hiroyasu

Director of Institute for Global Health Policy Research (iGHP), National Center for Global Health and Medicine

Program Officer (PO)

ICHIJO Hidenori

Distinguished University Professor, Advanced Research Initiative, Institute of Integrated Research, Institute of Science Tokyo

Program Officer (PO)

SEKITANI Tsuyoshi

Professor, SANKEN, Osaka University

Advisor

AOKI Ichio
Senior Principal Investigator, iQMS, National Institutes for Quantum Science and Technology

ASAHARA Hiroshi
Professor, Graduate School of Medical and Dental Sciences, Institute of Science Tokyo

UMEDA Satoshi
Professor, Department of Psychology, Keio University

OGAWA Koichi
Group Leader, Laboratory for Drug Discovery and Disease Research, Shionogi & Co., Ltd.

SUZUKI Tadashi
Chief Scientist, RIKEN Cluster for Pioneering Research

SUDO Nobuyuki
Professor, Graduate School of Medical Sciences, Kyushu University

NAKAYAMA Keiko
Vice President for Research Infrastructure, Institute of Science Tokyo /
Professor, Graduate School of Medicine, Tohoku University

NATSUME Tohru
Prime Senior Researcher, Cellular and Molecular Biotechnology Research Institute, National Institute of Advanced Industrial Science and Technology

HAMAZAKI Yoko
Head/Professor, Department of Life Science Frontiers, Center for iPS Cell Research and Application, Kyoto University

MORI Yasuo
Professor, Graduate School of Engineering, Kyoto University

YOSHIUCHI Kazuhiro
Professor, Department of Psychosomatic Medicine, The University Tokyo Hospital

AMED-CREST Started in 2023 · 1st period

Integrative understanding of molecular stress and individual stress for discovering new stress pathologies through innovative AI development

OKAZAWA Hitoshi
Professor, Medical Research Institute,
Institute of Integrated Research, Institute of Science Tokyo

In this research, we will use AI to comprehensively understand the relationship of big data corresponding to molecular stress, cellular stress, and individual stress, and based on this, we will reversely predict the stress state of cells and molecules from biological information. Furthermore, by incorporating the newly developed AI technology, the ultimate goal is to develop technology that can estimate the ""molecular stress state"" of human brain cells live and in real time using biological information devices such as wearable electroencephalography.

Mechanostress-induced brain DNA damage and its life-course disease risk

KENGAKU Mineko
Professor,
Institute for Advanced Study, Kyoto University

Neurons in the brain have a limited capacity for replacement and accumulate DNA damage due to high oxidative stress and transcriptional activity. Excessive DNA damage is a primary trigger of neurodegeneration and dysfunction in disease and normal ageing brains. The principal investigator has discovered massive and transient DNA damage in newborn neurons by mechanostress during normal brain development. The primary goal of this study is to identify the mechanisms of the formation and repair of the mechanostress-induced DNA damage in developing and adult neurons, and to verify the disease risk of its genetic disruption or external disturbance.

Study of mechanisms of mental stress-induced cardiovascular pathogenesis using stress response control technology

NAKAMURA Kazuhiro
Professor,
Nagoya University Graduate School of Medicine

The mechanism by which mental stress affects organ functions and causes disease is unknown. In this study, we will conduct animal experiments using the stress response control technology we developed, and elucidate the mechanism by which mental stress causes cardiovascular diseases based on the animal experimental data and human clinical data. In addition, we will explore the central neural circuits underlying the neuroscientific entity of mental stress to present central targets to mitigate stress. Through this research project, we will contribute to the development of new technologies for prevention and treatment of stress-induced cardiovascular diseases.

Integrated understanding of mental frailty from non-neuronal stress engrams and its application to diagnostic treatment

MASUDA Takahiro
Professor, Medical Institute of Bioregulation,
Kyushu University

In this study, we will reveal early life stress-induced persistent cellular/molecular alterations in non-neuronal cells and brain-periphery cellular network transformation (we define them as "stress engram"). In addition, by getting to the bottom of the stress engram, we will comprehensively understand the molecular mechanisms of mental frailty that can lead to disease development, and ultimately try to establish the functional intervention techniques for the development of diagnostic treatments in humans and create an objective index and measurement technology for evaluating susceptibility and vulnerability to stress.

Molecular mechanisms of pathogenesis of stress-induced disease and development of stress biomarker detection technology

MURAKAMI Masaaki
Professor, Institute for Genetic Medicine,
Hokkaido University

Stress induces the onset and exacerbation of various chronic inflammatory diseases. However, since sensitivity and tolerance to stress vary with individual genetic and environmental predispositions, it has been difficult to promptly identify the danger signals in the body in response to stress, and prevent diseases. In this R&D, we will (1) identify specific stress-responsive factors and cells, (2) prove their causal relationships with pathogenesis, and (3) establish a fast and high sensitive quantum measurement system for them using samples from novel disease models, and human patients and health examination cohorts.

AMED-CREST Started in 2024 · 2nd period

Exploration of life environmental stress markers in the skin and their application in stratified medicine for atopic dermatitis.

KABASHIMA Kenji
Professor,
Kyoto University Graduate School of Medicine

The skin is exposed to various environmental stressors, which can disrupt skin homeostasis and contribute to the onset or worsening of atopic dermatitis. This study aims to scientifically and comprehensively elucidate the biological responses to different environmental stressors, from the cellular level to the whole organism. By identifying specific stress markers associated with each type of stressor, we seek to classify and stratify endotypes of atopic dermatitis patients. This approach could lead to more personalized and effective treatments based on the individual stress responses in atopic dermatitis patients.

Understanding the pathogenesis of diseases and disorders resulting from metabolic/social stress by uncovering the mechanism behind the therapeutic/preventative effects of exercise-mimicking mechanical intervention

SAWADA Yasuhiro
Director, National Rehabilitation Center for
Persons with Disabilities, Hospital

Through mechanical stimulation-based interventions in animal models and molecular/cellular experiments, we aim to replicate the anti-metabolic and anti-social stress effects of exercise. This approach seeks to elucidate the mechanical factors involved in the pathophysiology and etiology of diseases caused by these stresses. Furthermore, clinical trials will be conducted to achieve proof of concept for findings obtained from animal and cellular studies, leading to the development of effective treatments and preventive strategies.

Elucidation of molecular mechanism of neurodegenerative and neuromuscular diseases pathogenesis by disruption of lysosomal stress response and development of ultra-early biomarker

NAKAMURA Shuhei
Professor,
Faculty of Medicine, Nara Medical University

In many neurodegenerative and neuromuscular diseases such as Alzheimer's disease and Parkinson's disease, dysfunction of intracellular degradation organelle, lysosome is observed from very early stage. In this study, we consider the failure of the 'lysosomal stress response', a resilience mechanism against various stresses to lysosomes, as the main cause of the lysosomal dysfunction and will elucidate its molecular mechanism and pathological significance in neurodegenerative and neuromuscular diseases. Furthermore, we aim to develop biomarkers to detect the failure of the lysosomal stress response and to realize ultra-early diagnosis of neurodegenerative and neuromuscular diseases.

Study of the early molecular pathways and drug discovery of idiopathic pulmonary fibrosis caused by lung stem cell stress.

MORIMOTO Mitsuru
Team Leader,
RIKEN Biosystems and Dynamics Research Center

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive respiratory disease of unknown cause, and various stresses into lung cells are thought to be the staring point of IPF development. We have innovated pulmonary fibrosis organoids to analyze the pathogenesis of IPF at the cellular and molecular level. Using various in vivo stress models, live-vivo imaging, human pathology sample analysis, and organoid culture systems, we will investigate the mechanism of IPF pathogenesis, identify early IPF markers, and search for drug discovery seeds.

PRIME Started in 2023 ····· 1st period

Study of regulation of metabolic stress–induced cell death and chronic inflammation in the liver and adipose tissue

INABA Yuka
Associate Professor,
Institute for Frontier Science Initiative, Kanazawa University

Metabolic stress caused by overnutrition triggers chronic inflammation in the metabolic organs, resulting in non-alcoholic steatohepatitis (NASH) and type 2 diabetes mellitus. Especially, chronic inflammation of the liver and adipose tissue interacts with each other, and plays a central role in these pathogenesis. In the development of chronic inflammation caused by metabolic stress, cell death plays an important role. This project aims to elucidate the regulatory mechanism of cell death by linking metabolic stress due to overnutrition with chronic inflammation of the liver and adipose tissue.

New genetic tools for spying on the stress-induced perturbation of hormone signaling

INO Daisuke
Lecturer,
Graduate School of Medicine Osaka University

The perturbation in hormonal levels has been proposed as a fundamental cause of the development of stress-induced disorders. Nevertheless, the direct observation of hormonal dynamics with precise spatiotemporal resolution has not been achieved. Furthermore, the causal relationship between dysregulated dynamics of stress-related hormones and disease onset remains elusive. Resolving these problems is of importance to bridge the gap between stress exposure and disease development. In this research, we aim to develop new tools to "visualize" and "manipulate" the signaling dynamics of stress-related hormones. We will also explore the application of these tools in experiments with animal models.

Molecular and circuit mechanisms responsible for behavioral changes induced by early-life stress

KAWAGUCHI Daichi
Associate Professor, Graduate School of Pharmaceutical Sciences, The University of Tokyo

Early-life stress is known to increase the risk of psychiatric disorders later in life. However, the mechanisms that explain postnatal stress vulnerability are not fully understood. In this study, we aim to identify specific cells and molecules that react to stress during development and how alterations in neural networks throughout the brain, based on these cells and molecules, can impact behavior in the long term.

Unconventional modifications of organellar membrane lipids by protein conjugation and cellular stresses

SAKAMAKI Jun-ichi
Associate Professor,
Juntendo University Graduate School of Medicine

Intracellular organelles regulate various cellular processes including signal transduction and biochemical reactions and activate quality control mechanisms in response to cellular and organellar stresses. We have discovered an unconventional modification of membrane lipids; the ubiquitin protein is covalently conjugated to phospholipids in organellar membranes. This study aims to understand the role of unconventional modifications of membrane lipids by protein conjugation in the regulation of organellar function and stress response mechanisms.

DNA damage response by the RNA spatiotemporal regulation via membrane-less organelles

SHICHINO Yuichi
Research Scientist,
RIKEN Cluster for Pioneering Research

When DNA is damaged by genotoxic stress such as ultraviolet, cells repair DNA using the response pathways. Dysregulation of this system led to diseases including cancer. In this study, I will investigate the relationship between the regulation of gene expression required for DNA damage responses and the spatiotemporal regulation of mRNAs via membrane-less organelles called Processing bodies (P-bodies) and elucidate the detailed molecular mechanism and its importance in DNA damage sensitivity of cancer cells.

Elucidation of novel mechanism of cellular stress response by the identification of components of stress-responsive liquid-droplets

TAKAHASHI Hidehisa
Professor, Yokohama City University
Graduate School of Medical Science

Stress from the outside is transmitted to cells, where it promotes the expression of genes which is necessary for cells to respond to stress. In this study, I focus on the stress-responsive liquid droplets that function in gene expression in response to stress and clarify their components. Furthermore, I aim to elucidate the mechanism by which liquid droplet formation is disrupted by excessive stress, thereby elucidating one aspect of the pathogenesis of stress-induced diseases.

Study of novel therapeutic methods for inflammatory bowel disease through an integrated understanding of the brain-gut network

Toshiaki Teratani
Associate Professor,
Keio University, School of Medicine

While inflammatory bowel disease induces psychological stress, many studies have suggested that psychological stress is also deeply involved in inflammatory bowel disease symptoms. However, the molecular mechanisms of how perturbation of the gut-brain axis is involved in inflammatory disease pathology have not been elucidated. Therefore, this study aims to explain inflammatory bowel disease's pathogenesis and progression mechanisms, focusing on the gut-brain axis.

Investigating Crohn's disease pathogenesis focusing on Paneth cells

MATSUZAWA Yu
Associate Professor, Graduate School of Medical and Dental Sciences, Institute of Science Tokyo

Crohn's disease is a type of inflammatory bowel disease, and the disruption of Paneth cells in the small intestine is associated with the disease. In this study, we first examine the mechanism by which the accumulation of cellular stress induces Paneth cell death. Next, we focus on a T cell effector API5 which protects Paneth cells against cell death, and examine the mechanism by which API5 functions and investigate what kind of stressor affects the API5-secretion. Our goal is to utilize API5 as a new therapeutic target and a novel biomarker for Crohn's disease.

Sensing brain metabolic flux responding to various stresses using singlet hydrogen gas.

MATSUMOTO Shingo
Professor, Faculty of Information Science and Technology,
Hokkaido University

Various endogenous and exogenous stresses commonly induce cognitive impairment including decline in concentration and working memory. In this study, hyperpolarized 13C magnetic resonance imaging (MRI) using parahydrogen-induced polarization, which enhances the sensitivity of 13C MRI more than 10,000 times, can be used to visualize metabolic alterations in local brain regions. We aim to realize an individualized diagnostic imaging technique that estimates the risk of developing cognitive impairment under combination of different types of stresses from metabolic alterations in brain using hyperpolarized 13C-labele pyruvate and other metabolic tracers.

Development of a stretchable pulse oximeter for long-term and continuous measurement of blood pressure

YOKOTA Tomoyuki
Associate Professor,
School of Engineering, the University of Tokyo

I will develop a "stretchable pulse oximeter" that can accurately and long-term measure dynamic changes of biological signals in response to stress. Furthermore, I will utilize biological signals such as pulse wave and blood oxygen ratio that can be continuously measured using the pulse oximeter as biological alternatives data to estimate biomarkers such as blood pressure, for which continuous changes could not be measured. Then I will analyze them using AI algorithms to give them medical significance.

PRIME Started in 2024 ····· 2nd period

Development of ultra-compact biosensors for real-time multi-monitoring of stress markers

ADACHI Taiki
Postdoctoral Researcher, Graduate School of Agriculture,
Kyoto University

This project aims to develop electrochemical biosensors that can measure stress markers and their candidates in vivo over a long period. The sensors are based on "conductive enzymes" that can directly transfer electrons from/to electrode materials, and have the features of real-time, multiple, and ultra-compact. This technology is expected to contribute to the discovery of new biomarkers by improving the spatial and temporal resolution of data and to the prediction and mechanistic elucidation of disease onset by simultaneous measurement of multiple markers.

Elucidation and control of the neural circuit of emotional responses to stress: regulation of depressive-like state in non-human primates

AMEMORI Ken-ichi
Associate Professor,
Institute for Advanced Study, Kyoto University

Chronic stress can increase the risk of developing depression, particularly in individuals with certain vulnerabilities. In this study, we aim to identify the neural circuits that regulate stress responses related to conflict and motivation in the decision-making processes of non-human primates. Using chemogenetics and transcranial focused ultrasound, we will control these stress responses and elucidate the mechanisms by which the striatopallidum pathway controls conflict and motivation. This research will also explore the potential for new non-invasive therapeutics to modulate stress responses in non-human primates.

R&D of Treatments Targeting Disease-Associated Immune Cells for Psychiatric Disorder Symptoms and Learning Disabilities Induced by Prenatal and Developmental Complex Inflammatory Stress

OHTSUKI Gen
Program-specific Professor,
Kyoto University Graduate School of Medicine

Mental disorders are not caused by a single stressor but rather by the accumulation of multiple factors, which increases the risk. Specifically, infections during a mother's pregnancy and childhood trauma raise the risk of developmental disorders and schizophrenia in children. Animal studies have confirmed that the combination of these factors leads to more severe behavioral abnormalities. Our research aims to unravel this mechanism and contribute to the development of future treatments.

Regulation of tolerance to temperature stress via trace metal ions

KUHARA Atsushi
Professor, Institute for Integrative Neurobiology /
Faculty of Science and Engineering, Konan University

Various metal ions are known as essential trace elements involved in the biological stress response. Among them, iron and copper ions are associated with relatively recently discovered cell death pathways. However, much remains unknown about the molecular mechanisms and their physiological roles in stress responses. This study aims to establish a new experimental model of cell death induced by temperature stress and to develop molecular markers using an original experimental system focused on the cold stress tolerance of a small model organism.

Development of therapeutic strategies by elucidating energy regulation disorders caused by metabolic stress in adipose tissue

SAKAGUCHI Masaji
Assistant professor,
Faculty of Life Sciences, Kumamoto University

Obesity is a modern health issue. Metabolic stress from excess energy intake due to a high-fat diet and lack of exercise leads to insulin resistance in organs. This is exacerbated by the atrophy of brown fat, which, especially with age, plays a significant role in maintaining body temperature through energy expenditure. This research aims to elucidate the mechanisms behind energy regulation failure caused by metabolic stress and to develop new treatment methods through the reactivation of brown fat.

Elucidating the mechanism behind chronic inflammation and its expansion triggered by stress memory and visualization of stress sensing

SHIBATA Sayaka
Associate Professor,
Graduate School of Medicine, The University of Tokyo

The effects of stress on cells are not merely temporary; they can accumulate as "stress memory," influencing future cellular responses and characteristics. This accumulation of stress memory is accompanied by epigenomic reprogramming, leading to qualitative changes in cells that may contribute to the chronicity and spread of inflammation. This study aims to elucidate how stress memory alters cellular plasticity and influences disease progression, and to visualize the sensing of environmental factors associated with stress memory.

Pathophysiology and clinical application of disrupted energy homeostasis mechanism linking stress with organ fibrosis

SOHARA Eisei
Associate professor, Graduate School of Medical and Dental Sciences, Institute of Science Tokyo

It is emerging that disease and environmental stresses prevent AMPK, the master switch for energy homeostasis, from correctly sensing intracellular energy failure states, leading to disruption of the energy state of organs and fibrosis. However, the mechanism is unknown. In this study, we will unravel the energy sensing mechanism of AMPK and its failure in fibrotic diseases, focusing on linkage between disease/environmental stresses and fibrosis. Then, we will develop novel therapeutic strategies for organ fibrosis diseases such as chronic kidney disease.

Development of Nano-PALDI mass spectrometry imaging technology to reveal mental health conditions from a single hair

TAIRA Shu
Professor, Graduate School of Agricutural Sciences, Fukushima University

Evaluation of mental health and diagnosis of mental disorder such as mood disorder, depression and manic depression is difficult by just blood test and interview. Thus, new scientific evaluation method is needed. Hair has daily information through the capillary vessel. Nano-Particle Assisted Laser Desorption/Ionization (Nano-PALDI) imaging mass spectrometry (IMS) can visualize stress signal (biomarker) from lengthwise section of hair. In this research, we aim to found stress biomarker via omics analysis to understand stress mechanism and easily evaluate mental health condition to avoid that change to mental disorder using Nano-PALDI IMS.

Study of integrated information in the brain-body network against social stress

NAKAI Nobuhiro
Project Associate Professor,
Graduate School of Medicine, Kobe University

This study addresses the unresolved issue of how social stress affects the brain and autonomic nervous system, and the mechanisms behind individual differences in stress response. By using VR technology and multi-sensory monitoring, the study aims to measure the real-time brain and body activity of mice subjected to social stress to better understand their stress states. Additionally, optogenetics will be employed to manipulate the peripheral and central networks, with the goal of developing new therapeutic approaches to improve stress conditions.

Mechanism of neurodegeneration by intranuclear RNA sequestration stress

YABUKI Yasushi
Associate Professor, Institute of Molecular Embryology and Genetics, Kumamoto University

Aggregation of prion-like proteins induced by disrupted proteostasis can be a pathogenetic factor in neurodegenerative diseases. RNA G-quadruplex (G4RNA) is an important nucleic acid secondary structure, forming scaffolds for the aggregation of various prion-like protein and contributing to their pathogenic acquisition. In this research project, we aim to elucidate the molecular mechanism of neuronal cell death by G4RNA-causing the intranuclear RNA sequestration stress response and in turn to reveal the pathogenesis mechanism of neurodegenerative diseases.

Aging

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

Research and Development Objectives

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

In the “ageing” research area, basic studies that aim at clarification of fundamental mechanisms underlying aging and researches that tackle age-related diseases by inhibiting the process that contribute to accelerating aging are encouraged to reduce the number of patients suffering from those diseases. The studies and researches follow the previous project on aging and bridge the fundamental molecular mechanism and clinical application. To facilitate understanding of aging,
researchers will use model organisms to investigate the genetic, cell biological and inter-tissue/organ regulation that determine aging. In addition to these challenges, environmental cues that regulate or affect the speed of aging are also examined.
Methods to control aging will also be developed. Following findings of new principles of aging and mechanisms involved in the impairment of robustness and resilience that intrinsically function against aging, the researchers will identify the biomarker of aging and find novel therapy against accelerated aging.

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AMED-CREST Started in 2022 · 1st period

Elucidation and control of “aging-signal network” originating from the gut

IGAKI Tatsushi
Professor,Graduate School of Biostudies,
Kyoto University

To understand the fundamental aging mechanism, it is crucial to identify the cell population responsible for animal aging and how the biological network originating from the aging-responsible cells causes age-related alterations in the organism. In this study, we focus on the "aging-responsible cells" that appear in the Drosophila gut with aging, and aim to elucidate how they are generated and induce the systemic aging-signal network, as well as to establish a methodology for manipulating this aging network.

Elucidation of the stem cell-centric mechanisms of skin resilience, aging and the associated inter-organ frailty network

NISHIMURA Emi
Professor, The Institute of Medical Science,
The University of Tokyo

The skin forms a large barrier organ that protects us from various environmental factors that cause errors and damage to the genome as well as wounds and microorganisms. Tissue stem cells are responsible for its resilience yet decline with aging. In this project, we aims to identify the cells, signals, and molecules responsible for the processes by focusing on stem cell dynamics and fates and to elucidate the actual mechanisms of the inter-organ frailty network through systemic factors and cell-cell interactions leading to individual frailty. We will finally apply the knowledge to treat or prevent aging-related diseases.

Study on the elucidation and regulation of crosstalk between gut bacteria and senescent cells that causes age-related homeostatic disruption

HARA Eiji
Professor,Research Institute for Microbial Diseases,
Osaka University

In addition to genetic factors, various external factors are involved in the maintenance of health throughout the life stages. However, it is difficult to identify external factors that act slowly across life stages and have not been elucidated until now. In this study, we clarify such external factors by focusing on the relationship between the gut microbiota and cellular senescence. Through this research, we aim to identify molecular targets for detecting and preventing the age-related decline in biological functions and the risk of developing diseases.

Elucidation of the regulatory mechanisms of neuronal and glial cell senescence and its application to the development of diagnostic and therapeutic methods for Alzheimer’s disease.

MIZUTANI Kiyohito
Professor, Institute of Advanced Medical Sciences,
Tokushima University

In Alzheimer’s disease (AD), physiological aging causes neuronal degeneration and death. However, the regulatory mechanisms of neuronal aging are largely unexplored. In addition, the mechanisms of disruption of the interaction between glial cells and neurons in the onset and progression of AD are also not fully understood. This project aims to elucidate the regulatory mechanisms of neuronal and glial cell senescence and their disruption in the onset and progression of AD, leading to the development of early diagnosis and curative therapy for AD.

Study of support and promotion for aging research

MINAMI Yasuhiro
Professor,Graduate School of Medicine,
Kobe University

In aging research, analysis using aging mice and a wide variety of high-precision, state-of-the-art technologies play an important role. In this R&D project, we will establish a stable and low-cost supply system of aging mice for R&D projects in the field of aging research, and distribute them appropriately and timely. This project will also aim to provide the multifaceted, high-precision, cutting-edge technical support necessary for the promotion of aging research in each R&D project as a joint research project in principle, and to foster young researchers who will lead aging research.

AMED-CREST Started in 2023 · 2nd period

Elucidating the Mechanisms by which Mitochondrial Homeostasis Impacts the Hierarchy of Cellular Senescence, Organ Dysfunction, and Individual Aging Phenotypes

OIKE Yuichi
Professor, Graduate School of Medical Sciences,
Kumamoto University

Mitochondria have pleiotropic biological functions, and their dysfunction cause not only reduced energy production but also changes in various cellular functions and organ dysfunction. The details of how mitochondrial homeostasis mechanisms change with aging and how these changes contribute to aging and its-related diseases are largely unknown. In this project, we aim to elucidate the molecular mechanisms governing the relationship between mitochondrial homeostasis and aging, ultimately leading to the development of strategies to extend healthy lifespan through appropriate intervention in mitochondrial homeostasis mechanisms.

"Study of Age-Related Phosphoinositide Transformations and Mechanisms of Aging and Disease"

SASAKI Takehiro
Professor, Medical Research Institute,
Institute of Science Tokyo

Aging influences various biological processes, leading to a decline in physical functions and an increased risk of disease development. Similarly, phosphoinositides (PIPs), a family of membrane lipids, are involved in the regulation of diverse cellular functions and the pathogenesis of diseases. In this study, we aim to genetically elucidate the mechanisms of aging control by PIPs metabolizing enzymes, understand the profiles of aging-regulatory PIPs molecular species, and develop aging control methods through interventions in the PIPs metabolic system.

Development of anti-aging methods focusing on qualitative changes in skeletal muscle

TAKAHASHI Satoru
Professor, Transborder Medical Research Center, Institute of Medicine, University of Tsukuba

Skeletal muscle dysfunction is directly linked to a decline in quality of life and has a significant impact on cognitive and metabolic functions via neural activity and blood flow, as well as immune function, and is therefore well related to individual lifespan, prognosis of various diseases, and cognitive function. In this study, we will elucidate the relationship between skeletal muscle "quality" and individual aging, which has been elusive. The results of this research will lead to the development of methods to induce qualitative transformation of skeletal muscle, and the possibility of anti-aging methods targeting skeletal muscle quality will be explored.

Study of the mechanisms underlying organismal aging induced by loss of organ-specific endothelial cell heterogeneity

FUKUHARA Shigetomo
Professor, Institute of Advanced Medical Sciences, Nippon Medical School

The precise roles of blood vessels in organismal aging remain incompletely understood. While blood vessels are vital for sustaining life by transporting oxygen and nutrients to all cells throughout the body, recent research has unveiled that they are not just conduits for delivering blood but also acquire organ-specific functions to maintain homeostasis. In this study, we aim to explore how aging impacts the diverse organ-specific functions of endothelial cells and clarify their significance in organ and organismal aging. This research will help in developing strategies to prevent and treat endothelial cell aging and age-related diseases.

Physiology of extracellular disposal of the waste during aging, and the pathophysiology of age-related diseases caused by its disruption

MATSUI Hideaki
Professor,
Brain Research Institute, Niigata University

We study the relationship between the extracellular waste disposal system as a physiological mechanism of aging and the pathophysiology of diseases caused by its failure. Through the extra-cellular disposal of waste products, we will understand the commonalities and individual pathophysiology of aging and various aging-related diseases at the molecular and individual levels, thereby laying a major foundation for the prevention and treatment of aging-related diseases and for healthy longevity.

AMED-CREST Started in 2024 ····· 3rd period

Mechanism underlying iron-mediated induction of cellular and organismal aging and its manipulation

IWAI Kazuhiro
Executive Vice president/Professor,
Graduate School of Medicine, Kyoto University

Although contribution of iron to senescence has long been suggested, its detailed mechanism has not been clear. We have found that senescent cells are resistant to ferroptosis, an iron-induced cell death. However, to achieve the resistance, senescent cells safely store iron too excess, which leads to acquisition of senescence traits. We also found that a newly discovered molecule that is required for iron acquisition contributes to the development of senescence-related diseases. In this study, we challenge to elucidate the mechanisms by which iron accumulation induces cellular senescence and senescence-related diseases, and to develop methods to control senescence.

Investigation of mechanisms underlying age-related alterations by in vivo imaging and machine learning approaches

KIKUCHI Kazu
Director, National Cerebral and Cardiovascular Center Research Institute

No therapeutic approaches have been established that enable early treatment of aging-related diseases. This conundrum could be attributed to our limited understanding of how aging is initiated and propagated in an organism. In this study, we will perform longitudinal imaging of age-related alterations using an emerging model organism with life-long transparency in all organs. The imaging data will be analyzed using a machine-learning approach to reveal the earliest alteration that occurs during aging, and the underlying cell and molecular mechanisms will be identified using single-cell and spatial multi-omics analysis. The results of this study will help us develop a therapy for aging-related diseases.

Development of innovative diagnostic and therapeutic strategy based on an understanding of the fundamental principles of cellular senescence

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

Cellular senescence is involved as one of the fundamental mechanisms of aging. However, senescent cells in the body are highly diverse, and there are many unknown aspects regarding their induction mechanisms and their resistance to cell death. Additionally, there is currently no universal markers and noninvasive detection methods of senescent cells in vivo. In this study, we aim to understand the diversity of senescent cells and identify biomarkers that can be detected in vivo, with the goal of developing diagnostic and therapeutic strategies for age-related diseases.

PRIME Started in 2022 1st period

Research and Development to Decode Age-Related Changing Cells

OKI Shinya
Professor,
Kumamoto University

This study will attempt to understand the effects of senescent cells on surrounding cells, and to analyze the "whole" transcriptome of non-membranous organelles that form during aging.

Mechanisms and pathophysiological significance of age-associated reprogramming of liver macrophages

SAKAI Mashito
Professor,Department of Biochemistry and Molecular Biology, Nippon Medical School

Chronic systemic inflammation is associated with an increased incidence of age-related diseases, such as metabolic and cardiovascular diseases and cancer. In addition, it has been postulated to play a critical role in regulating physiological aging. Liver macrophages are the largest population of tissue macrophages in vivo that increase in number with aging and secrete inflammatory cytokines to induce chronic inflammation. This study aims to clarify the mechanisms of age-associated reprogramming of liver macrophages and how macrophages of aged liver alter biological robustness to cause diseases.

Elucidating the stem cell aging process caused by glycosylation abnormalities

SADA Aiko
Professor,
Medical Institute of Bioregulation, Kyushu University

The presence of glycans determines the structure, stability, and localization of glycoproteins, and it plays a crucial role in physiological and pathological conditions, such as development, tumorigenesis, and inflammation. Glycans are also required for stem cell regulations by modulating cell-cell and cell-matrix interactions. Using lectin microarray, a platform for high-throughput glycome analysis, our previous study provided a comprehensive glycan profiling of mouse epidermal stem cells during skin aging. This study aims to reveal the glycan-dependent mechanisms of skin aging at the stem cell level, with implications for applications in regenerative therapy and future treatments of age-related disorders, including cancer.

Unraveling the pathogenesis of age-related diseases by targeting a metaboltie sensor for clinical applications

SEKIYA Motohiro
Associate Professor, University of Tsukuba, Faculty of Medicine, Department of Endocrinology and Metabolism

We identified a novel metabolic system orchestrated by a transcriptional cofactor with metabolite sensing capabilities. The system plays a critical role in the pathogenesis of obesity and therapeutically targetable. Metabolism has been known to be profoundly intertwined with ageing processes, and indeed our recent observations support an attractive and plausible idea that our metabolic system can be targeted to extend lifespan and healthspan as well. We will unravel basic mechanisms of ageing and advance the clinical translation from a unique metabolite-centered perspective.

Clarification of the impacts of oxidative stress on tumor initiation by a novel intra-tumoral H_2O_2 imaging technique

TAKAHASHI Nobuaki
Associate Professor,
The Hakubi Center, Kyoto University

Reactive oxygen species (ROS) has long been implicated to serve as a key factor that initiates age-related diseases. However, it remains poorly defined how ROS induce the pathogenesis and whether ROS really act as a critical mediator for the pathogenesis. This proposal aims to clarify the impacts of ROS on 'tumor initiation' using a tumor-targeted ROS probe that we have recently developed. I believe that the proposed study will offer a new avenue in oxidative-stress and aging researches.

Elucidation of the mechanism of memory decline associated with age-related disruption of proteostasis

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

Age-related memory impairment such as dementia is caused by the accumulation of abnormal proteins in neurons and the disruption of neural circuits that support brain function. The proteostasis system degrades proteins within the cell, but its function declines with age. In this study, we aim to elucidate the mechanism by which age-related decline in the proteostasis mechanism disrupts neuronal functions and neural circuits, leading to a decline in memory.

Elucidating mechanisms of aging due to the disruption of NAD metabolism

NAKAGAWA Takashi
Professor,
Faculty of Medicine, University of Toyama

Nicotinamide adenine dinucleotide (NAD) is a co-enzyme and has attracted attention as one of the regulators of aging. However, the metabolic pathway of NAD in vivo is not fully understood, and its relationship with aging are remained unclear. In this research project, I will elucidate the spatiotemporal regulation of NAD metabolism in vivo and clarify how the disruption of NAD metabolism affects physiological aging and aging-related diseases. These results will lead to the development of future drug discovery and nutritional intervention for anti-aging.

Uncovering cell-cell communication within aged intestinal stem cell niche with a highly parallel analysis platform

HATTORI Kazuki
Project Assistant Professor,
RCAST, The University of Tokyo

The intestinal barrier deteriorates along with aging, which is a risk factor for aging-associated diseases. In this study, we will recapitulate the stem cell niche of the aged intestine by culturing the aged intestinal organoids and aged immune cells together in tiny wells or in micro-scale hydrogel units, which allows us to analyze cell-cell communication in a high-throughput manner. Leveraging this platform, we will identify the perturbation that re-activates aged stem cells and uncover the mechanisms of how the microenvironment contributes to stem cell aging.

Redefinition of aging as a function that optimizes longevity and physiology

MORI Masaki
Laboratory Chief,
National Center for Child Health and Development

How longevity is determined is a long-sought question that was cast on human beings, highly social animals. Why do human beings live long after losing fertility, while insects such as cicada and beetles die soon after mating? The existence of long-lived animals that keep much knowledge is profitable to society. Thus, persistent longevity after the loss of fertility is important and indispensable in terms of species conservation for human beings. From the viewpoint of "juvenility" and "juvenile gene program", we redefine the aging process as the system that maximizes longevity and values of aged animals to society.

Age-related changes in germline cells that cause chromosome translocations

YASUHARA Takaaki
Professor,
Graduate School of Biostudies, Kyoto University

The risk of infertility and chromosome aberrations in newborns increases with age. The increased risk is often explained by “aging”, however, what age-related changes in germline cells exactly cause the problem is not well understood. In this study, I aim to assess the tolerance of germline cells to transcriptional and nucleolar stresses that potentially induce chromosome translocations and elucidate how age-related changes affect that tolerance. Through this study, I will redefine the phenomenon previously vaguely referred to as "aging" in germline cells to explain what age-related changes actually cause chromosome aberrations in germline cells.

PRIME Started in 2023 ····· 2nd period

Dynamism of the immune cells in the cardiovascular tissues

UEDA Kazutaka
Assistant Professor,
The University of Tokyo

Most cardiovascular diseases are affected by aging. Recently, it has become clear that the adipose tissue surrounding blood vessels plays pathophysiological roles in the development of the diseases. This study aims to deeply understand the interactions among various cell types in blood vessels and their surrounding tissues through the latest spatiotemporal analysis, which leads to the development of therapies based on aging control for cardiovascular diseases.

Brain aging due to the decline of the nucleus-mediated novel regulatory system of neuronal activity

KUWAKO Ken-ichiro
Associate Professor,
Shimane University School of Medicine

Physiological brain aging is believed to be caused by a gradual decline in the activity of individual neurons and their plasticity, which results in the deterioration of neural functions. However, the mechanism of brain aging remains largely unknown, and no fundamental anti-aging strategy has been established. In this study, we will explore the mechanism of universal physiological brain aging based on the "new regulatory system of neural activity starting from the nucleus" and lead to the development of technologies to promote brain health and longevity.

Functions and mechanisms of nectin-1 in hypothalamic tanycytes for regulating individual

SHIMIZU Tatsuhiro
Assistant Professor,
Graduate School of Medicine, Kobe University

Feeding behavior closely relates to regulation of aging and longevity as dietary restriction prolongs lifespan of organisms. Hypothalamic tanycytes not only sense glucose concentration to control feeding behavior but also function as neural stem cell in adults. Much of the regulatory mechanism, however, remains unexplained. In this study, we will focus on nectin-1, a cell adhesion molecule, which is expressed in tanycytes, to elucidate its function and mechanism of action in individual aging.

Elucidation of the regulatory mechanisms of hematopoietic stem cell aging that causes chronic inflammatory diseases

TADOKORO Yuko
Assistant Professor,
Cancer Research Institute, Kanazawa University

Aging is characterized by a low-grade chronic inflammation. To understand the aging process, it is crucial to elucidate the fundamental mechanisms of age-associated systemic chronic inflammation, which is caused by hematopoietic stem cell (HSC) aging. However, it is unclear how this “HSC aging” occurs. In this study, we aim to elucidate the molecular mechanisms of HSC aging progression. Based on these findings, we also aim to develop approaches to suppressing the progression of age-related chronic inflammatory diseases by regulating HSC aging.

Elucidation of senescence-associated antigen-expressing cells that induce autoimmune response, and the mechanism underlying their pathological changes.

TSUKAMOTO Hirotake
Tenure-Track Associate Professor,
Center for Cancer Immunotherapy and Immunobiology,
Graduate School of Medicine, Kyoto University

While diverse types and traits of senescent cells make it difficult to predict susceptibility to disease and risk of frailty in aged individuals, they would be promising targets for the development of therapeutic strategies. In this study, we aim to clarify the differences in senescent cells that accumulate or are eliminated during the aging process through evaluating age-associated self-antigens that are targets of immune cells. Our results should lead to finding the targets for objective evaluation of aging status and "positive" and "negative" aspects of cellular senescence.

Analyses of Age-Related Transformation of Logistics through Vascular System with in toto Imaging Analyses

NAKAJIMA Hiroyuki
Section Chief,
National Cerebral and Cardiovascular Center Research Institute

Blood and lymphatic vessels are central tissues responsible for logistics in the body. Such vascular logistics are essential for the maintenance of biological homeostasis. Age-related deterioration of vascular function is implicated in major aging-related diseases. This research aims to understand aging as an age-related alteration of vascular logistics. Here, in toto live imaging analysis will be performed using multimodal reporter fish that capture age-related changes in vascular logistics as well as aging of blood vessels and tissues. This research is expected to provide an essential understanding of aging and elucidate therapeutic targets for age-related diseases by targeting vascular logistics.

Elucidation of the cellular senescence mechanisms of myofibroblasts involved in the exacerbation of age-related chronic inflammatory diseases and its therapeutic application

NAKAYA Michio
Professor,
Research Institute of Environmental Medicine, Nagoya University

Fibrosis is a condition characterized by the excessive accumulation of extracellular matrices, such as collagen, within tissues. It is observed in tissues afflicted with a multitude of age-related chronic inflammatory diseases. Myofibroblasts, responsible for the synthesis of collagen and various extracellular matrices, orchestrate the process of fibrosis. Their cellular senescence leads to the exacerbation of numerous age-related chronic inflammatory conditions. Consequently, in this study, we will analyze the cellular senescence mechanism of myofibroblasts and aim to develop new treatments for age-related chronic inflammatory diseases that target this mechanism.

Elucidating the immunosenescence mechanism associated with the decreased plasticity of resident memory T cells.

WATANABE Rei
Professor,
Graduate School of Medicine, Juntendo University

Many peripheral tissues embrace a sessile memory T cell fraction called resident memory T cells (TRM). TRM exhibit a strong response to antigens, acting as "guardians of the tissue." At the same time, they exert plasticity through activation, transitioning from sessile to circulating memory T cells, functioning as a "reservoir of systemic immunological memory." This study aims to investigate the potential link between decreased plasticity of skin TRM and immunosenescence, and explore strategies to counteract immunosenescence.

Age-dependent changes in brain-specialized endothelial lipid metabolism as a trigger of cerebrovascular dysfunction

YANAGIDA Keisuke
Senior Research Fellow,
National Center for Global Health and Medicine

Brain vasculature has unique properties to manage both high energy demand of neurons and their defense from harmful substances. Of note, aging is associated with a decline of these brain-specialized vascular functions, which underlies the risk of dementia. However, the molecular mechanisms underlying age-dependent cerebrovascular dysfunction is still unclear. In this study, we will reveal the age-dependent changes in brain-specialized endothelial lipid metabolism. Moreover, we will assess the possibility that the lipid changes would be a direct trigger of cerebrovascular dysfunction and dementia.

Study of the biological mechanisms of aging through multi-omics analysis of normal cells using single cell-derived models

YOSHIDA Kenichi
Chief,
National Cancer Center Research Institute

Accumulation of somatic mutations in normal cells caused by intrinsic and environmental factors has been implicated in the development of age-related disease such as cancers. Somatic mutations itself has also been associated with aging. In this study, we will grow single cell-derived organoids or colonies from normal cells derived from healthy donors and patients with premature aging syndromes, and perform multi-omics analysis, including whole-genome sequencing, to reveal the mechanism of normal and premature aging.

PRIME Started in 2024 ····· 3rd period

Study on the development of mitochondria-targeted treatment for aging in the hematopoietic system

NAKAMURA-ISHIZU Ayako
Professor, Tokyo Women's Medical University, Department of Microanatomy and Developmental Biology

Organismal aging maybe complicated by disruption of hematopoiesis and loss of functional hematopoietic stem cells which associates with the occurance of various age-related diseases. This study aims to investiagte the change in mitochondrial function, especially that of mitochondrial iron and mitochondrial dynamics, in aged hematopoietic stem cells. We wish to develop novel mitochondria-targeted strategies to manipulate hematopoietic stem cell fate.

Study of elucidation and overcome the mechanism of neuro-aging caused by abnormal protein accumulation and lysosomal dyshomeostasis

KAKUDA Keita
Assistant Professor,
Graduate School of Medicine, Osaka University

The brain is an organ that continues to decrease in the number of cells with aging. A pathological condition where abnormal protein accumulation accelerates aging is called a neurodegenerative disease. Developing treatments for such diseases requires understanding and overcoming the principles of neuronal aging. In neuronal aging, the damage to lysosomes, which are responsible for intracellular degradation, and the decline in damage response—referred to as lysosomal aging—are crucial factors. This study aims to elucidate the mechanisms of lysosomal damage response to abnormal protein accumulation in neuronal aging and contribute to the development of therapies.

Deciphering mitophagy as an anti-ageing programme

KATAURA Tetsushi
Assistant Professor,
Institute of Medicine, University of Tsukuba

Mitophagy eliminates dysfunctional mitochondria via autophagic degradation. We recently identified that mitophagy is necessary to suppress cellular aging, though the mechanism is yet to be defined. In this study, we will discover key factors responsible for cellular aging by investigating the target molecules of mitophagy. By using our unique small-molecule mitophagy activators, we will demonstrate that reactivating mitophagy can combat cellular aging, with the goal of establishing a new intervention strategy to promote healthy aging.

Functional restoration of Aged Hematopoietic Stem Cells Targeting the Program of Metabolic Plasticity

KOBAYASHI Hiroshi
Associate Professor,
Tohoku University Graduate School of Medicine

Hematopoietic stem cells are responsible for lifelong blood production, but with aging, the number of stem cells with reduced blood production capacity increases. It has been found that aged hematopoietic stem cells have higher metabolic plasticity compared to young hematopoietic stem cells, but the molecular mechanisms underlying this remain unclear. In this study, we aim to establish a machine learning model that integrates transcriptional information with metabolic analysis, including single-cell analysis, to predict the responsible genes. Comprehensive functional analysis will be conducted with the goal of restoring the functionality of aged stem cells.

Analysis of the functional roles of PNPO-PLP axis in age-related diseases

SEKINE Hiroki
Associate Professor,
Tohoku University Graduate School of Medicine

Chronic tissue hypoxia is associated with the pathogenesis of age-related diseases, but its molecular basis remains unclear. We have recently shown that chronic hypoxia leads to a decrease in pyridoxal 5'-phosphate (PLP), the active form of vitamin B6, leading to the phenotypes associated with chronic hypoxia. This study aims to elucidate the impact of tissue hypoxia on age-related diseases by examining PLP dynamics, ultimately contributing to the development of new diagnostic and therapeutic approaches for these diseases.

Alteration of microglial characteristics regulated by micronuclear propagation and its impacts on aged cerebral blood vessels

TSURUTA Fuminori
Assistant Professor, Institute of Life and Environmental Sciences, University of Tsukuba

Microglia, the immune cells in the central nervous system, are known to undergo characteristic changes with aging and to regulate the functions of cerebral blood vessels. However, the precise mechanisms and physiological significance of these microglial transformations remain insufficiently understood. In this study, we aim to determine whether microglial changes induced by micronuclear propagation are involved in regulating the functions of aging cerebral vessels and in removing waste products. We will employ a comprehensive range of approaches, from molecular biology analyses to in vivo imaging in mice, to address these fundamental questions.

Study of the proteasome dynamics along aging and its application to aging control

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

Recent findings have revealed that functional alterations in the proteasome, the key machinery for intracellular protein degradation, are implicated in the onset of numerous pathologies, including aging, neurodegenerative disorders, and inflammatory diseases. However, a comprehensive understanding of the regulatory mechanisms of the proteasome dynamics and their connection to aging remains elusive. This study aims to modulate aging and related pathologies by elucidating novel proteasome control mechanisms and applying these insights to develop targeted interventions.

Elucidating aging mechanism associated with clonal hematopoiesis originating from kidney DNA damage

HAYASHI Kaori
Professor,
Keio University School of Medicine

Recently it has shown that chronic kidney disease is a major factor that accelerates systemic aging; however, the reasons for the strong involvement of the kidneys remain unclear. This study aims to investigate the possibility that DNA damage in the kidneys may contribute to systemic aging through hematopoietic stem cell aging, such as clonal hematopoiesis, leading to development of new therapeutic strategies for age-related diseases.

Study of specialized ribosomes and impaired nucleolar dynamics during cellular senescence

YOSHIKAWA Harunori
Assistant Professor, Fujii Memorial Institute of Medical Sciences,
Institute of Advanced Medical Sciences, Tokushima University

Senescent cells increase in the translation particularly of specific proteins promoting senescence e.g. SASP factors. Senescent cells also exhibit morphological changes in nucleoli where ribosome biogenesis occurs. Using my unique techniques to analyze the ribosomes and nucleolar pre-ribosomal particles by size exclusion chromatography together with mass spectrometry-based proteomic analysis, I aim to elucidate how altered ribosome biogenesis in the nucleoli and specialized ribosomes and their roles in the translation contribute to cellular senescence. This project will lead to the development of new tools to identify the senescent cells.

Elucidating the Mechanisms of Osteocyte senescence and Its Pathophysiological Significance Through a Mechanobiology Approach

YOSHIMOTO Tetsuya
Assistant Professor, Dept. of Innovation and Precision Dentistry,
Hiroshima University Hospital

Appropriate mechanical stress, such as exercise, is effective in preventing musculoskeletal disorders in middle-aged and older adults. However, the systems and mechanisms by which mechanical stress improves bone quality and counteracts aging remain poorly understood. In this study, we will focus on osteocytes, which are central to bone metabolism and act as important mechanosensors, aiming to elucidate the molecular mechanisms by which mechanical stress regulates osteocyte aging, thereby contributing to the prevention and treatment of age-related bone metabolism disorders.

Immunological Memory

Immunological memory:
Understanding, regulation and medical innovation

Research and Development Objectives

**Immunological memory:
Understanding, regulation and medical innovation**

Immunological memory is an important host defense system that functions against infectious microorganisms, but is also closely implicated in the pathogenesis of various diseases, including cancer and allergy/autoimmune disease. Immunological memory is a potential target for the development of clinical methods to predict, prevent, and treat such diseases, so a better understanding of the mechanisms will be vital to lay the foundations for medical advances in the management of these diseases. Creation of new concepts of immunological memory will be expected by investigating the mechanism on the establishment of memory based on recognition of self and non-self, memory against pathogenic and symbiotic microorganisms, and pathogenic memory vs. beneficial memory.
Basic research on immunology to date has mostly been performed using mice and has focused on investigating short-term immune responses. The difference in the immune system between humans and animal models such as mice has been a barrier to the application of basic research achievements to the clinical setting. However, the importance of the understanding of the human immune system is rapidly becoming clear as a countermeasure against the COVID-19 pandemic, and basic research to understand human immunological memory is now seen as even more important. A better understanding of how immunological memory in humans is formed and maintained, how it is activated according to the environmental situation, and how it becomes weaker and disappears, will help us to develop new perspectives on the management of the numerous diseases in which the immune system is closely involved.
The goal of this R&D area is to create medical innovations that will contribute to predicting and regulating diseases like cancer, infectious disease, and allergy/autoimmune disease, through a hierarchical and multifaceted understanding of immunological memory in humans by applying advanced research technologies such as the recently developed single-cell/repertoire analyses and structural analyses using cryo-electron microscopy.

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AMED-CREST Started in 2022 · 1st period

Establishing renovative autoimmune therapies targeting novel types of self-reactive memory T cells

OKAZAKI Taku
Professor, Institute for Quantitative Biosciences, The University of Tokyo

Self-reactive memory T cells play pathogenic roles in many autoimmune diseases, while their phenotypic and functional properties remain ill-defined. In this project, we aim to identify novel types of self-reactive memory T cells by focusing on immune-checkpoint molecules and elucidate how each type of self-reactive memory T cells escapes immune tolerance to induce persistent immune responses and tissue damage under disease conditions. Based on these findings, we try to establish novel and effective autoimmune therapies that target disease-relevant types of self-reactive memory T cells.

Elucidation of immunological memory underlying human immunotherapy by single-cell analysis of multi-timepoint and multi-region samples

KATAOKA Keisuke
Professor, Keio University School of Medicine

We have collected multi-timepoint and/or multi-region samples from patients receiving immunotherapies, such as allogeneic hematopoietic stem cell transplantation and immune checkpoint inhibitors against malignancies. In addition, we have established cutting-edge single-cell and immune repertoire analysis technologies, which enable immunological analysis in a comprehensive manner. Therefore, here we will examine cellular and molecular dynamics underlying the efficacy and complications of immunotherapies by applying our cutting-edge analytical techniques to these human samples. In addition, we plan to perform in-depth characterization of the related protective and/or pathogenic memory using functional assays and mouse models.

Study of innate immune memory control via neuro-immune linkage

KUMANOGOH Atsushi
Professor and chair, Graduate School of Medicine, Osaka University

Immune memory has been thought to be a property unique to the acquired immunity. However, it has been shown that immune memory exists in the innate immune system as well. It has also been reported that the central nervous system regulates the innate immunity, pointing to the importance of innate immune memory control in humans from the perspectives of both disease control and enhancing and maintaining vaccine efficacy. From the unique perspective of "human innate immune memory regulation by neuro–immune coupling," this study aims to elucidate the mechanisms of immune memory induction, maintenance, and regulation in the human innate immune system with the goals of enhancing vaccine efficacy and controlling autoimmune diseases.

Evolution of humoral immune memory for resisting viral escape

TAKAHASHI Yoshimasa
Director,Research Center for Drug and Vaccine Development, National Institute of Infectious Diseases

Humoral immune memory is pivotal for durable protection provided by SARS-CoV-2 vaccines. Repeated vaccination accelerates an evolution of antibody presenrved in humoral immune memory; the phenomenon is an immunological basis for combating Omicron variants by the vaccination. We aim to understand the evolution by introducing novel immune profiling approach. The findings may guide the development of next-generation of vaccines that are effective to viral escapes.

Study of T cell subsets associated with immune memory for both cytotoxic and adaptive immune responses in autoimmune diseases

FUJIO Keishi
Professor, Graduate School of Medicine, The University of Tokyo

The mechanisms of organ inflammation important in autoimmune diseases are still unknown. We have found that highly proliferating CD4-positive T cells expressing cytotoxic and B-cell function-promoting molecules infiltrate the inflamed organs of autoimmune diseases. This cell population, which increases with age in the peripheral blood of healthy individuals, has been named as age-associated T (ThA) cells. This study aims to elucidate the function of ThA cells and to develop new therapeutic strategies and stratification of autoimmune diseases.

AMED-CREST Started in 2023 · 2nd period

Elucidation of the pathogenesis and development of therapeutic strategies for autoimmune diseases by targeting neo-self-responsive memory T cells.

ARASE Hisashi
Professor, Research Institute for Microbial Diseases, Osaka University

Neoself antigens, which is different from normal self antigens, has been shown to be involved in autoimmune responses in autoimmune diseases. Therefore, this study aims to elucidate the mechanisms of neoself generation and recognition, to understand how neoself-reactive memory T cells are involved in the pathogenesis of autoimmune diseases, and to develop new methods for the treatment and prevention of autoimmune diseases by targeting neoself-reactive memory T cells.

Study on regulation of generation, maintenance, and activation of protective or pathogenic memory helper T cell repertoire and development of novel immune therapy

ISE Wataru
Professor, Center for Infectious Disease Education and Research, Osaka University

The humoral immune memory is essential for defense against infection and is also strongly involved in the onset and relapse of allergies and autoimmune diseases. Thus, it could be possible that various immunological diseases can be controlled by regulating the development or activation of humoral immune memory cells. This study aims to understand molecular mechanisms underlying differentiation, long-term survival, and re-activation of follicular helper T cells that function as drivers of humoral immune memory response. We will also develop highly accurate immunoregulatory methods that target antigen-specific, pathogenic memory helper T cells.

Understanding of autoimmune response mechanism and disease pathology by pathogenic memory B cells

BABA Yoshihiro
Professor, Medical Institute of Bioregulation, Kyushu University

Autoreactive B cells are censored to avoid autoimmune diseases by immune tolerance. Autoreactive memory B cells are presumed to be key in the pathology of autoimmune diseases, but their pathological significance is unknown. The aim of this research is to identify key memory B cell subtypes associated with autoimmune pathology and establish the molecular mechanism underpinning the generation, maintenance, and activation of pathogenic memory B cell subtype in autoimmune disease in mice and humans, and define the target pathways/molecules to prevent it. Through this research, we hope to contribute to understanding autoimmune disease pathology and developing a new therapeutic strategy.

Elucidation of the pathophysiology of tissue inflammatory memory formation by external environmental stimuli: Toward the development of a new strategy for treating intractable allergic diseases

HIRAHARA Kiyoshi
Professor, Graduate School of Medicine, Chiba University

The formation of “tissue inflammatory memory” including CD4+ tissue resident memory T (TRM) cells and tertiary lymphoid structures (TLSs) plays a crucial role in the pathophysiology of intractable allergic diseases. However, precisely how the external environmental stimuli, such as hypoxia and changes in airway pressure under chronic inflammatory conditions, are involved in the formation and maintenance of tissue inflammatory memory is still unclear. Therefore, we plan to comprehensively analyze the regulatory mechanisms of tissue inflammatory memory at the molecular, cellular, and biological levels to establish a basis for developing new therapeutic strategies to successfully treat intractable allergic diseases in humans.

AMED-CREST Started in 2024 ····· 3rd period

Deciphering Human Liver Immune Responses and Unveiling Novel Therapeutic Targets

UENO Hideki
Professor,
Graduate School of Medicine, Kyoto University

The liver has a specialized immune system to handle substances and pathogens from the intestinal tract and portal vein. Despite its importance, the global understanding of human liver resident immune cells is limited, especially regarding immune responses in human liver diseases. Our research will focus on the human liver immune system using liver specimens, including liver tissues and perfusate. We aim to elucidate mechanisms associated with immune tolerance, immunological memory, breakdown of homeostasis, and pathogenesis of hepatobiliary diseases.

Population, individual, and single cell level omics elucidates how immune memory can be acquired, accumulated, and lost.

OKADA Yukinori
Professor,
Graduate School of Medicine, the University of Tokyo

By interpreting human omics information in a multilayered manner from population, individual, and single-cell resolution, we aim to understand immune memory along life stages and elucidate the mysteries of human immune memory “introduction, accumulation, and loss” through integrated cross-sectional omics analysis. We would like to challenge to elucidate the long-standing riddle of clinical immunology, “why, when, and how immune memory can be introduced, accumulated, and lost”.

Understanding Age-Related Characteristics and Individual Differences in Human Immunological Memory

HAMAZAKI Yoko
Professor, Center for iPS Cell Research and Application, Kyoto University

The immune status in humans significantly changes with age. This study aims to elucidate the transitions, age-related differences, and individual variations in immunological memory across a wide range of age groups, from childhood to old age, using multi-layered omics analysis. Based on this knowledge, we intend to scientifically define immune capability and immune age, and to establish a molecular basis and develop technologies that enable the efficient induction and maintenance of memory responses based on individual immune status.

MultiSensing

Integrated understanding of multi-sensing networks and elucidation of their control mechanisms leading to the innovation of medical technologies

Research and Development Objectives

Integrated understanding of human multi-sensing networks and elucidation of their control mechanisms

This Objective aims to develop an integrated understanding of multi-sensory systems, including sensory systems and peripheral nerve networks, and to develop methods to visualize and control these systems. Specifically, this Objective aims to achieve the following:

(1) Understand peripheral neural circuit mechanisms and clarify disease pathology to help overcome disease
(2) Develop methods to visualize and control peripheral nerve activity and new treatment methods
(3) Clarify and apply the mechanisms involved when sensory systems receive, process, and act on signals
(4) Develop technology platforms for methods to visualize and control sensory systems

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YONEDA Yoshihiro
Director, The Research Foundation for Microbial Diseases of Osaka University

AMED-CREST Started in 2021 · 1st period

Elucidation of roles and functions of neural network underlying intractable hematologic disorders in aged bone marrow and building of new technology platforms for nervous system-targeting clinical applications

KATAYAMA Yoshio
Junior Associate Professor,
Hematology, Kobe University Hospital

The healthy service life of bone marrow is approximately 50 years, and along with the age, the incidence of particular intractable hematologic disorders, each of which displays unique alteration of bone metabolism, rapidly increases. The aim of this research is to elucidate the alteration in the network of nervous—skeletal—hematopoietic systems, develop neural activity based-biomarkers for disease status and prognosis, and identify new pharmacological targets for development of therapeutic drugs for aged marrow-based hematologic malignancies as new technology platforms for nervous system-targeting clinical applications.

Integrated understanding of functional asymmetry of the autonomic nervous system and development of electrical nerve stimulation to treat cross-organ disorders

KANAI Takanori
Professor,
School of Medicine, Keio University

The organism is a collection of organs that control cognition, nutrient absorption, circulation, immunity, and metabolism. To unite these independent biological processes, organ-organ interactions are essential for the organism to function. This project focuses on the functional asymmetries of the autonomic nervous system and aim to clarify how the interaction between the gut and the brain impacts on higher brain functions. Furthermore, we plan to develop super-selective vagus nerve stimulation techniques as new treatment strategies for visceral and central nervous system diseases such as inflammatory bowel disease and multiple sclerosis.

Theoretical basis for human clinical application of sensory medicine

KOBAYAKAWA Ko
Professor,
Institute of Biomedical Science, Kansai Medical University

Organisms have protective abilities to survive crisis situations. However, medical technology to artificially induce these abilities has not yet been developed. We found that thiazoline-related innate fear odors bind to TRPA1 in sensory nerves and activate the crisis response center in the brainstem-midbrain, thereby increasing survival rates in lethal environments and pathological models. In this research, we aim to elucidate the principles by which TRPA1 distinguishes agonists to induce distinct responses and the principles by which the brain center integratively induces protective effects, in order to achieve early practical application of sensory medicine.

Age-related hearing loss: analysis of the pathological mechanisms and development of a technological basis for next-generation therapeutic interventions

HIBINO Hiroshi
Professor,
Graduate School of Medicine, Osaka University

Age-related hearing loss lowers quality of life and increases risk for dementia and depression. This disease stems primarily from damage of the cochlea in the inner ear, and the pathological processes remain largely uncertain. In this project, we will analyze the cochleae of animal models by multiple approaches including a cutting-edge imaging technology and clarify the mechanisms underlying age-related hearing loss. Using such observations, we will provide technical basis for preventive and therapeutic medicine and prototypes of a next-generation cochlear implant. The outcomes may contribute to extension of healthy life.

Development of neuroscience based intelligent neuromodulation system for complex regional pain syndrome (CRPS)

HIRATA Hitoshi
Professor, Innovative Research Center for Preventive Medical Engineering, Nagoya University

The objectives are to investigate the pathological mechanism underlying the multi-sensing network failure in patients with complex regional pain syndrome (CRPS) using advanced neuroscience technologies, and to develop an innovative neuromodulation technology to restore normal conditions within the nervous system by deploying a specially developed multi-channel nerve stimulator, original artificial intelligence and unique sensor technologies. This will be undertaken by 3 groups, each having responsibility for a core project yet in close interdependent collaboration with the others. The goal is to develop a multi-faceted innovative neuro-modulation system that addresses the multiple nervous systems involved in the pathological mechanism of CRPS.pathological mechanism of CRPS.

Establishment of therapeutic strategies for neurodevelopmental disorders through an integrated understanding of brain-sensing networks focusing on retinal circuit function

FURUKAWA Takahisa
Professor,
Institute for Protein Research, Osaka University

Neurodevelopmental disorders (NDs) including autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) have become one of the important social issues worldwide. Recently sensory abnormalities (atypical sensory features) in NDs have gathered an increasing attention, because NDs, especially ASD, are often accompanied with atypical sensory features. In the present R&D proposal, we aim to elucidate multi-sensing-brain relationship by analyzing the effect of a specific retinal pathway defect on sensory and brain functions. Furthermore, we aim to develop a novel visual stimulation-mediated therapeutic device to ameliorate symptoms of NDs including ASD.

AMED-CREST Started in 2022 · 2nd period

Understanding of light multi-sensing by non-visual opsins and development of novel light therapies

KURIHARA Toshihide
Associate Professor,Department of Ophthalmology,
Keio University School of Medicine

Non-visual opsins are also expressed in the retina and other tissues, and control various multi-sensing mechanisms other than visual signals. Our study aimed to verify whether the non-visual opsins (OPN3, OPN4, OPN5) in the eye are involved in the suppression of myopia progression toward the development of novel treatments for myopia. Then, we shed light on the neural circuits of opsins that control the ocular tissues and develop ligands other than light that intervene in opsin activity or circuits. From our study, a paradigm shift will be expected in understanding light sensing systems other than the vision with the eyes.

Study of the mechanism for integration of multi-sensing systems by emotion and the development of innovative therapy for pain

MINAMI Masabumi
Professor,Faculty of Pharmaceutical Sciences,
Hokkaido University

How diverse sensory information is integrated to generate negative emotions such as aversion, anxiety, fear, and depression remains unclear. In this study, we will focus on the neural circuits centered on the extended amygdala to elucidate the mechanisms for integration of diverse sensory information and for emotion-mediated interaction mechanism between sensory information of different modalities. We also aim to develop an innovative pain treatment method that improves patients' quality of life (QOL) and social activity by removing anxiety, fear, and "captivity" to pain through exercise and successful experience in a virtual space.

Identification of the malignant loop for the brain disorder involving endocrine and neuronal functions

MURAMATSU Rieko
Director,
National Center of Neurology and Psychiatry

This study aims to elucidate how a multilevel network of the brain and peripheral organs causes brain disorders. Until now, most researches on the pathological mechanisms of brain diseases have focused on elucidating the roles of cells and molecules in the brain. This study will focus on the role of peripheral environment that affects brain disorders, and will show the evidence that the malignant loop formed between the brain and peripheral environment is a major mechanism for the progression of brain disorders. We also aim to develop therapeutic approaches for treating brain disorders by intervening in the malignant loop.

Research and development of next-generation retinal prosthesis device based on the development of innovative BMI technology and understanding and controlling visual cognitive networks

MORIMOTO Takeshi
Associate professor,
Osaka University Graduate School of Medicine

Retinal prosthesis is a device to reconstruct vision by implanting an electrode array in the eye of a blind patient. The current retinal prosthesis gives patients hope of seeing, but it is inadequate for daily life. In this project, we will research and develop a new retinal prosthesis device by developing an internal device with dramatically improved performance using innovative BMI technology, an external device that can effectively project visual information through information processing, and by understanding and controlling visual cognitive networks. The goal is to enable patients to read and perform daily activities at home as well as normal people.

AMED-CREST Started in 2023 ········· 3rd period

Perinatal drug discovery based on multi-sensing network between mother and child via sex steroid hormone

KIMURA Ikuo
Professor,
Graduate School of Biostudies, Kyoto University

Sex steroid hormones are involved in many physiological functions. Most of them involve immediate responses that cannot be explained by the nuclear receptors, and the mechanisms are still unclear. In this research, we focus to sex steroids that rapidly increase in mother during pregnancy. Based on our novel finding that the novel membrane progesterone receptors (mPRs) are highly expressed in various sensory tissues of the fetus during the late stages of pregnancy, we aim to unravel the molecular mechanisms. Additionally, by developing mPRs-selective compounds, we aim to divide the various functions of sex steroids and to treat perinatal disorders.

Development of novel therapeutic strategy for chronic kidney disease based on understanding of responses to mineral stress

KUROO Makoto
Professor,
Division of Anti-aging Medicine, Jichi Medical University

Phosphorus is one of the 6 elements essential for life. In vertebrates, phosphorus exists as phosphate and is stored predominantly in the bone in the form of calcium-phosphate. However, when precipitated ectopically besides the bone, calcium-phosphate induces inflammation and cell senescence, potentially accelerating aging. In the blood and urine, calcium-phosphate exists as colloids called calciprotein particles (CPP). We define (patho)physiology that involves CPP as responses to "mineral stress". Our long-term goal is to explore novel anti-aging medicine based on a better understanding of molecular mechanisms underlying mineral stress.

Elucidation of the mechanisms for pain generation and modulation by stress and development of diagnostic and therapeutic technologies for chronic pain

TSUDA Makoto
Professor, Graduate School of Pharmaceutical Sciences,
Kyushu University

The relationship between chronic pain, which afflicts many people in Japan, and physical/mental stress has attracted attention. In this study, using advanced neural circuit labeling/manipulation techniques, we aim to identify brain regions critically involved in pain generation/modulation, analyze the effects of stress, and clarify the brain regions and neural circuits responsible for stress-related chronic pain. Based on these findings, we aim to develop new diagnostic and therapeutic strategies for chronic pain.

PRIME Started in 2021 ········· 1st period

The generation of human taste organoids and their characterizations as taste sensors

IWATSUKI Ken
Professor,
Tokyo University of Agriculture

Although we have been analyzing taste cells using the mouse or monkey taste stem cell culture system, it became clear that humans have different taste preference from other animals. Therefore, in this study, we expect to generate human taste organoids so that we will be able to analyze taste cell function that is peculiar to humans. In the future, we hope to contribute to the new drug development and regenerative medicines using human taste organoids.

Development of somatosensory prosthesis with reference to somatosensory processing in the brain

UMEDA Tatsuya
Associate Professor,
Graduate School of Medicine, Kyoto University

Brain-machine interface (BMI), which directly connects brain and machine, has the potential to improve the quality of life for patients suffering from brain or spinal cord injuries, because they can operate a prosthesis or machine based on brain activity. However, the poor performance in the somatosensory prosthesis is a problem in the practical use of BMIs. This study will develop a somatosensory prosthesis that can elicit shape perception by activating the primary somatosensory cortex with electrical stimulation with a pattern that is designed based on the somatosensory processing in the brain during active exploration of the hand.

From vision to hippocampal cognitive map: underlying circuit mechanisms

KITANISHI Takuma
Associate Professor, Graduate School of Arts and Sciences, The University of Tokyo

When we visit a new place, we look around to get a sense of where we are. As we know from these experiences, vision is the key to support spatial cognition. However, how visual information is transmitted and converted into spatial representations in the hippocampus and its associated areas remains unclear. This study will uncover the neural circuit mechanism that converts visual information to hippocampal spatial representations by using large-scale neural recordings and novel optogenetic techniques.

Regulation of temperature acclimation by integration and modulation of multi thermosensory information

KUHARA Atsushi
Professor, Konan University

Since temperature is one of the environmental information that is directly linked to animal's lives, malfunction of thermo-sensing and its information processing causes various diseases. In this study, we aim to elucidate how multi-thermosensory information received at multiple locations in the body or in a single cell are integrate or discriminate to regulate temperature acclimation in the body. We also aim to elucidate how sensory information other than temperature affects the temperature signaling on neural circuit. These studies will be conducted using nematode C. elegans, a model animal that allows for high-throughput analysis.

Response mechanism of skin sensing system to mechanical stress

KOBAYASHI Tetsuro
Deputy Team Leader, RIKEN IMS

The skin is a barrier organ organized by an epithelial-immune network, and disruption of the crosstalk leads to the development of various diseases. This project will reveal a skin sensing system constructed by the interaction between epithelial sensors that receive mechanical stress and immune cells that act as responders. We aim to understand the pathogenesis of atopic dermatitis, which is aggravated by persistent mechanical stimuli such as scratching behavior, and to develop novel therapeutic strategies.

Establishment of a novel pain evaluation system using nerve organoids derived from human iPS cells

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

Among various biological sensing systems, abnormal pain sensation produced a largest number of patients and induced the lowest QOL (quality of life). Many studies were conducted to analyze the mechanism of pain development, but most of the studies analyzed based on subjective evaluation criteria. In this project for the multi-sensing network program, we will develop objective and quantitative pain-sensing devices by combining the advanced imaging technology with using various kinds of microscopes, the precise skills for the molecular biological analysis, and the sophisticated technologies of machine engineering specialists for developing special culture devices.

Developing somatosensory system on a chip toward novel pain control method

SHIMBA Kenta
Associate Professor, School of Engineering, The University of Tokyo

Developing a novel treatment for neuropathic pain requires comprehensive understanding of dynamics in the relevant neural networks. In this study, somatosensory networks including pain processing circuits will be reconstructed on a chip using microfabrication technology. With precise optogenetic stimulation and extracellular recording of the network, we aim to elucidate the neural basis for pain transmission and amplification in pathological conditions. Furthermore, we will explore the possibility of novel pain control methods using the integration of multisensory information.

Study of whole-body humidity sensing mechanisms via skin humidity receptor

CHIKUMA Mariko
Associate Professor, School of Medicine, Keio University

The ability to detect and sense variation in humidity is important for terrestrial animals to protect the body from the environment. However, the cellular and molecular basis for hygrosensation and the genes involved in detecting humidity remain unknown. The aim of this study is to investigate how the skin senses variations in humidity consequently controlling the whole-body. We will identify the "humidity sensor" expressed in the skin and examine the mechanism controlling the sensing, response, and transmission of humidity stress in the skin and the whole body. The findings may establish the underlying mechanism of skin-mediated whole-body sensing networks of humidity stress.

Deciphering the mechanism of impairment in homeostatic energy metabolism regulated by brain and finding the way to improve it

TODA Chitoku
Associate Professor, Department of Neuroscience for Metabolic Control, Faculty of Life Sciences, Kumamoto University

The brain monitors the amount of nutritional energy in the body and environmental food availability by multi-sensing systems. Animals change feeding behavior and energy utilization according to these internal and external situations. Obesity attenuates the function of multi-sensing systems and thus leads to diabetes. Our project is to clarify how our brain integrates a wide variety of inputs from both inside and outside of the body. We also try to understand the mechanism by which obesity impairs the multi-sensing systems. Our project will develop a way to improve the impaired sensing systems.

Elucidation of homeostatic mechanism and its failure mechanism by new sensing and integration mechanism of cardiovascular stress

FUJIU Katsuhito
Professor, The University of Tokyo Hospital

The heart and blood vessels are subject to various stresses. These stresses are integrated into the brain and multiple organs via peripheral nerves and humoral factors. In addition, the system keeps circulatory control homeostatic. In this study, I will treat various cells that make up the brain and nervous system and investigate how the brain and nervous system sense and control cardiovascular stress. Furthermore, we will elucidate when the disease develops beyond being able to overcome the burden.

Pain & loneliness: Neural basis for sociality formation through peripheral nociception tuning

ISHII Kenichi
Assistant Professor,
Graduate School of Science, The University of Tokyo

Loneliness, or lack of social interactions among individuals, often leads to pathogenic sensation of physical pain. Moreover, nociception abnormalities in autism spectrum disorder (ASD) patients are epidemiologically linked with impaired interpersonal relations. Here I propose to use fruit fly as a genetically tractable model to unravel the neurogenetic mechanism of peripheral nociception tuning and its potential importance in animal/human sociality formation. The present study further aims to provide mechanistic insights for the ASD-related pathologies in nociception.

The neural circuit of multisensory integration and emotion in eating behavior

OZAWA Takaaki
Assistant Professor,
Institute for Protein Research, Osaka University

Food palatability is generated by the complex synergy among perception from multiple senses during a meal, such as taste and odor. However, neural circuit mechanisms through which a taste generates food palatability, or an aroma promotes the food palatability remain largely unknown. This study aims to elucidate the neural systems that integrate multisensory information and convert them into positive emotions by taking advantage of cutting-edge neuroscience tools. Results of this research will contribute to solving health problems related to our eating behavior, which may improve our quality of life (QOL).

Study of multisensory integration in pathological cascade in neurodegeneration

SHIMOJO Masafumi
Principal Researcher, National Institutes for
Quantum and Radiological Science and Technology

The dysregulation of the sensory integration process is currently proposed as a key component in the pathophysiological cascade of various neurological disorders. However, the disease-associated mechanism is still largely unknown due to the lack of appropriate methods to monitor the dynamics of circuit reorganization in the brain network of living animals. This project aims to establish genetic and neuroimaging technologies for the analysis of multisensory integration in the brain of animal models for tauopathy. Furthermore, we will also explore the possibility to modify the pathophysiological progress of neurodegenerative disorders.

Characterization of ether lipids in multi-sensory processes and the oxidative stress-induced dysfunction

SOKABE Takaaki
Associate Professor, Exploratory Research Center on Life and Living
Systems, National Institutes of Natural Sciences

The countermeasures to maintain our sensory functions are demanded for elongation of healthy life expectancy, however, the mechanisms underlying sensory defects caused by aging and chronic diseases have not been elucidated. We are focusing on lipid molecules that participate in the sensory processes and will investigate their regulatory roles, and also clarify how oxidative stress during progress of aging and diseases deteriorates lipid-mediated sensory functions. We will strive to improve impaired sensory functions and establish the methodologies that are beneficial for increasing quality of life(QOL) in the longevity society.

Non-invasive, spatiotemporal control of internal organs via sonogenetic stimulation of the autonomic nervous system

TAKEUCHI Yuichi
Professor,
Faculty of Pharmacy, Kindai University

Ultrasound can not be heard by humans and is considered a suitable modality for non-invasive neuromodulation due to its transmittability in our body, spatio-temporal specificity, and safety. In this study, I will develop a new technology to precisely control cardiac functions via ultrasound-sensitive ion channels exogenously expressed in sympathetic and parasympathetic nuclei in the medulla of rats. This research will provide a seed for an innovative medical technology that precisely controls visceral functions in a spatiotemporal specific manner via an all-non-invasive pipeline from gene transduction to functional regulation.

Reno-protective/anti-inflammatory mechanisms via neural circuits activated by various stresses/stimuli

TANAKA Shinji
Assistant Professor, Division of Nephrology and
Endocrinology, The University of Tokyo Hospital

Anti-inflammatory effects via neuro-immune interactions are promising novel treatment strategies for inflammatory disorders in many organs. Inflammation plays a critical role in the pathophysiology of kidney disease; however, little is known about the role of neuro-immune interactions in kidney disease. In this proposed research, we will elucidate anti-inflammatory and reno-protective mechanisms via neural circuits activated by various stresses and stimuli, which can lead to a novel strategy for the treatment of kidney disease.

Study of neuronal networks for the sub-second timing perception

HASHIMOTO Kouichi
Professor,
Hiroshima University

Time perception is an important sense for animals. A certain type of the time perception is initiated by a sensory input and perceived as the elapsed time from the sensory input. We plan to analyze the neuronal networks working for such sensory-driven timing task in the sub-millisecond range. We will particularly focus on the contribution of the cerebellar networks.

Elucidation of diverse innervation in the stomach that senses luminal and psychological stress and its relationship with gastric diseases

HAYAKAWA Yoku
Lecturer,
The University of Tokyo Hospital

There are a large number of patients with gastric diseases in Japan, and chronic gastritis is a serious clinical problem since it causes gastric ulcers and cancers. The stomach contains abundant nerves, and while it transmits stimuli from intraluminal stressors to the brain, it also transmits signals from central nervous system activated by mental stress into the stomach. In order to understand this stress sensing and response mechanism, we will utilize our original mouse model and cutting-edge omics imaging technology. We aim to elucidate the novel mechanism of gastric disease through the gastro-brain interaction and contribute to new prevention and treatment strategies.

Neural substrate of muti-sensory integration and separation

FUNAMIZU Akihiro
Lecturer,
The University of Tokyo

To estimate the external world from multi-sensory inputs, humans and animals are not simply required to integrate all the sensory inputs. Instead, they are required to predict and integrate a series of inputs coming from a same source, while separate them from other sources. The aim of our study is to investigate the neural mechanism of determining the multi-sensory integration and separation by combining methods of psychology, biology, and computations. Our future goal is to develop an AI to perceive the external world like our brain.

Regulation of sensory integration and developmental disorders by synaptic pruning

MARUOKA Masahiro
Program-Specific Lecturer,
Institute for Advanced Study, Kyoto University

Neural circuits mature through "synaptic pruning", which removes unnecessary synapses after excessive synapse formation in the early phase of brain development. During this process, the neural circuits are modified to integrate the individual senses in response to the various stimuli received by the sensory modalities. Failure of this process leads to developmental disorders. In this study, I will establish a mouse model of developmental disorders caused by the defect of synaptic pruning and elucidate the mechanism of sensory integration through analysis of this mouse model.

PRIME Started in 2023 ······ 3rd period

Elucidation of brain system to integrate multi-modal sensory information constructing episodic memory

OHKAWA Noriaki
Associate Professor,
Dokkyo Medical University

Episodic memory is encoded in our brain like a photograph or a diary. During a novel experience, various contextual information composed of multiple sensory information are integrated into one episodic memory. However, it remains unclear how individual memory including various sensory information is encoded in our brain. In this research, by applying our unique technique for multi-channel electrocorticogram recording for mouse, we propose to identify characteristics of large-scale cortical waves expressed across multiple sensory areas at timing when engram cells of the hippocampus are representing memory information. Through this research, we elucidate large-scale brain system to integrate multiple sensory information for encoding and consolidation of one episodic memory.

Functional analysis of hippocampal dCA1 neurons underlying odor information processing.

SAKAMOTO Masayuki
Associate Professor,
Graduate School of Biostudies, Kyoto University

Many living animals, including humans, make various behavioral choices based on odors, such as recognizing food, sensing danger, and identifying mating partners. However, it is not well understood how olfactory information processed in the olfactory bulb is represented in higher brain regions. In this study, I will develop an innovative high-precision measurement technology that allows for the visualization and manipulation of the sensory system, and will elucidate the function of dorsal hippocampal neurons in olfactory information processing.

Therapeutic targeting of macrophage thermosensor in inflammatory diseases

TAKEDA Norihiko
Professor,
The University of Tokyo Hospital

The occurrences or symptom of inflammatory diseases or cardiovascular disorders are strongly influenced by external environment; thus, those disorders are termed as living environment-related diseases. Among them, some of the bacterial and viral infection develops more frequently in winter season. While cold environment is estimated to suppress immune response and inflammatory reaction, the molecular link between cold temperatures and immune system are largely unknown. In this study, we will focus on the effects of cold environments on macrophage activation to explore novel therapeutic approaches to living environment-related diseases.

Elucidation of a novel visceral pain-sensing mechanism and development of therapeutic methods

TANAKA Tatsuhide
Lecturer,
Nara Medical University

Irritable bowel syndrome (IBS) is a functional disorder of the gastrointestinal tract caused by mental stress or autonomic nervous system dysfunction, resulting in abnormal bowel movements and abdominal pain. In this study, we will clarify how the primary afferent nerves distributed in the distal colon receive pain information from the aspect of neuroimmune crosstalk. We hope to develop novel analgesics as molecular targeted therapies for visceral pain in the future.

Defecation mechanism via rectal sensation through the brain defecation center

TANAKA Yoshimasa
Assistant Professor,
Kyushu University Hospital, Hepatology & Pancreatology

Chronic constipation has received increasing attention in recent years because it is a risk factor for cardiovascular and cerebrovascular disease and has a negative impact on life expectancy. One of the causes of constipation is a decrease in rectal sensation, but the mechanism is not fully understood. In this study, we aim to elucidate the mechanism of defecation by rectal sensation through both basic research focusing on the relationship between rectal sensation - brain defecation center - anorectal motility, and clinical research using anorectal function tests in patients with chronic constipation.

Gut sensing system with mesenchymal cells-enteric nervous -central nervous system interaction

TAMADA Hiromi
Assistant Professor,
Graduate School of Medical Sciences, University of Fukui

"Gut-Brain Axis" is one of the current topics in health and medical care fields. In this study, to understand the whole sensing mechanism in the gut, the complicated and unique interactions among mesenchymal cells, the enteric nervous system and the central nervous system are explored from the aspects of morphology and physiology. The novel sensory circuit leads to comprehension of very complex and varied GI sensory mechanisms and functions reflecting them.

Elucidating the human circadian rhythm sensing network using master clock organoids and exploring chronotherapeutic drugs for personalized medicine

TAMIYA Hiroyuki
Assistant Professor,
Institute of Biomedical Science, Kansai Medical University

Our circadian clock is regulateed by the suprachiasmatic nucleus (SCN), the brain's master clock, which integrates multiple inputs including light and other stimuli to define our internal body time. However, it is still largely unknown how the multiple senses are integrated. I've recently succeeded in generating SCN from ES/iPS cells in vitro. In this research, we aim to reproduce the circadian sensing network expanding our SCN organoid system and shed light on the time-information integration mechanism. This work holds promise for creating chronotherapeutic drugs personalized to individual circadian needs.

Development of Innovative Treatment for Intractable Visual Impairment Using Innate Immune Memory to Restore Neuro-Immune Network Alterations and Disrupted Light Sensing Mechanisms

HATA Masayuki
Associate Professor,
Kyoto University

Age-related macular degeneration (AMD), one of the leading causes of blindness in the world, is an intractable retinal disease whose basic pathogenesis is neuroinflammation and pathological angiogenesis caused by innate immune responses. We have shown that past obesity and infection form epigenetic memories in innate immune cells, which accumulate with age, leading to the onset and progression of AMD. In this project, we aim to elucidate the regulatory mechanism of the neuro-immune network by innate immune memory and link it to therapeutic applications.

Elucidating the significance and rule of the neural dynamics change between wakefulness and sleep

NOMOTO Masanori
Associate Professor, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama

As in dreaming, the brain is active not only during wakefulness, but also during sleep. Brain activity during sleep is necessary for memory consolidation and various cognitive functions. However, the mechanism of how the brain processes information on cognitive functions during sleep remains unclear. In this study, we focus on the olfactory pathway, which is not easily affected during sleep, and use an optogenetic pseudo-olfactory stimulation to seamlessly track brain representations and memory information related to smells during wakefulness and sleep. Results of this research will elucidate the dynamics and principle of brain information processing during wakefulness and sleep states.

Study of primate dopamine neural circuit mechanisms underlying impulse control for action selection based on sensory information Professor

MATSUMOTO Masayuki
Professor, Center for the Evolutionary Origins of Human Behavior, Kyoto University

Impulse control is a fundamental ability in our daily life. For example, we can suppress the impulse to reach a destination quickly when we see a trafic red light, and also we can suppress the impulse to obtain a small immediate reward and wait for a large delayed reward. However, this ability is impaired in many psychiatric disorders, which is closely related to the dopamine system. Using macaque monkeys, which are genetically close to humans, this study investiagtes the dopamine circuit mechanism that causes impairments in the ability of impulse control.

Anti-infectives

Generating research infrastructure and novel technologies for anti-infective drug and vaccine discovery

Research and Development Objectives

New approaches in drug and vaccine discovery for infectious diseases

The goal of this R&D area is to establish technologies and infrastructure to accelerate basic research in the field of infectious disease drug discovery.
In order to respond immediately to emerging and re-emerging infectious diseases, we need an understanding of the pathogens involved and the interactions with the host as a prerequisite to the development of prophylactic, diagnostic, and therapeutic interventions. Furthermore, there is a need to accelerate the processes required for clinical application. However, the basic research process has become a bottleneck for drug discovery because of the diversity of pathogens, various phases of disease from acute to chronic and latent infections, and the need to respond immediately during a pandemic. These are problems unique to infectious diseases.
This R&D area aims to address the issues in the basic research phase of infectious disease drug discovery by combining existing drug discovery seeds, infrastructure/technologies, research resources for the discovery of drugs against infectious diseases caused by bacteria, fungi, and viruses, etc.; developing an array of robust drug discovery modalities that ultimately translate into clinical application; and strongly promoting interdisciplinary research. We will accumulate research findings that lead to development of new drug discovery modalities, optimization of existing modalities, and development of new platform technologies. The purpose of this R&D area is to accelerate infectious disease drug discovery as part of our efforts to build expertise to respond immediately when new pathogens emerge in the future.

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AMED-CREST Started in 2021 · 1st period

Study of the host cell membrane and ion dynamics during virus infection

OHBA Yusuke
Professor, Faculty of Medicine, Hokkaido University

In this research and development, we visualize the host cell membrane nano-dynamics that face virus particles during entry using high-speed atomic force microscopy. In addition, we will simultaneously visualize the interactions between virus and host cell molecules and the dynamics of intracellular signaling to understand the host machinery that regulates the virus entry process. Our aim is to decode the "common language" used by viruses to enter host cells and establish the basis for drug discovery targeting such languages.

Generating novel antibacterial capsid technologies toward combating bacterial infection diseases

CUI Longzhu
Professor, School of Medicine, Jichi Medical University

Despite the fact that we are facing an imminent crisis caused by antimicrobial resistant (AMR) bacteria, no effective treatment has yet been found. A more serious problem is that the development of antimicrobials is currently at a standstill. In this study, we proposed to produce phage capsid medicines effective against bacterial infections that are difficult to treat with existing antimicrobial agents by using bacteriophage as a new drug discovery modality. Specifically, we will develop new antibacterial agents, detection reagents, and vaccines against refractory bacterial infectious diseases by packaging various foreign gene cassettes on phage capsid.

Development of novel antimicrobial adjuvants by innovative compound discovery and synthesis methods

SUZUKI Masato
Senior Research Scientist, AntimicrobialResistance Research Center, National Institute of Infectious Diseases

Recently, bacterial infections caused by ESKAPE pathogens and mycobacteria, including nontuberculous mycobacteria, have become a global public health threat. Novel drug discovery for bacterial infections has stalled for decades, which necessitates research and development with different strategies, including re-evaluation of existing compound libraries based on alternative indicators. In this project, we aim to discover and develop novel antimicrobial adjuvants to potentiate the activity of antimicrobials that human beings have developed over a long period of time by using high-content imaging-based compound discovery methods and AI-guided compound synthesis methods.

Study of the molecular mechanism of persistent infection and identifying novel privileged molecular structures for the next-generation antibacterial drug discovery

TAKAYA Akiko
Associate Professor, Graduate School of Pharmaceutical Sciences, Chiba University

The generation of antimicrobial-tolerant cells called persisters is a strategy used by bacteria to develop antimicrobial resistance. However, the molecular mechanisms by which bacteria as persister cells survive by avoiding antibiotics and host immune responses are still unknown. This project aims to elucidate the molecular mechanisms that enable persister cells to survive in harsh environments, determine the activity and efficacy of compounds targeting persister regulators for the treatment of bacterial infections, and identify novel privileged molecular structures for antimicrobial drug discovery.

Infrastructure for anti-infective drug discovery using a synthetic human body model

TAKAYAMA Kazuo
Junior Associate Professor,Center for iPS Cell Research and Application, Kyoto University

To minimize the damage caused by the pandemic of emerging and re-emerging infectious diseases, it is necessary to generate and maintain an infectious disease drug discovery platform that can be used for the rapid development of therapeutic drugs. In this project, we will an in vitro evaluation system with high clinical predictability through development of a virtual human body model. This model will be able to evaluate disruption of biological barriers caused by various pathogens including viruses, particularly the causative virus of respiratory tract infections, and subsequent organ dysfunction.

Establishment of anti-infective human antibody discovery platform leveraging animals with humanized immune system

TOMIZUKA Kazuma
Professor, Laboratory of Bioengineering, Tokyo University of Pharmacy and Life Sciences

On the back of COVID-19 pandemic, there are increasing societal needs for the development of preventive and therapeutic agents. By utilizing our proprietary human antibody-producing animals and mRNA drug discovery technologies we will establish "Express Hu-mAb system" to quickly identify human antibody drug candidates against various infectious diseases. This platform should enable the early implementation of neutralizing antibody therapy that is a key to counter the devastating impact the viruses have in vulnerable populations and in high-risk patients.

AMED-CREST Started in 2022 · 2nd period

Natural product 2.0 for a new modality of drugs for infectious diseases

ASAI Teigo
Professor, Graduate School of Pharmaceutical Sciences, Tohoku University

Natural products are one of the most attractive sources for drug discovery, especially in the field of infectious diseases. In this R&D, we aim to generate unprecedented natural product-based screening sources by leveraging vast genetic resources encoding novel natural products and useful biocatalysts through awaking of silent biosynthetic genes, genome mining, synthetic biology, and chemo-enzymatic synthesis. Our goal is to establish "Natural Products 2.0", a new modality that will be a fundamental technology for sustainable development of drugs for infectious diseases.

Creation of new virology research through innovative reverse genetics

FUKUHARA Takasuke
Professor, Fuculty of Medicine, Hokkaido University

The main objective of this research is to develop and improve rapid and simple reverse genetics methods for various viruses to enable swift production of recombinant viruses in the event of an outbreak of any emerging/re-emerging viruses. With the following five concepts: comprehensiveness, speed, simplicity, application, and library construction - we aim to establish a system that enables not only our own group but also all researchers to start drug discovery rapidly and vaccine development using various recombinant viruses when emerging/re-emerging viruses threaten public health.

Frontier of New Middle Molecule Drug Discovery Field by Targeting Pathogens' Intrinsically Disordered Proteins (IDPs)

MATSUMOTO Sohkichi
Professor, School of Medicine,
Niigata University

Intrinsically disordered proteins (IDPs), which are changing the concept of proteins, are mostly untapped as drug targets since they deviate from the traditional lock and key model of drug discovery. In this proposal, the IDPs of Mycobacterium tuberculosis, which slows down growth and induce dormancy, will be used as a model target, and will be the subject of a research project that combines "Biophysics," "Structural Biology," "Molecular Dynamics Calculation," "Organic chemistry," and "Microbiology." We aim to establish a practical framework to discover anti-IDPs drugs and also develop a therapeutic agent against intractable mycobacterial diseases.

Establishment of platforms for drug discovery and development of novel drugs with broad-spectrum antiviral activity

WATANABE Tokiko
Professor, Research Institute for Microbial Diseases,
Osaka University

Emerging diseases like Ebola, avian influenza, and COVID-19, threaten the global economy and public health. Many of these diseases are caused by RNA viruses; therefore, it is imperative that we prepare for outbreaks of the various types of RNA viruses. In this project, we aim to establish platforms for the development of innovative drugs with broad-spectrum antiviral activity to combat viral diseases. We propose to identify host factors that play universally important roles in the interactions between hosts and various RNA viruses as potential drug targets, and to develop mid-sized molecules (e.g., nucleic acid- and glycan-based drugs) as next-generation antivirals.

AMED-CREST Started in 2023 ····· 3rd period

Development of novel modalities to rejuvenate aged immunity against infectious diseases

OSHIUMI Hiroyuki
Professor, Faculty of Life Sciences,
Kumamoto University

Aging is the most significant risk for infectious diseases, so vaccination is recommended, but vaccines are less effective in preventing infections in older people. In this study, we will develop novel modalities to rejuvenate aging immunity to better protect the elderly from various infection. We will then investigate the effectiveness and mechanisms of candidate modalities in mouse models with the ultimate goal of solving the aging problem.

Study of the development of new modality creation technology against bacterial infections using non-antimicrobial substances

SATO Toyotaka
Associate Professor, Fuculty of reterinary Medicine,
Hokkaido University

This research aims to establish a highly original modality for treating bacterial infections that utilizes substances with physical properties and actions that are different from those of conventional antimicrobial agents. Specifically, we will leverage "non-antimicrobial active substances" and develop a new approach for treating bacterial infections through a new technology that confers antimicrobial activity to these substances.

Bio-hysteresis-based identification of treatment resistance factors in refractory infectious diseases and its application to discovery of universally effective next-generation antimicrobial agents

MINATO Yusuke
Associate Professor, Center for Infectious Disease Research,
Fujita Health University

Development of novel treatment options for chronic bacterial infections, such as nontuberculous mycobacterial infections, for which therapeutic efficacy is difficult to predict, is desperately needed. We will characterize bacterial and host factors using a unique approach we designated "bio-hysteresis analysis" to comprehensively identify treatment resistance factors. Furthermore, we will establish drug target evaluation models that reflect the therapeutic resistance factors and develop a target identification platform for developing new antimicrobial agents that show universal efficacy against a wide variety of refractory cases.

Proteostasis

Understanding proteostasis and discovering innovative medical applications

Research and Development Objectives

Understanding and medical application of proteostasis

This R&D area aims to clarify the relationship between structure and function based on evidence obtained from biochemical and structural biological approaches, to understand the molecular pathways that cause various diseases, and to discover potential solutions for healthcare or methods to maintain good health. The R&D is focused on understanding the molecular basis of proteins during the processes that occur between initial protein translation and synthesis to ultimate degradation, and will investigate denaturation, aggregation, and degradation processes that set proteins on a final, irreversible pathway, as well as posttranslational modifications that have irreversible effects on protein function. Target diseases include, but are not limited to, neurodegenerative disease, mental health disorders, intractable cancers, chronic inflammatory diseases, amyloidosis, fibrosis, rare diseases, infectious diseases, and lifestyle diseases like arteriosclerosis and diabetes, as well as insights into how to avoid aging and maintain a healthy state. As well as researchers involved in the fields of proteins and glycans, we welcome participation by basic science or clinical researchers in structural biology, immunity, metabolism, or nerve systems, as well as researchers from other fields, including analytical chemistry and bioinformatics. The goal is to make progress in world-class, highly innovative research and development by bringing together and leveraging the strengths of a range of disciplines.

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AMED-CREST Started in 2020 · 1st period

Protein aggregation and translation: yin and yang of diseased neurons

IWASAKI Shintaro
Chief Scientist,
Cluster for Pioneering Research, RIKEN

Recent years have seen growing evidence that unbalanced proteostasis leads to neurodegenerative diseases. Although studies have revealed that tight coupling between aggregation and protein synthesis is fundamental for proteostatic regulations, our understanding of the mechanism is quite poor.
Here, we aim to demystify the mutual interactions between protein aggregation and translation in diseased neurons. For this purpose, we will unveil the local translation in axon and its dysregulation in neurodegenerative diseases.

Study of mitochondrial proteostasis controlled by protein trafficking

ENDO Toshiya
Professor, Faculty of Life Sciences,
Kyoto Sangyo University

Most mitochondrial proteins are imported from the cytosol and failure in this mitochondrial protein trafficking leads to the collapse of “mitochondrial proteostasis”, which will deteriorate cellular functions and in human, eventually manifest in ageassociated diseases such as neurogenerative disorders. In this project, we will reveal the roles of protein trafficking and related quality control, including those of PINK1 and MICOS, in the mitochondrial proteostasis primarily by structural biology approaches. We will thus unveil the still elusive mechanisms of the contribution of protein trafficking to the proteostasis, which could represent new targets for preventative and/or therapeutic treatments of aging and aging-related diseases.

Cytosolic Glycobiology – Toward comprehensive understanding of the cellular homeostasis

SUZUKI Tadashi
Chief Scientist, RIKEN Cluster
for Pioneering Research (CPR)

N-Glycosylation occurs in the lumen of the endoplasmic reticulum (ER), and glycosylated proteins are delivered to their respective destinations via a secretory pathway. On the other hand, there are also phenomena in the cytosol, which is segregated from the secretory pathway by a lipid bilayer, for which N-glycans play pivotal roles. We will aim at comprehensive understanding, as well as medical application, of glycan-regulated proteostasis, with particular focuses on NGLY1, a well-conserved de-N-glycosylating enzyme, and FBS proteins, E3 ubiquitin ligase subunits that recognize N-glycans, through diverse approaches.

Study on organelle homeostasis by post-translational modifications

MATSUDA Noriyuki
Professor, Department of Biomolecular Pathogenesis,
Medical Research Laboratory, Institute of Science Tokyo

Organelle homeostasis is maintained through a cycle of biogenesis and degradation. In this process, organelles destined for degradation are distinguished by the autophagy adaptors. Recently, it has become clear that the spatiotemporal aspects of degradation are precisely controlled via coordination of the autophagy adaptors and posttranslational modifications. However, the physiological importance of this highly coordinated process and the molecular mechanisms underlying the coupling of post-translational modifications with organelle degradation are still obscure. Through this project, we aim to clarify the mechanisms underlying recognition and degradation of target organelles, the physiological roles in organelle homeostasis, and the relevance of the process in human diseases.

Study on understanding of the molecular mechanisms of tissue-specific unfolded protein responses for radical cure of human chronic diseases

MORI Kazutoshi
Deputy Director-General and Distinguished Professor,
Kyoto University Institute for Advanced Study

Social demand for development of radical cure methods to chronic diseases such as neurodegenerative diseases, nonalcoholic steato-hepatitis, and chronic kidney disease is extremely high in these days. Endoplasmic reticulum (ER) stress (accumulation of unfolded/misfolded proteins in the ER) is a key for development and progression of various chronic diseases. Therefore, all eukaryotic cells are equipped with a signaling cascade termed the unfolded protein response (UPR) to cope with ER stress We will deepen the understanding of the molecular mechanisms of tissue-specific UPRs, which will lead to paradigm shift in the understanding of unmet chronic diseases and development of radical therapy.

AMED-CREST Started in 2021 · 2nd period

Study on chemical proteostasis: novel mechanisms of protein quality control ensured by the cooperation of redox, pH and metal ions

INABA Kenji
Professor,
Medical Institute of Bioregulation, Kyushu University

Over the past decades, many scientists have studied on molecular chaperones that assist in productive protein folding, and degradation systems that eliminate misfolded proteins. Here, we aim to elucidate novel protein quality control systems ensured by three chemical parameters, namely, redox, pH, and metal ions, in the early secretory pathway comprising the ER and Golgi. To this end, we employ comprehensive approaches including structure analysis, live-cell imaging, and proteomics. We focus particularly on membrane transporters that govern these chemical parameters in cells, and elucidate the close linkage of their loss of function to diseases. In this context, we will also develop inhibitors specific to the membrane transporters.

The neo-ubiquitin code for improving proteostasis dysregulation

OHTAKE Fumiaki
Associate Professor,
Hoshi University, Institute for Advanced Life Sciences

We clarify the formation and decoding mechanisms of the "neo-ubiquitin code" responsible for the degradation of abnormal proteins such as those that cause neurodegenerative diseases. Our goal is (i) to understand the mechanism of proteostasis maintenance from the standpoint of the ubiquitin–proteasome system, and (ii) to develop a basis for chemical control of proteostasis. Using quantitative proteomics, we will elucidate the mechanism by which aberrant proteins are decorated with the neo-ubiquitin code and are delivered to the proteasome. We will also analyze proteostasis by using newly developed model mice and synthesize chemicals to degrade aberrant proteins that cause neurodegeneration.

Comprehensive study of in vivo protein folding in proteostasis network

TAGUCHI Hideki
Professor,
Institute of Innovative Research, Institute of Science Tokyo

All proteins in cells are synthesized via translation at the ribosome, folds into correct tertiary structures, and are translocated to the appropriate place to perform their function. Protein folding is essential for life as the first step in the proteostasis network. Although its disruption or perturbation is known to lead to many human diseases such as cystic fibrosis, the molecular mechanism is not well understood. This project aims to elucidate the mechanism of cotranslational folding of disease-related proteins by introducing novel experimental approaches from the reconstituted level to the cellular level and lead to novel therapeutic strategies and drug discovery.

Studies on amyloid formation and disaggregation mechanisms and medical applications for neurodegenerative diseases

TANAKA Motomasa
Team Leader,
RIKEN Center for Brain Science

Amyloid deposition in the brain is associated with many neurodegenerative diseases. Therefore, the formation and disaggregation of amyloid are the key processes for neurodegeneration including cell-to-cell propagation of amyloid. However, molecular mechanisms of amyloid disaggregation have been poorly understood due to the lack of appropriate techniques and experimental systems. To address this long-standing question in amyloid biology, we aim to decipher amyloid disaggregation process by developing new biophysical methods and less-invasive, in vivo imaging techniques. Furthermore, we will develop novel techniques for selective disaggregation and degradation of amyloid in cellular and mouse models of neurodegenerative diseases. These studies will provide important implications for therapeutic development.

Molecular basis for progressive and age-related cardiorenal damages mediated by irreversible protein methylation

FUKAMIZU Akiyoshi
Professor, Life Science Center for Survival Dynamics,
Tsukuba Advanced Research Alliance, University of Tsukuba

Heart and renal failures induced by cardiorenal damages are one of the leading cause of death in the world, and they are known to affect our quality of life (QOL). Although the modification of proteins such as methylation is required for regulating cellular actions, little is known regarding the roles for protein methylation in tissue damages. In this project, combining approaches of biochemistry, bioinformatics, and structural biology, we will unlock molecular basis for progressive and age-related cardiorenal damages mediated by irreversible protein methylation.

AMED-CREST Started in 2022 — 3rd period

Regulation and Disruption of Neuronal Circuit Formation by Glycans: Pathophysiology of Mental Disorders

KADOMATSU Kenji
Professor,
Nagoya University Graduate School of Medicine

Glycans are beginning to be understood to induce plastic changes such as synapse formation and removal by regulating protein-glycan interactions to generate structural plasticity in neurons. In this study, we will apply a new technology that enables comprehensive acquisition of glycan structures and use patient-based materials such as iPS cell-derived brain organoids to understand the neural regulatory functions of glycans in a multilevel manner and elucidate pathological conditions caused by glycan alterations through a single integrated study from genome to glycoproteins and neural circuits.

Analysis of Golgi proteostasis and its medical application

SHIMIZU Shigeomi
Professor,
Pathological Cell Biology, Institute of Science Tokyo

Golgi membrane-associated degradation (GOMED) plays a central role in Golgi proteostasis, which is a qualitative and quantitative regulation of plasma membrane proteins and secreted proteins. In this study, we will clarify where and when GOMED is executed in our body. In addition, we will conduct drug discovery and development research for diseases caused by GOMED abnormalities.

Elucidation of mechanisms underlying degradation of misfolded proteins in neurons and their role in neurodegenerative diseases

NAKANISHI Makoto
Professor, Institute of Medical Science,
The University of Tokyo

Failure of protein quality control (PQC) system promotes the accumulation of misfolded proteins and is closely associated with various age-related changes. Especially in the nervous system, the impaired PQC system is directly related to various symptoms of brain aging. In this research project, we will uncover the molecular and structural basis for selective removal of misfolded proteins. Based on these findings, we will also elucidate the pathophysiology of various age-related diseases, including neurodegenerative diseases.

Elucidation of Proteostasis Regulation by Intracellular Membrane Dynamics for Healthy Longevity

YOSHIMORI Tamotsu
Specially appointed professor, Graduate School of Medicine
Division of Health Sciences, Osaka University

The autophagy and endocytosis pathways, which transport proteins to lysosomes for degradation and recycling of proteins inside and outside the cell, are important membrane dynamics for proteostasis regulation. Abnormalities in these membrane dynamics lead to accelerated aging and shortened lifespan. This research aims to clarify the molecular background of proteostasis regulation by lysosome-associated membrane dynamics and to create seeds that will lead to the healthy longevity, thereby solving an urgent problem in our super-aging society.

PRIME Started in 2020 ····· 1st period

Phase-separation-initiated proteolysis by degraders (*)

ARIMOTO Hirokazu
Professor, Graduate School of Life Sciences, Tohoku University

Autophagy, an intracellular degradation system, contributes to the suppression of diseases and aging by removing harmful materials. In this study, we aim to create new compounds that promote the selective removal of the harmful materials through autophagy by elucidating the importance of liquid-liquid phase separation in the mechanism of selective autophagy.

The quality control mechanisms of nascent organellar proteins (*)

IZAWA Toshiaki
Associate Professor, University of Hyogo, Graduate School of Science

Accumulation of aberrant proteins is a common feature of neurodegenerative diseases such as Alzheimer's, Parkinson's or Huntington's disease. Recent studies have revealed that aberrant proteins produced by failure of translation can be tagged at their C-terminus with multiple alanyl and threonyl residues, so called "CAT-tail". However, its function and physiological significance are poorly understood. In this study, I will uncover the roles of CAT-tail by focusing on the fate of organellar proteins and establish the molecular basis for regulation of CAT-tailing and cellular proteostasis.

Understanding of cell-type-specific proteostasis of ribosome and elucidation of novel disease development mechanism (*)

IWASAKI Mio
Junior Associate Professor, Center for iPS Cell Research and Application, Kyoto University

Diamond-Blackfananemia (DBA) is a disease caused by ribosomal protein mutations with malformations such as impaired erythropoiesis, microcephaly, and micrognathia. Multiple gene mutations have been reported in ribosomal genes for DBA disease. However, these mutations cannot be found for about 40% of DBA patients, suggesting there must be another mechanism of disease development. In this study, I focus on proteostasis of ribosomal proteins responsible for DBA disease to know a novel factor is involved in the control of the disease onset.

Development of Ultra-sensitive Quantitative Glycome Analysis Method and Elucidation of Spatial Glycostasis in Tissue Microenvironment and its Medical Application (*)

KAWAI Takayuki
Associate Professor
Faculty of Science, Kyushu University

Glycosylation is an important post-translational modification of proteins. However, there has been no standard method that achieved sensitive and quantitative profiling of glycans, hindering researches on glycobiology. In this research project, an ultra-sensitive capillary electrophoresis technique will be applied to achieve 10 zmol (6200 molecules) detectability and absolute quantitation in glycan analysis. Based on this next-generation glycome analysis, we aim to clarify unknown functions of glycans in pathogenic tissue microenvironment.

Proteostatic regulation for maintaining the function of adult neural stem cells (*)

KOBAYASHI Taeko
Associate Professor, The Institute of Medical Science, The University of Tokyo

The majority of neural stem cells in the adult mammalian brain are quiescent. Quiescence is essential for retaining adult neural stem cells for a long period, and its dysregulation contributes to a decline of brain function. I have revealed the significant involvement of lysosomes in quiescence of neural stem cells. In the current study, I aim to elucidate the molecular mechanism to control proteostasis in quiescent and proliferating neural stem cells. I focus on proteostatic changes via physical properties of extracellular environments and develop a new approach for maintaining the function of adult neural stem cells.

Use of polySia-NCAM for development of diagnosis and treatment of mental disorders (*)

SATO Chihiro
Professor, Graduate School of Bioagricultural Sciences and Institute for Glyco-Core Research, Nagoya University

The diagnosis and treatment of the mental disorder are the urgent problem worldwide. Many mental disorders-associated molecules are reported to show structural and functional abnormalities in brain. Precise understanding of the molecular mechanism of functions of those molecules would finally lead to a new drug discovery in diagnosis and treatment. Focusing on polysialylated NCAM (polySia-NCAM), whose impairments are known to be related to mental disorders, such as schizophrenia, bipolar disorder and autism, this project seeks to understand its proteostasis in normal and pathogenic states.

Study of cellular proteostasis dynamics by imaging or manipulation of proteasome activity (*)

HAMAZAKI Jun
Lecturer, Graduate School of Pharmaceutical Sciences, Tokyo University

The proteasome plays an essential role in proteostasis by the degradation of ubiquitinated proteins. In recent years, it has been known that the expression level of proteasome influences the onset of cancer or neurodegenerative diseases and lifespan in model organisms. In this project, I will establish a method to quantitatively evaluate or image cellular proteostasis level, mainly monitored by proteasome activity. Furthermore, I will establish a method to manipulate proteasome activity based on the elucidation of the regulation mechanisms of the proteasome.

Mechanism of autophagy driven by liquid-liquid phase separation (*)

FUJIOKA Yuko
Associate Professor, Institute for Genetic Medicine, Hokkaido University

Accumulation of denatured proteins in cells, which is caused by ageing, leads to onset of severe diseases such as neurodegeneration and cancer. Autophagy protects us from these diseases by degrading proteins and providing amino acids for synthesis of new proteins. In this study, I aim to elucidate the molecular mechanisms of autophagy initiation and sequestration of proteins into autophagosomes using the concept of phase separation of proteins.

Study for physiological regulation and cancer metastasis through modification with glycerol phosphate as a glycosylation termination factor of dystroglycanof dystroglycan (*)

YAGI Hirokazu
Associate Professor, Graduate School of Pharmaceutical Sciences, Nagoya City University

In our previous study, we discovered a novel post-translational modification in which the non-reducing end of a dystroglycan glycan was capped with glycerol phosphate (GroP). Such capping suggests that GroP suppresses elongation of glycan chains. More interestingly, we recently found that GroP expression was enhanced in colon cancer cells with high metastatic capability. Thus, the proposed study aims to elucidate physiological regulation and cancer metastasis through modification with glycerol phosphate operating as a glycosylation termination factor of dystroglycans. This study will also attempt to develop anticancer drugs targeting GroP.

PRIME Started in 2021 ····· 2nd period

Understanding and control of cytotoxic TDP-43 phase transition

ASAKAWA Kazuhide
Associate Professor,
National Institute of Genetics

Amyotrophic lateral sclerosis (ALS) is a fatal neurological disorder characterized by progressive degeneration of motor neurons in the brain and spinal cord. A major hallmark of ALS is the deposition of cytoplasmic inclusions containing aggregates of the RNA/DNA-binding protein TDP-43. In this study, by using an optogenetically controllable TDP-43 variant, we aim to reveal the mechanisms of TDP-43 cytotoxicity and develop methods to intervene toxic TDP-43 phase transition in the motor neurons, which present a potential avenue for novel ALS therapeutics.

Ubiquitin-dependent proteasome phase separation for maintaining proteostasis

ENDO Akinori
Associate Investigator,
Department of Basic Medical Sciences,
Tokyo Metropolitan Institute of Medical Science

Proteolysis mediated by the ubiquitin-proteasome system plays an essential role in the regulation of proteostasis. It has been speculated that dysregulations in this system lead to neurodegenerative diseases, however, the direct causal relationship remains elusive. In this program, I will investigate the molecular mechanism of proteostasis regulation by ubiquitin-proteasome phase separation and evaluate the hypothesis that defects in the regulation of ubiquitin-proteasome phase separation cause neurodegenerative diseases, aiming to further understand proteostasis and establish a basis for new therapeutic strategies for neurodegenerative diseases.

Study on the novel complexed ubiquitination-regulated cell death and its involvement on the inflammatory bowel diseases

OIKAWA Daisuke
Associate professor,
Department of Medical Biochemistry, Graduate School of Medicine, Osaka Metropolitan University

Protein ubiquitination generates a variety of ubiquitin chains via seven lysine residues and N-terminal methionine residues in the ubiquitin molecule, as well as complexed ubiquitination including multiple types of linkages, such as hybrid and branched chains, and regulate a variety of cellular functions. This project aims to elucidate the details of the complexed ubiquitination that regulates cell death, and to clarify the molecular background of inflammatory bowel disease caused by its functional disruption, to create seeds for drug discovery and health maintenance.

Study of development of interventions for aged-related diseases and longevity based on understanding of proteostasis during aging

JOHMURA Yoshikazu
Professor, Division of Cancer and Senescence Biology, Cancer Research Institute, Kanazawa University

Senescent cells in living organisms originate from various cell types, and it is assumed that heterogeneous inducing mechanisms and functional diversity thereof differ greatly depending on the cell types contained in organs and tissues. Therefore, in this study, by performing omics analysis using mice capable of identifying, isolating, tracing, and genetically modifying at the single-cell level, the proteostasis dysfunction of senescent cells in individual aging and aging-related diseases would be investigated. Furthermore, the underlying mechanisms and regulatory factors behind them will be also extensively clarified.

Development of Innovative Therapeutics for Neurodegenerative Diseases Based on the Understanding of Lysosome Maintenance Mechanisms

SHIRAKAWA Ryutaro
Lecturer, Institute of Development,
Aging and Cancer, Tohoku University

The elimination of abnormal proteins by the autophagy-lysosome pathway is known to be important for the prevention of many diseases including neurodegenerative disorders. In this study, we aim to elucidate the molecular mechanism of autophagosome-lysosome membrane fusion by the atypical SNARE protein Ykt6, which undergoes a rare posttranslational modification with double prenyl groups, and to identify new therapeutic pathways for neurodegenerative diseases.

Comprehensive analysis of the slit diaphragm that plays a role in the clearance of proteins in body fluid

FUJITA Naonobu
Associate professor, Cell Biology Center,
Institute of Integrated Research, Institute of Science Tokyo

This study aims to elucidate the relationship between the clearance of body fluid proteins in the kidney and the pathogenesis of systemic amyloidosis. Using a high-throughput in vivo RNAi screening system, I will also uncover the mechanisms shaping the renal slit diaphragm, which plays a central role in the filtration of body fluids. This study would provide important clues for establishing new therapeutic strategies for chronic diseases; systemic amyloidosis and kidney diseases.

The regulation of amyloidostasis using the amyloid-selective Histidine oxygenation

HORI Yukiko
Associate Professor, Laboratory of Neuropathology and Neuroscience, Graduate School of Pharmaceutical Sciences, The University of Tokyo

There is a strong need to establish disease-modifying therapies for neurodegenerative disorders, such as Alzheimer disease. Since these diseases are caused by amyloid deposition, the regulation of amyloidostasis in vivo is important as therapeutic strategy. We provide the amyloid-selective artificial oxygenation, which is our original technology using oxygenation catalyst to regulate amyloidostasis. In this study, to show the possibility of this technology as new therapeutics approach, we would like to reveal the mechanisms of amylodiostasis by oxygenation and develop the new oxygenation technology that is applicable for humans.

Regulation of proteostasis and disease development by Non-AUG translation initiation

MATSUMOTO Akinobu
Professor, Group of gene expression and regulation, Department of Biological Science, Graduate School of Science, Nagoya University

We have developed a new method named TISCA (Translation Initiation Site detection by translation Complex Analysis) to precisely identify initiation codons, and found that a large number of proteins are translated from Non-AUG initiation codons. Translation from the Non-AUG initiation codon significantly increases the complexity of the proteins. In this study, I aim to elucidate the mechanism of proteostasis regulation and diseases related to Non-AUG translation initiation.

Proteostasis through selective autophagy in vivo: from the molecular mechanisms to disease states

MORISHITA Hideaki
Professor, Department of Molecular Cell Biology, Graduate School of Medical Sciences, Kyushu University

In order for a living organism to develop normally and maintain homeostasis, a system that selectively degrades intracellular proteins and organelles should be essential. In this study, we will focus on "selective autophagy," a typical selective degradation system, and use zebrafish and mice to elucidate its role in various intracellular degradation phenomena in vivo, as well as the mechanism of cooperation with other degradation systems. Through this research, we aim to achieve a comprehensive understanding of various intracellular degradation mechanisms.

Disruption of Organelostasis and Vascular Disease

MORITO Daisuke
Associate Professor,
Showa University School of Medicine

Technological innovations such as imaging and mass spectrometry are changing the face of cell biology. Organelles, which were previously thought to be homogeneous and independent structures, actually have heterogeneous and complex structures, and seem to form a complex network. We will analyze the mechanism of organelle homeostasis and the vascular damage caused by its disruption.

RNA phase transition induces dysfunction of cellular proteostasis on prion-like proteins

YABUKI Yasushi
Associate Professor, Institute of Molecular Embryology and Genetics, Kumamoto University

G-quadruplex (G4) is one of DNA/RNA secondary structures which consist of G-rich sequences. We have recently demonstrated that G4RNA phase transition triggers to agglutinate prion-like proteins associated with a hereditary neurodegenerative disease. In the present study, we will elucidate a common mechanism underling dysfunction of cellular proteostasis on prion-like proteins by G4RNA phase transition in sporadic neurodegenerative disorders.

PRIME Started in 2022 ····· 3rd period

Regulation of inner nuclear membrane proteostasis

ARII Jun
Associate Professor, Center for Infectious Diseases, Graduate School of Medicine, Kobe University

A collapse of proteostasis in the membranous organelles can result in various diseases including hereditary disorders. Recently, the inner nuclear membrane (INM)-specific protein degradation systems have been reported, but their full details are unknown. The aim of this R&D program is elucidation of the INM-specific proteostasis regulation system and development of an innovative therapy that can help treat the diseases caused by abnormal protein accumulation at the INM.

Dissecting the mechanisms of phase separation formation and barrier homeostasis of epithelial tissues in stress response

ODA Yukako
Professor,
Graduate School of Biostudies, Kyoto University

In epithelial cells, the barrier function is carried by cell–cell adhesions called tight junctions (TJs). Regulation of TJ formation is important because disruption of TJs leads to inflammation and cancer progression. Recently, it has been reported that phase separation of ZO-1 promotes TJ formation. In this study, we will clarify the mechanism of ZO-1 phase separation to TJ formation and the role of TJ formation in the stress response of epithelial tissues.

Understanding the proteostasis linkage inside and outside the endoplasmic reticulum via co-translational degradation

KADOWAKI Hisae
Assistant Professor,Department of Biochemistry and Molecular Biology, Faculty of Medicine, University of Miyazaki

Protein quality is strictly regulated. Proteins that are not properly translated, folded, and transported are either repaired or degraded. When this protein quality control system is disrupted, the protein aggregation occurs, triggering a variety of diseases. This project aims to elucidate the molecular mechanisms by which proteins synthesized in the endoplasmic reticulum (ER), such as secretory proteins, are co-translationally degraded in the cytoplasm during ER stress, thereby maintaining proteostasis inside and outside the ER. Furthermore, I will attempt to develop novel molecular targets for the treatment of neurodegenerative diseases.

Single-cell covariation network analysis for proteostasis of metabolism-related proteins

KANO Fumi
Professor,
Institute of Innovative Research, Institute of Science Tokyo

By combining the cell image-based network analysis with the unique multiplex immunofluorescence method, we establish the novel single-cell covariation network analysis, that enables protein correlation analysis at the specific condition and time point. In this study, we focus on the proteostasis of metabolism-related proteins, and create a covariation network during neuronal differentiation of healthy or Alzheimer's disease patient-derived iPS cells. We will elucidate the regulatory mechanisms of how proteostasis of metabolic proteins respond to fluctuating intracellular environment by cell cycle, neuronal differentiation, and pathological conditions of Alzheimer's disease.

Study of synaptic proteostasis and its defects in neuronal disease

KISE Yoshiaki
Associate Professor,Graduate School of Science, The University of Tokyo

Neurons rely on the spatiotemporal protein quality control for their proper functions. Neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease are reportedly caused by the defects in the local proteostasis of the synaptic proteins. This study aims to reveal the mechanism of the synaptic proteostasis by structural biology using cryo-EM, thereby contributing to the development of the novel therapeutic strategies to cure neurodegenerative diseases.

Endothelial amyloid b precursor protein: posttranslational modification, proteostasis and clinical application

KITAZUME Shinobu
Professor,Clinical Laboratory Sciences, Fukushima Medical University

We have recently generated a new Alzheimer's disease (AD) model mouse, in which human amyloid b precursor protein (APP) is specifically expressed in the vascular endothelial cells. By crossing the mice with AD model mice, the resulting mice exhibited massive vascular amyloid deposition with age. In this research project, we focused on endothelial APP and elucidate the molecular mechanism by which the post-translational modification of APP is linked to the Aβ production pathway, and to clarify the in vivo fate of endothelial APP.

Function and mechanism of chaperone RNA maintaining proteostasis in the cell

KITAMURA Akira
Associate Professor, Faculty of Advanced Life Science, Division of Functional Life Sciences, Hokkaido University

Based on various challenges in the molecular and cellular biology field, we know well that protein-based molecular chaperones make a significant contribution to the maintenance of proteostasis. However, is it true that the molecules that play the role of molecular chaperones are limited to proteins? This question was our starting point. We are now elucidating how RNAs with molecular chaperone functions, i.e., chaperone RNAs, work dynamically on proteins in the cell.

Study on proteostasis control of polar-localized membrane proteins and related diseases

SEGAWA Katsumori
Professor,Medical Research Institute, Institute of Sciecne Tokyo

Bile acid transporters are polarly localized in epithelial cells, and their proteostasis is tightly regulated. Flippases are molecules that distribute membrane phospholipids asymmetrically, and their mutations disrupt the proteostasis of bile acid transporters, leading to progressive familial cholestasis (PFIC). This study aims to elucidate the molecular mechanism of membrane lipid-mediated proteostasis of bile acid transporters and the pathogenesis of PFIC.

Chronoproteostasis: Mechanisms and clinical approach for the circadian rhythm sleep disorder by dysfunction of protein proteostasis.

HIRANO Arisa
Assistant Professor,Faculty of Medicine/ WPI-IIIS, University of Tsukuba

Circadian clock is a fundamental biological system regulating many physiologies showing 24-hour rhythms, and disruption of circadian rhythms is known to induce various physical and mental disfunctions. The circadian molecular oscillation is tightly regulated by proteostasis of clock proteins (chronoproteostasis). In this study, we used circadian rhythms sleep disorders model mice and try to understand the mechanism and impact on physiology of the disorders caused by abnormal chronoproteostasis. We also aim to establish a method of medical intervention for the circadian rhythms sleep disorders.

Molecular basis of proteostasis in pancreatic β cell of pre-diabetes

MIYAKE Masato
Associate Professor, Institute of Advanced Medical Sciences, Tokushima University

Proteostasis in the endoplasmic reticulum is important for insulin production and secretion in pancreatic β cells to maintain glucose metabolism. Disruption of proteostasis by over-production of insulin to compensate for insulin resistance reduces its secretion, leading to the onset of type 2 diabetes. In this study, I aim to clarify the changes in proteostasis in pre-diabetes, especially focusing on translational regulation and molecular interactions. This project will contribute to the development of a therapy for type 2 diabetes by restoring pancreatic β-cell function.

(＊) indicates completed R&D projects.
Institution names, affiliations, and titles are as of the final year.

Early Life Stage

Understanding of the Biological Phenomena and Responses at the Early Life Stages to Improve the Quality of Health and Medical Care

Research and Development Objectives

Molecular understanding of the biological phenomena and responses at the early life stages to improve the quality of health and medical care

The goal of this R&D area is to develop a comprehensive understanding of various biological phenomena at the early stage of life (between fertilization and young adulthood) and the effect of environmental factors on the body during that period for better health and medical care in the future.
Over the past decade, we have come to understand that various biological and environmental factors at the early stage of life later affect health and disease. There have also been a series of studies suggesting that these factors could be risk factors for disease during middle-to-late stages of life (from adulthood into old age) and that the risk factors can even be passed on to subsequent generations.
Research focusing on the early stages of life is expected to contribute to improved quality of life (QOL) across all stages.
To develop an understanding of biological phenomena and responses at the early life stages, this R&D area will bring together and promote interactions between scientists from diverse fields, including basic biology, medical science, agriculture, engineering, and informatics. This R&D area also aims to establish analytical technology platforms to deepen our understanding, develop applications for these technology platforms, and discover new control technology seeds.

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Member of the Managing Board and Senior Executive officer, Senior Managing Director, CTO, Sysmex Corporation

AMED-CREST Started in 2019 · 1st period

Elucidation of the mechanisms underlying human placental development and design of a placenta-on-a-chip platform

ARIMA Takahiro
Professor , Tohoku University
Graduate School of Medicine

In this study, we aim to understand the molecular mechanisms underlying human placental development and pregnancy-related diseases. Firstly, we perform epigenome analyses of disease-specific placentas, and identify epigenetic mutations and identify diagnostic biomarkers. Secondary, we establish disease-specific Trophoblast Stem (TS) cells and clarify the molecular mechanisms causing these diseases. We contribute International Human Epigenetic Consortium (IHEC). Lastly, we establish a three-dimensional TS cell system (an artificial placenta) using a channel device to recapitulate placental development and function in vitro.

Elucidating cellular and molecular mechanisms of Tfh2 response in allergy in human infants and toddlers

UENO Hideki
Professor, Graduate School of Medicine,
Kyoto University

The main goal of this project is to establish the molecular mechanism underpinning the development of exaggerated Tfh2 response in allergic infants/toddlers in humans and to define the target pathways to prevent it. Integrative analyses of the multi-hierarchical comprehensive data at single-cell level with cutting-edge mathematics will allow us to identify molecular pathways that determine cell fates and functions. We anticipate that this study 1) will reveal fundamental immunological events causing allergic symptoms in infants and toddlers, and 2) will yield novel strategies to prevent the development of allergic responses in infants and toddlers, and eventually to decrease the population with allergy.

Innovative imaging platform for elucidating pathophysiology of neurodevelopmental disorders

OKABE Shigeo
Professor, Graduate School of Medicine,
The University of Tokyo

Accumulating evidences indicate inappropriate neural connectivity and dysregulation of experience-dependent remodeling as pathological bases of autism spectrum disorder (ASD) and schizophrenia. In this project we develop an innovative imaging platform by applying state-of-the-art synapse nano-imaging technology together with in vitro differentiation and in vivo transplantation of patient-derived human induced pluripotent stem cells (iPSCs). We create a new imaging-based platform for “nanoscale synapse pathology” and identify the molecular mechanisms of the core synapse pathophysiology using efficient imaging-based assays both in vitro and in vivo.

Regulation of embryonic neural stem cells and its relation to postnatal brain development and autism spectrum disorder

GOTOH Yukiko
Professor, Graduate School of Pharmaceutical Sciences, The University of Tokyo Principal Investigator, International Research Center for Neurointelligence (IRCN), The University of Tokyo

Modulation of proliferation and differentiation processes of neural stem-progenitor cells (NSCs) during early developmental stages can affect the size and function of the brain at postnatal and adult stages. In this project, we aim to understand the mechanisms underlying the control of embryonic NSC fate and how their defects of such regulation may cause long-lasting changes in the brain such as those related to autism spectrum disorder (ASD). Maternal immune activation (MIA) during pregnancy increases the risk to the embryo for development of ASD later in life. We therefore also aim to reveal the effects of MIA on embryonic NSCs and immune cells and how they relate to brain malfunction associated with ASD.

Molecular basis for fetomaternal immune cross-talk controlling homeostasis and disease susceptibility

FUKUI Yoshinori
Distinguished Professor, Medical Institute
of Bioregulation, Kyushu University

Although the unique system to defend and cherish our offspring has been evolved via fetomaternal immune cross-talk, the molecular basis remains unknown. In this project, we are going to reveal the mechanism controlling fetus-associated immune privilege and clarify the pathophysiological roles of maternal antibodies transferred to their offspring. In addition, we will examine how maternal inflammation affects susceptibility to allergic diseases and neurodevelopmental abnormalities, and identify the key molecule involved in the pathogenesis of each disease. Particularly, we will focus on atopic dermatitis (AD), a representative allergic disease in the early life stage, and develop drug seeds for controlling AD-associated itch.

AMED-CREST Started in 2020 · 2nd period

Identification of the mechanisms of epigenetic fragility and strategy to prevent AYA cancers

USHIJIMA Toshikazu
President,
Hoshi University

Many types of cancers in adolescents and young adults (AYAs) can be more aggressive than their adult counterparts, but the mechanisms are mostly unknown. In this project, we focus upon epigenomic plasticity of AYA tissue stem cells, and will demonstrate that plasticity turns into fragility when exposed to chronic inflammation, such as H. pylori-triggered gastritis. Molecular mechanisms of epigenetic plasticity and fragility in AYAs will be identified, and a strategy to prevent aggressive cancers in AYAs will be established.

Elucidation of the molecular basis of environmental memory from early life that prevents lifestyle diseases

SAKAI Juro
Professor, Tohoku University,
Graduate School of Medicine,
Division of Molecular Physiology and Metabolism

Paternal exposure to cold environmental temperature prior to reproduction results in offspring exhibiting greater energy consumption and heat generation. These traits counteract the deleterious effects of overnutrition, such as obesity and metabolic syndrome. In this study, using single-cell analyses, we will elucidate mechanisms of epigenetic memory in the central nervous system-adipose axis that mediate adaptation to cold. We will identify and manipulate candidate genes in a cell-type-specific manner in mice. We will confirm our studies in humans by analyzing relationships between thermogenic brown adipose tissue activity assessed as fluorodeoxyglucose-positron emission tomography and paternal environment.

Elucidation of common mechanistic principle for environmental change-induced neuropsychiatric disorders and development of a therapeutic strategy using completely noninvasive cell replacement

NAKASHIMA Kinichi
Professor, Graduate School of Medical Sciences, Kyushu University

Mutations in the methyl DNA binding protein MeCP2 and changes of environmental factors in early life stages are known to be involved in the development of neuropsychiatric diseases, while the precise mechanisms are largely unknown. In this project, we will elucidate molecular mechanisms shared among these diseases. Furthermore, we will develop a novel strategy to treat neuropsychiatric diseases by replacing malfunctional cells with normal ones through completely noninvasive cell replacement.

Elucidation of metabolic and immune imprinting by prenatal exposure to maternal gut environmental factors

HASE Koji
Professor,
Faculty of Pharmacy, Keio University

Accumulating evidence has revealed that antibiotic treatment early in life enhances the incidence of allergic diseases and metabolic syndromes, although the underlying mechanism remains to be clarified. We recently determined that, upon exposure to a high-fat diet, offspring from germ-free mothers develop severe metabolic syndrome characterized by obesity and glucose intolerance. Our proposed research seeks to clarify the molecular mechanism by which maternal gut microbiome program embryonic energy metabolism. The second objective aims to dissect the biological significance of the maternal gut microbiome in the regulation of uterine decidual immunity.

AMED-CREST Started in 2021 — 3rd period

Researches on developmental control of pain sensitivity in peripheral tissues and novel platforms for studying pain development

EMOTO Kazuo
Professor, Department of Biological Sciences, Graduate School of Science, The University of Tokyo

In this research, our goal is to elucidate the mechanisms of how individual pain sensitivity is defined by external factors as well as genetic factors in early-life and how its dysfunction leads to related disease such as hyperalgesia and neuropathic pain. We will focus on molecular and cellular mechanisms that fine-tune pain sensitivity in the nociceptive circuits in peripheral tissues using fruits fly and mice as model systems. In addition, we seek to establish an ex vivo culture system for a 3D human skin tissues with nociception that is supposed to contribute to novel drug screens and biomaterial development.

Creating innovative human embryology using stem cells

TAKASHIMA Yasuhiro
Associate Professor,
Kyoto University, CiRA,

The knowledge of human early development especially just after implantation into the uterus is limited due to ethical and technical reasons regarding in vivo human embryo research. In this project, to understand early human development, we will establish more robust and precise stem cell-based 3D models in vitro developmental models. Using these models, we will generate genetic and epigenetic catalogues of human peri-implantation together with imaging modalities. To carry out our R&D while respecting appropriate ethical considerations, we will investigate domestic and foreign regulations on human development research and establish a research ethics consultation system.

Study on the dynamism of subplate neural activity during brain development

OHTAKA-MARUYAMA Chiaki
Project leader, Developmental Neuroscience Project, Department of Brain & Neuroscience, Tokyo Metropolitan Institute of Medical Science

During fetal brain development, the migration, arrangement, and neuronal circuitry of a huge number of neurons are precisely controlled, and subplate neurons (SpNs) play a crucial role in this process. Although SpN dynamics are associated with developmental disorders, the detailed mechanism remains unclear. Our research team will unravel the relationship between SpNs and neural network development in mice and humans at various levels to understand how transient early neural networks affect the permanent neural networks that continue throughout life.

PRIME Started in 2019 — 1st period

Clarification of neuronal network maturation in early life stages (*)

ITO-ISHIDA Aya
Team Leader,
RIKEN Center for Brain Science

The brain is composed of multiple regions connected by synapses that undergo dynamic changes during postnatal development. While this process is influenced by both genetic and environmental factors, the exact mechanism which regulates neuronal circuitry maturation remains unclear. The aim of this project is to clarify how neuronal circuitry matures in early life stages. To achieve this aim, we will visualize neuronal circuitry using viral tracing tools and identify key molecules responsible for the circuitry development. Recent fMRI studies in individuals with autism have detected abnormalities in long-range connectivity between various brain areas. Findings from our study will provide essential knowledge to understand how neuronal connectivity is altered in developmental disorders.

Developing treatment for abnormal emotional circuits in early-life stress model (*)

UEMATSU Akira
Team Leader, Human Informatics and Interaction Research Instute, National Institute of Advanced Industrial Science and Technology

Fear extinction models, where previously learned fear is weakened by repeated presentation of fearful stimuli, have a key role in our understanding of anxiety disorders and their treatment. Malfunction of fear extinction results in mental disorders. In fact, early-life stress (ELS) causes extinction deficit and anxiety disorders in adulthood. However, it is not clear how ELS affects specific neural circuits for initiating extinction. Thus, I propose to identify 1) novel pathway which controls initiation of fear extinction, 2) how this neural circuit is affected by ELS, and 3) develop optogenetic or genetic manipulation in a circuit specific manner.

Molecular and neural mechanism of polyphenism responding to light (*)

OKUMURA Misako
Associate Professor, Hiroshima University,
Graduate School of Integrated Sciences for Life

Light is essential for organisms, both as an energy source and environmental signals. However, it is largely unknown how light exposure during early life stages affects animal development, adult health, and diseases. Polyphenism is a phenomenon that the same genotype produces discrete phenotypes depending on environmental conditions during early life stages. In this study, I use the nematode which shows polyphenism in a mouth form responding to light to reveal the molecular mechanism by which light in the early stage of life influences morphogenesis.

Study of intestinal immune tolerance induced by activated Innate Lymphoid Cells (*)

SAWA Shinichiro
Professor, Medical Institute of Bioregulation,
Kyushu University

In Japan, the prevalence rate of allergic disease has been increasing. Hyposensitization is one of the promising strategies that enables us to obtain tolerance against allergens. In this study, from the point of epigenomic gene regulation, I will investigate roles of innate lymphoid cells (ILCs) and regulatory T cells on the induction of oral tolerance during early stage of life. I believe our study will provide us cellular and molecular insight of hyposensitization.

Molecular Evolutional Study Reveals the Pathogenesis of Maternal and Child Diseases Caused by Hypoxemia during Pregnancy (*)

TAKAHASHI Nobuaki
Associate Professor,
Graduate School of Engineering, Kyoto University

Life has evolved to acquire viviparity, the great system that allows fetus to be protected from enemies and obtain nutrients directly from mother. However, this system requires lots of blood and the O_2-transport protein hemoglobin – therefore, pregnancy often causes severe anemia. Indeed, most of maternal and child diseases during pregnancy are associated with maternal hypoxemia. This study aims to elucidate the molecular mechanisms underlying O_2 sensing and adaptation to hypoxia in the interface between mother and fetus, namely in uterus, placenta, or umbilical cord. Moreover, we will investigate how defects in this system cause maternal and child diseases.

Is epigenome transgenerationally inherited or not? (*)

MORITA Sumiyo
Assistant Professor, Gunma University,
Institute for Molecular and Cellular Regulation

Recently, number of studies shows that environmental factors, such as dietary conditions, affect offspring phenotype. This could be explained by the transmission of epigenetic alteration caused by the environmental factors from one generation to the next. To elucidate whether epigenetic alteration transmit to the next generation and affect the phenotype, we try to manipulate epigenome specifically at candidate transgenerationally-inherited locus in germ cells and clarify whether these alterations is transmitted to offspring and affect their phenotype.

Study of mechanisms that environmental factors result in developmental disorders (*)

KUBO Ken-ichiro
Professor, Department of Anatomy,
The Jikei University School of Medicine

In this study, I propose to investigate, using recently established a mouse model of embryonic ischemic brain injuries, how environmental factors, including ischemia, during early development affect brain functions in later life. In particular, I shall focus on which molecules/cells/systems are responsible for later brain dysfunctions in animals that sustain brain injuries during early development. In the future, the results will to be translated to prevention and treatment of brain dysfunctions arising in later life as a result of brain injuries during the early developmental period in humans.

Understanding human-specific developmental mechanism of the cerebral cortex at the early life stages (*)

SUZUKI Ikuo K.
Associate Professor, Graduate School of Science,
The University of Tokyo

The organs, such as the brain, which had been highly specified in the course of human evolution, have to be studied directly on the human experimental systems. In this project, I aim to comprehensively identify the genomic features unique to human and subsequently experimentally verify the significance of each feature in the development of the cerebral cortex by fully utilizing the pluripotent stem cells. For this purpose, I develop a novel screening platform of human-specific genomic features in the in vitro corticogenesis model and an interspecies chimeric mouse model in order to approach the tissue-tissue interaction during human corticogenesis.

Comprehensive study of CHD8-mediated chromatin remodeling on the neurogenesis underlying the onset of ASD (*)

NISHIYAMA Masaaki
Professor, Department of Histology and Cell Biology,
Kanazawa University

Recently, chromodomain-helicase-DNA-binding protein 8 (CHD8), a chromatin remodeling protein, has emerged as one of the most critical genetic risk factors for autism spectrum disorder (ASD). I have created new ASD-model mice that reproduce CHD8 haploinsufficiency, which is observed in human ASD cases, and have gained the direct evidence that functional ablation of CHD8 can be a cause of ASD. However, a fundamental question, “When, where, or how is ASD caused?”, remains unknown. In this study, I aim to elucidate this question by utilizing a variety of ASD-model mice, in which the function of CHD8 can be temporally and/or spatially ablated or gained.

Study of the establishment of DNA methylation during primate germ cell development (*)

WATANABE Toshiaki
Profession,
Center for Regenerative Medicine,
National Center for Child Health and Development

DNA methylation in gametes is established at the specific period during germ cell development. Abnormal DNA methylation pattern established at this period could affect later gametogenesis and embryogenesis. This research aims to uncover the developmental timing and the underlying molecular mechanisms of the establishment of methylation in primate germ cells. This study provides an important basis for future understanding and overcoming of infertility and developmental abnormalities caused by abnormal DNA methylation in germ cells.

Regulatory mechanism of longevity through developmental environment (*)

OBATA Fumiaki
Team Leader,
RIKEN Center for Biosystems Dynamics Research

It has been suggested that a transiently exposed environment during development predisposes a risk for many aging-related diseases and alters healthspan. However, it is difficult to elucidate the mechanism of developmental programming of ageing at the molecular level. In this study, we aim to reveal how nutritional and microbial environment during development impacts the organismal lifespan, by taking advantage of the short life cycle and abundant genetic tools of a fruit fly Drosophila melanogaster.

Development of a robust computational platform for data-driven epigenome analysis (*)

NAKATO Ryuichiro
Associate Professor, Institute for Quantitative Biosciences,
The University of Tokyo

Next-generation sequencing technologies have been used to observe gene transcription, histone modification and three-dimensional chromatin structure in a whole-genome manner. With the rapid accumulation of epigenomic databases, there is a great demand for "data-driven analysis" that handles large-scale datasets consisting of multiple assays for multiple cells and extracts important biological insight without prerequisite knowledge. However, such analysis is complexed and requires many human resources and has become a bottleneck so far. Our goal is to develop a robust and flexible computational platform for large-scale epigenome analysis and implement data-driven analyses to elucidate the key molecular mechanisms for early-life stages.

A new foundation for post-implantation developmental biology in primate. (*)

NAKAMURA Tomonori
Associate Professor, The Hakubi Center for Advanced Research, Kyoto University

Primates, including humans, begin morphogenesis immediately after implantation. Due to the extreme difficulty of sampling, the nature of these events has been largely unknown. In this project, using cynomolgus monkeys I will elaborate the gene expression dynamics of all cell types that appear in primate embryo until the beginning of organogenesis. Then, based on those insights, I aim to establish an ex vivo culture system of embryos that precisely recapitulates in vivo development soon after implantation in order to enable a stable supply of "implanted embryos". I hope this would be a new foundation for post-implantation developmental biology in primate.

Study of the Contribution of Mechanosensory Neurons to Establishing Proper Breathing Pattern in Mammalian Newborns (*)

NONOMURA Keiko
Associate Professor, School of Life Science and Technology,Tokyo Institute of Technology

Starting breathing after birth is the biggest event for mammalian newborns. However, the mechanism how mammalian newborns establish proper breathing patterns after birth is not well understood. We have previously revealed that PIEZO2 mechanosensor channel expressed in sensory neurons is essential for newborn mice to breathe properly and survive. In this study, by utilizing optogenetic methods, I will elucidate how PIEZO2-expressing sensory neurons control breathing pattern of newborn mice in detail.

Validation of the causal relationship between early-life myelination in the prefrontal cortex and social behavior (*)

MAKINODAN Manabu
Associate Professor, Department of Psychiatry,
Faculty of Medicine, Nara Medical University

Adverse childhood experiences have a long-term psychological impact such as social deficits and the impairment of myelination in the PFC later in life. However, the relevant underlying mechanisms linking them are still unknown. In this study, we will validate whether there is a causal relationship between early-life myelination in the PFC and social behavior in mice. In addition, our MRI study for humans measuring myelination with the information on their sociability will allow us to extrapolate the results of animal studies to human psychopathology such as developmental disorders and depression, in which myelin deficit in the PFC is observed.

Understanding of normal brain development and the CNS pathologies through early life stages of the CNS immune cells (*)

MASUDA Takahiro
Professor, Medical Institute of Bioregulation,
Kyushu University

The CNS tissue hosts macrophages at the CNS boundaries, so-called CNS-associated macrophages (CAMs). However, little is known about the nature of CAMs in the CNS, especially their functions during development. In this project, I'm planning to establish a basic database with regard to the kinetics, distribution, and gene expression profiles of CAMs during the course of development, and study how dysfunction of CAMs at the early stage of development increase the risk of CNS pathologies. Those results may provide new insights into the nature of the CNS and novel therapeutic opportunities for treatment of the CNS diseases.

Study of maternal-effect anemia caused by defective ribosome quality control (*)

MISHIMA Yuichiro
Associate Professor, Faculty of Life Sciences,
Kyoto Sangyo University

Dysfunction of the ribosome, the protein synthesis machinery, can be a cause of organismal abnormalities. However, how the ribosome quality is maintained during oogenesis and how the ribosome abnormalities affect the developmental processes are not well known. This study focuses on maternal-effect anemia caused by the defect in the ribosome quality control mechanism to clarify ribosome quality dynamics during oogenesis and early development. We try to elucidate how the defective ribosomes cause anemia in early development at the molecular level.

Tracing and manipulation of maternal-to-fetal/infant essential fatty acid transmission to understand molecular basis of mental development (*)

YANAGIDA Keisuke
Senior Research Fellow,
National Center for Global Health and Medicine

Essential fatty acids including docosahexaenoic acid and arachidonic acid are major fatty acids of membrane phospholipid in the brain. Essential fatty acid deficiency in the early life stages has been associated with various mental disorders. However, it remains largely unknown how they are delivered from mother to fetus and infants, and how they affect mental development. This study aims to unveil the metabolic route from mother to fetal brain as well as the molecular basis of the role of essential fatty acids in mental development by utilizing lipidomics, genetically engineered mouse model, and epigenomic analysis.

Understanding molecular mechanisms of post-weaning environmental effects on adaptative winter survival strategies (*)

YAMAGUCHI Yoshifumi
Professor, Institute of Low Temperature Science, Hokkaido University

In modern society, problems arise due to the mismatch between seasonal changes in the body's physiology and the living environment with well-developed air conditioning and lighting. Seasonal diseases such as winter depression in humans are one of them. In this study, we will address the molecular mechanism how light and nutrition during development influence the occurrence of mammalian hibernation, aiming to understand the molecular basis of winter adaptation strategies in mammals.

Study of environmental factor-induced diversity in disease phenotype (*)

YOSHIDA Keisuke
Associate Professor, Institute for Advanced Medical Sciences, Nippon Medical School

Most of diseases are thought to be caused by interaction between both genetic and environmental factors (so-called “multifactorial disorder”). Recent reports from epidemiological and experimental studies suggest that environmental stresses in parents affect pathogenic phenotype in offspring. In this study, to reveal pathogenic mechanisms in multifactorial disorders, I will establish model system of the disease in model organism by the use of genome-editing technique and parental environmental treatment.

PRIME Started in 2021 ····· 3rd period

Study on reproductive life span using infertile model animals

ISHIGURO Kei-ichiro
Professor, Institute of molecular embryology and genetics, Kumamoto University

In female, meiosis is initiated in fetal ovaries, and oocytes undergo long-term dormant status before sexual maturation. Thus, in women, reproductive life span is largely determined by the limited number of oocyte pool, that have been produced in fetal period. To elucidate the underlying mechanism, we will investigate gene expression program in the germ cells from fetal ovaries, and examine disease model mice. Thus, our proposed studies will be beneficial to our understanding the previously unknown mechanism that underlies reproductive life span, which promises to develop new diagnostic screening and therapeutic technologies to predict infertility pregnancy.

Mechanisms of disease predisposition by transgenerational histone modifications

INOUE Azusa
Team Leader,
RIKEN Center for Integrative Medical Sciences

Since the epigenome is environmentally responsive, the environment of the parental generation may affect the next generation through epigenomic changes in the gametes. However, its mechanisms are unknown. We have recently discovered histone modifications that are transmitted from oocytes to the placenta of the next generation. In this study, we focus on this transgenerational histone modification and test the hypothesis that the environment before conception affects the next generation via the oocyte–placenta axis.

Identification of tolerogenic bacteria in the neonatal gut microbiota

KAMADA Nobuhiko
Specially Appointed Professor, WPI Immunology Frontier Research Center, Osaka University

It has been reported that exposure to the gut microbiota in early life reduces the risk for various inflammatory diseases, including inflammatory bowel disease (IBD), in adulthood. We hypothesized that neonatal microbiotas harbor unique protective bacteria whose colonization induces immune tolerance and reduces the risk of IBD. In this project, we will aim to identify and isolate immune tolerance-inducing bacteria in human neonatal microbiotas.

Study of the molecular mechanisms for thymic Neonatal T cell development and for its lifelong functions

KIMURA Y. Motoko
Professor, Graduate School of Medicine, Chiba University

It has been suggested that the immune system is stratified into layers of distinct immune cells that develop sequentially from distinct waves of hematopoietic stem cells. However, the details of Neonatal T cells developed in early life have not yet been much elucidated. In this study, we first establish the system in which Neonatal T cells are labeled and monitored in whole life and analyze the details of its characteristic features. Furthermore, we reveal the impacts of environmental factors on Neonatal T cell development and its lifelong functions.

Novel definition of placental function as the transmitter of exercise information from trained mother to offspring

KUSUYAMA Joji
Associate Professor, Graduate School of Medical and Dental, Institute of Science Tokyo

Maternal lifestyle and metabolic health have been shown to influence the risk of various diseases in offspring. Determining feasible and practical means to reduce the transmission of metabolic dysfunction from mother to offspring will have invaluable impacts on medicine and health care policy. In this study, we define the placenta as an interface to transmit maternal information to offspring and elucidate intergenerational pathway of the benefits of maternal exercise to offspring. Furthermore, we will try to establish the preemptive medicine that can permanently reduce the risk of diseases in next generation by regulating placental function.

Elucidating the developing factors and expanding mechanisms of juvenile somatic mosaicism to establish novel therapeutic strategies

KUBO Akiharu
Professor, Kobe University Graduate School of Medicine

Mosaic disorders are caused by genetic alterations in somatic cells that result in the formation of colonies of mutant cells through cell competition with wild-type cells. In the field of dermatology, there are a variety of mosaic disorders caused by somatic mosaicism occurred in the early life stages. Through this research and development, we will gain an integrated understanding of the development and expansion of somatic mosaicism with regarding on genetic and/or epigenetic alterations and cell competition in human skin, which will provide fundamental knowledge for the development of novel therapeutic strategies for mosaic disorders.

Study of gastric-related diseases regulated by microbiota and innate lymphoid cells in the early stage of the stomach.

SATOH-TAKAYAMA Naoko
RIKEN ECL Unit Leader,
RIKEN Center for Integrative Medical Sciences

Helicobacter pylori (H. pylori) is known to cause not only gastritis or cancer, but is also involved in the induction of Immune Thrombocytopenia (ITP) or MALT lymphoma. *H. pylori* infection is basically established during childhood, however, the immunological mechanisms of gastric diseases appearing in adulthood are still unclear. So, the goal of this study will be to identify the molecular mechanisms and immune regulation affected by commensal microbiota and *H. pylori* morphological changes in the stomach by comparing with ages of young and adult. The study will also try to elucidate the mechanisms that lead to prevention in the early life stage.

Elucidation of molecular mechanisms underlying maintenance and disruption of bone growth at early life stages

TSUKASAKI Masayuki
Professor,
School of Dentistry, Showa University.

The bony skeleton functions as a locomotor organ and a mineral reservoir as well as a primary lymphoid organ. The mechanisms underlying bone development and growth remain poorly understood. In this project, we aim to clarify molecular mechanisms underlying maintenance and disruption of bone growth at early life stages by focusing on skeletal stem cells. The outcomes of this project will contribute to the development of new treatments for various bone diseases including short stature.

Elucidation of the molecular and neural circuit basis of individual differences in stress resilience

SHINOHARA Ryota
Associate Professor,
Kobe University Graduate School of Medicine

Stress early in life significantly reduces stress resilience and increases the lifetime incidence and severity of psychiatric disorders such as depression. However, the mechanism by which early life stress reduces stress resilience is unknown. This study will identify neural circuit dysfunction associated with reduced stress resilience caused by early life stress to reveal the neural basis for individual differences in stress resilience. Furthermore, we will elucidate the molecular basis of functional maturation of neural circuits related to stress resilience. Collectively, this study will lead to a novel concept to develop risk prediction, prevention, and treatment methods for psychiatric disorders.

Unveiling novel roles for maternal bile acids in fetal organ development

MIHARADA Kenichi
Professor, International Research Center for Medical Sciences, Kumamoto University

During fetal development, essential factors that fetuses cannot synthesize by themselves are presumably supplied from the maternal body. However, concrete factors and their exact roles are largely unknown. Recently, bile acids have been implicated in stem cell regulations and cellular differentiation through their functions as chemical chaperones and signaling molecules other than the detergent function. In this project we aim at unveiling novel roles of bile acid, transferred from the maternal circulation, in fetal organ development using analyses of mouse models and single cell gene expression analyses as well as advanced proteomics approaches.

(＊) indicates completed R&D projects.
Institution names, affiliations, and titles are as of the final year.

Tissue Adaptation and Repair

Understanding of Pathophysiological Processes and Discovery of Medical Technology Seeds through Spatiotemporal Research of Tissue Adaptation and Repair Mechanisms

Research and Development Objectives

Investigations into life phenomena and the discovery of medical technology seeds based on spatiotemporal insights into biological tissue adaptation and repair mechanisms

Program Supervisor (PS)

YOSHIMURA Akihiko

Professor, Research Institute for Biomedical Sciences, Tokyo University of Science

Program Officer (PO)

YOKOMIZO Takehiko

Professor, Juntendo University School of Medicine

The goal of this R&D area is to significantly accelerate the discovery of technology seeds that contribute to health and medical care by deepening the spatiotemporal understanding of biological tissue adaptation and repair mechanisms.

The body maintains its functions through tissue adaptation and repair against various types of tissue injury or excessive stress. It remains to be elucidated how the organism responds to the damages from the inside and outside of the living body, what types of cells in the tissues are involved in adaptation and repair, and what kind of interactions proceed during adaptation and repair. When the regulatory mechanisms for the tissue adaptation and repair become dysfunctional, tissue homeostasis is broken down, thereby eventually leading to the onset of serious diseases. These processes are also not fully understood. The aim of this R&D area is the elucidation of mechanisms of tissue adaptation and repair, their maintenance and broken-down. We will develop new technologies to obtain greater spatiotemporal insights, and will discover the seeds for preventive, diagnostic, and therapeutic technologies.

Advisor

ISHII Masaru
Professor, Graduate School of Medicine, Osaka University

IMAI Yumiko
Director of Medical Infection System Laboratory, Research Institute, Nozaki Tokushukai Hospital

KATAGIRI Hideki
Professor, Tohoku University Graduate School of Medicine

TAKAKURA Nobuyuki
Professor, Research Institute for Microbial Diseases, Osaka University

TAKAHASHI Masahide
Designated Professor, Director of Academic Program, Academic Advisor, Director of International Center for Cell and Gene Therapy, Fujita Health University

TAMURA Kouichi
Executive Officer CSO (Chief Scientific Officer) in charge of research and manufacturing Head of Kobe Research Institute, Helios K.K.

FURUYASHIKI Tomoyuki
Professor, Graduate School of Medicine, Kobe University

MATSUSHIMA Kouji
Professor, Research Institute for Biomedical Sciences, Tokyo University of Science

MINAMINO Tohru
Professor, Juntendo University Graduate School of Medicine

MIYAJIMA Atsushi
Project Professor, Institute of Quantitative Biosciences, The University of Tokyo

AMED-CREST Started in 2018 · 1st period

Dissecting intestinal fibrogenic diseases by a newly developed 4D disease model system (*)

SATO Toshiro
Professor,
Keio University School of Medicine

Epithelial injury is healed by prompt epithelial regeneration and stromal responses, whereas impaired epithelial healing system leads to fibrotic diseases through aberrant activation of stromal cells. Thus far, owing to a lack of tractable epithelial-stromal functional assay system, the mechanism underlying the impaired epithelial healing and fibrotic diseases remains elusive. In this project, we seek to establish an organoid-based spatio-temporal analysis system and elucidate the molecular basis of how intestinal epithelium orchestrate tissue healing and whether its disorder leads to gut fibrotic diseases.

Study of the regulatory mechanisms of cell-cell interaction underlying liver remodeling in NASH for the development of therapeutic and diagnostic procedures (*)

TANAKA Minoru
Laboratory Head, Research Institute, National Center for Global Health and Medicine

The liver is known to possess high capacity of regeneration upon injury. However, inadequate regeneration in chronic hepatitis often causes fibrosis and carcinogenesis in the liver. The research objective is to elucidate the regulatory mechanisms underlying the pathogenesis and progression of chronic liver diseases, especially non-alcoholic steatohepatitis (NASH) for the development of diagnostic and therapeutic methods. We focus on two representative liver remodeling (i.e. fibrosis and regeneration) from a perspective of cell death, tissue stem cell and cell-cell interaction.

Elucidation of the pathophysiology of tissue remodeling fibrosis in the airway; towards the development of a new strategy for treating fibrotic diseases (*)

NAKAYAMA Toshinori
President,
Chiba University

The aim of this project is to investigate the cellular and molecular mechanisms underlying pathological tissue remodeling (fibrotic changes) and elucidate the pathogenesis of chronic intractable diseases with tissue fibrosis. We focus on fibrotic changes in the airway. We will use our established techniques together with new cutting-edge technologies to define how epigenetic pathways, fibrosis-inducing pathogenic Th2 (Tpath2) cells, inflammatory eosinophils and inducible bronchus-associated lymphoid tissues (iBALT) can control development of fibrotic diseases. Our final goal is to establish a comprehensive and multidisciplinary research platform of immunology, pathology and regenerative science.

Stem cell system-based four dimensional ocular tissue remodeling in homeostatic and pathological states (*)

NISHIDA Kohji
Professor, Graduate School of Medicine,
Osaka University

Our hypothesis is that specialized cells such as vascular and neural cells which were thought to be quiescent are constantly being replaced by newly emerged cells originated from somatic stem cells with different timespans. Moreover, disruption of those physiological remodeling may lead to pathological change. Based on the fact that eye ball is a unique organ which contains multiple component of tissue such as vascular, nervous and epithelial system, we aim to elucidate whether time-dependent remodeling of these specialized cells are involved in disease model in the eye which is constantly exposed by various external stress (e.g. light exposure) or internal stress (e.g. high glucose).

Comprehensive study of resilience control by interaction between the nervous system and the biological system (*)

YAMASHITA Toshihide
Professor, Graduate School of Medicine,
Osaka University

We will conduct research to elucidate a maintenance mechanism of the central nervous system with the focus on “resilience control by biological system network”, in order to develop methods for the prevention, delay, and recovery from neurological diseases. In neurological diseases, the bi-directional functional interaction between the nerves and the biological system deteriorates, causing exacerbation of pathological conditions as a result of the attenuated recuperative and restorative ability of nervous tissue or its decreased resilience. Our goal is to elucidate the mechanism of resilience controlled by biological system interactions and the neurological conditions caused by its failure.

AMED-CREST Started in 2019 · 2nd period

Adaptation and repair of skin barrier via multi-cellular interactions

KABASHIMA Kenji
Professor, Graduate School of Medicine
Kyoto University

We would like to perform research focusing on the skin barrier function, which is deeply involved in the onset of skin immunity and allergy. To this end, we set three objectives: I, Elucidation of the skin barrier formation and failure by keratinocyte crosstalk; II, Elucidation of the mechanism of the skin barrier by peripheral nerves and immunity; III, Forming foundation of clinical application. These results are expected to overcome atopic dermatitis and other skin barrier dysfunction-mediated diseases, including other allergies, which lead to improving the QOL of allergic patients and reducing medical costs in the future.

Neuronal migration: strategies for adaption and endogenous repair in the injured brain

SAWAMOTO Kazunobu
Professor, Nagoya City University
Graduate School of Medical Sciences

There are still no promising strategies for regenerating lost neurons at the appropriate positions in the injured brain, which will be necessary for functional recovery. In this project, we focus on the migration of new neurons generated from neural stem cells (NSCs) in the postnatal ventricular-subventricular zone (V-SVZ), and seek to understand the molecular mechanisms for “adaptation” and “repair” of the injured brain. Since the postnatal human brain also contains NSCs in the V-SVZ, these endogenous mechanisms of neuronal regeneration will provide bases for novel strategies for treating brain diseases such as neonatal hypoxia/ischemia and adult stroke.

Discovery of tissue repairing immune cells for the development of therapeutic strategy

TAKAYANAGI Hiroshi
Professor, Graduate School of Medicine,
The University of Tokyo

The immune system contributes to not only host defense but also tissue repair throughout the body. Activation of immune cell subsets specific for tissue repair and the proper cooperation with the mesenchymal cells and parenchymal cells within the injured tissue is necessary for tissue regeneration. In this study, during various external and internal injuries, we identify immune cell subsets that specifically direct the tissue repair. We will understand the entire process of tissue repair mediated by the tissue repairing immune cells, aiming at the development of tissue regeneration technology by targeting tissue-repairing immune cells.

Identification of cellular and molecular constituents in unique microenvironments regulating tissue damage and repair to prevent chronic kidney disease

YANAGITA Motoko
Professor and Chair, Graduate School of Medicine Kyoto University

Kidney injury and repair are dynamically controlled depending on the disease condition, however, precise molecular mechanisms regulating these processes remain unclear. In kidney injury, proximal tubules, the most vulnerable segment in the nephrons, are frequently damaged. Proximal tubule injury subsequently alters the pre-existing intercellular interaction between proximal tubules and surrounding cells, and recruit hematopoietic cells to form new distinct “microenvironments”, which act as driving engines for tissue remodeling. In this proposed research, we identify the cellular and molecular targets orchestrating kidney injury and repair, particularly focusing on above-mentioned unique “microenvironments” regulating dynamic tissue remodeling after injury.

AMED-CREST Started in 2020 ········· 3rd period

Achieving sustainable reconstruction of damaged neural network toward complete recovery in stroke and dementia

SHICHITA Takashi
Professor, Medical Research Laboratory,
Institute of Integrated Research, Institute of Science Tokyo

The pathologies of cerebrovascular diseases and dementia often co-exist and worsen each other in the aged brain, leading to the progression of neurological dysfunction and cognitive decline. There are few established therapeutic drugs that improve the brain function of patients with stroke and dementia which have become major causes of reduced healthy life expectancy in an aging society. In this study, we will identify the key genes that regulate neural network reconstruction and will develop innovative therapeutic drugs that enable neural network reconstruction to be sustained until complete recovery from the neurological deficits caused by stroke and dementia is achieved.

Metabolic reprogramming driving hematological aging

TAKUBO Keiyo
Professor,
Tohoku University Graduate School of Medicine

The functional and populational changes in hematopoietic stem cell (HSC) have been implicated in the rise of infections, cancers, rheumatoid, and cardiovascular diseases. Little is known about inducers and changes affecting the metabolic program in HSC aging. Our primary objective is to define mechanisms that underlie aging-related metabolic reprogramming of HSCs, and consequently, defects in the blood system. We will evaluate the effect of environmental factors on metabolic reprogramming of HSCs during aging. We will also identify transcriptional, epigenetic, and metabolic alterations that induce aging-related changes and methods to reverse these changes in HSCs and the blood system.

Mechanism of endocrine dysregulation in hepatic inflammation and fibrosis using patient-derived organoids

TAKEBE Takanori
Professor, Graduate School of Medicine,
Faulty of Medicine, Osaka University

Emerging evidence suggest that endocrine dysregulation involving insulin like growth factor 1 correlates to liver inflammation and fibrosis. We have pioneered multicellular liver organoid technology, establishing a novel inflammatory disease model in human. Here, we propose to investigate endocrine interaction mediated mechanisms governing liver inflammation and fibrosis using human organoids. At the conclusion, the proposed study will delineate the humanistic mechanisms mediating hepatic inflammation, and will identify compounds to attenuate fibrosis via patient-relevant disease model. Our proposal will establish the foundation for future personalized mechanistic testing, thus facilitating novel diagnostic and drug discovery tools against diseases with no approved treatments.

New mechanisms of tissue adaptation and repair based on disease-associated lipid metabolism and their applications to novel medical seeds

MURAKAMI Makoto
Professor, Graduate School of Medicine,
The University of Tokyo

Disturbed lipid metabolism often hampers tissue adaptation and repair, thereby leading to various diseases. The purpose of this research project is to identify novel PLA_2-driven lipid pathways that are linked to tissue adaptation and repair, putting a specific focus on those in skin diseases, fibrosis, and multi-organ failure. Using gene-manipulated mice for various phospholipid-metabolizing enzymes and clinical specimens, in combination with comprehensive metabolomics, we aim to clarify the molecular mechanisms of disorders associated with lipid failure toward development of novel treatment, prevention and diagnosis of the diseases.

PRIME Started in 2018 ········· 1st period

Study on the roles and mechanisms of adaptive remodeling of the intrahepatic biliary epithelial tissue that supports liver regeneration (*)

ITOH Tohru
Project Associate Professor, Institute for
Quantitative Biosciences, The University of Tokyo

The liver is an essential organ for life with multiple important functions, and is renowned for its tremendous regenerative activity. We have recently revealed that the intrahepatic biliary epithelial tissue possesses a unique and unprecedented structural flexibility and that its dynamic and adaptive remodeling likely constitutes the basis for robust liver regeneration. The aim of this R&D project is to elucidate the cellular and molecular frameworks as well as the modes of action of the biliary remodeling, thereby contributing to our understanding of the mechanisms for liver regeneration and future development of diagnostic and therapeutic strategies to tackle liver diseases.

Elucidation of neuronal signal-regulated cell proliferation for tissue adaptation and repair (*)

IMAI Junta
Associate Professor,
Tohoku University Graduate School of Medicine

When organs are damaged, cells proliferate to repair the organs. On the other hand, pancreatic β-cells adaptively proliferate in insulin-resistant states to increase insulin production. Therefore, these proliferations are compensatory mechanisms aiming at maintaining whole body homeostasis and survival. In this project, we aim to clarify the mechanisms by which neuronal signals regulate compensatory cell proliferation in tissue adaptation and repair processes. These research efforts are anticipated to enhance our understanding of adaptation and recovery systems of organs/tissues as well as clarifying pathogenesis of several diseases attributable to impaired adaptive tissue proliferation. Furthermore, these researches may provide novel clues for developing tissue regeneration strategies based on endogenous biological systems.

Study of the central nervous system regeneration by regulating glial scar (*)

OKADA Seiji
Professor, Graduate School of Medicine, Osaka University

The glial scar is a main cause of the limited regenerative capability in the mammalian central nervous system. Although the glial scar has been studied for more than half a century, the cellular and molecular mechanisms of glial scar formation remain unclear. In this project, we will examine the reversibility of glial scar formation and possibility of novel therapeutic strategy for the injured central nervous system by regulating the glial scar formation.

Study of the cellular and cell adhesion molecule mechanisms underlying peripheral nerve axon regeneration (*)

KADOYA Ken
Associate Professor, Faculty of Medicine and Graduate School of Medicine, Hokkaido University

In spite of the fact that peripheral nerve can regenerate, the clinical outcomes of peripheral nerve injuries are not satisfactory. To induce meaningful recovery, novel therapy to promote axon regeneration needs to be developed. However, the cellular and molecular mechanisms underlying axon regeneration remains to be fully clarified. Therefore, to generate the evidence contributing to the development of effective therapy for peripheral nerve injury, the current study aims to elucidate the cellular and molecular interactions among axons, Schwann cells, and macrophages, with special focuses on cell surface molecules.

4D multi-scale imaging study sheds light on the tissue remodeling mechanism (*)

KIKUTA Junichi
Associate Professor, Graduate School of Medicine, Osaka University

When the tissue is damaged, it is repaired through the dynamic interaction of organs. If an error occurs during the repair process, the affected organ will undergo fibrosis. In this study, using an advanced 4D imaging technology, I will observe the pathogenesis of fibrosis in multiple organs, and analyze the time-course of the complex cell-cell interactions and function of different cell populations. This approach will yield compelling insights into the common molecular mechanisms underlying fibrosis, which could also serve as the basis for developing novel anti-fibrotic therapies.

Molecular mechanisms underlying resilient system for organogenesis during development (*)

SHINDO Asako
Associate Professor, Institute of Molecular Embryology and Genetics, Kumamoto University

In nature, oviparous embryos develop normally despite unfavorable extrinsic stressors. This fact implies that embryos are equipped with molecular machinery to resist and repair the impact of such stresses. This may be accounted for by their active gene expression and diverse cellular behaviors. In this study, I focus on nutrient-dependent organogenesis in *Xenopus* as a model to investigate the molecular and cellular strategies for surviving adverse conditions. I aim to uncover possible mechanisms for controlling organ shape by exploring this unique ability of developing animals.

The cellular and molecular basis of lymphoid tissue remodeling by adrenergic nerves (*)

SUZUKI Kazuhiro
Professor, Immunology Frontier Research Center, Osaka University

Excessive immune responses sometimes destroy highly organized microenvironments in lymphoid organs, leading to an immunodeficient condition. Reacquisition of immunocompetence requires restoration of the lymphoid microarchitecture. However, the mechanisms of the lymphoid tissue remodeling are incompletely understood. We found that inputs from adrenergic nerves promote restructuring of lymphoid tissues after virus infection. In this study, we aim to clarify the cellular and molecular basis for lymphoid tissue remodeling by investigating how adrenergic nerves control immune cell functions to restore the integrity of lymphoid tissues. This study would lead to the development of a useful therapeutic approach for immune disorders targeting lymphoid tissue remodeling.

Study on the mechanism of inflammatory memory in intestinal regeneration (*)

TANIGUCHI Koji
Professor, Hokkaido University Graduate School of Medicine

Previously, it was thought that cellular memory for inflammation and infection occurs only in immune cells. However, recent studies reported that not only immune cells but also epithelial stem cells remember inflammation in the skin, and respond quickly to the next stimulus to promote wound healing. Like the skin, the intestines also function as a barrier between the human body and the outside world, but inflammatory memory has not been studied in the intestines. In this research, we aim to elucidate the mechanism of inflammatory memory in intestinal regeneration.

Study of endothelial stem cell and vascular homeostasis (*)

NAITO Hisamichi
Professor, Graduate School of Medical Sciences, Kanazawa University

Blood vessels delivering oxygen and essential molecules are critical for maintaining homeostasis in all tissues of the body and for recovery from the injury. We recently identified a stem cell population in the endothelial cells which cover the inner surface of the blood vessels. However, little is known about their physiological role and cell regulatory mechanisms. The aim of this project is to understand, through analysis of endothelial stem cells, how blood vessels are repaired and tissue homeostasis maintained.

Organism-level single-cell 4D dynamics in cardiac stress response (*)

NOMURA Seitaro
Assistant Professor, The University of Tokyo Hospital

Hemodynamic overload to the heart induces heart failure and ischemia to the heart causes myocardial infarction. During these processes, various cells and/or molecules are considered to show spatio-temporal dynamics for adaptation and repair, but its whole picture remains unclear. In this study, by analyzing multi-organ communications in cardiac stress responses at the single-cell level, we will address the question how cells exert their functions in adaptation and repair processes and what cells/molecules interact with each other to contribute to these processes, providing new avenues for the development of novel therapeutic strategies for heart diseases.

Study of how beige fat induction by environmental thermal stress adaptation and how aging affects beige fat induction (*)

IKEDA Kenji
Associate professor, Tokyo Medical and Dental University

Mammal has adaptive mechanism against environmental thermal cold stress. Thermogenic fat, Beige fat is induced by cold stress and induced beige fat makes heat. Though aging strongly inhibits the induction of beige adipocytes, it is poorly understood for molecular mechanism. In this study, we focused on the subtypes of beige adipocytes, we will identify all subtypes of beige adipocytes and then analyze the molecular control mechanisms of each subtype. We will elucidate the mechanism of how aging affects beige adipocytes induction. Finally, we will identify new treatment targets, which can induce beige adipocytes, even under aging condition. These targets will lead to novel treatment to obesity and type2 diabetes.

Elucidation of neural repair mechanism by immune cells in the brain injury (*)

ITO Minako
Associate Professor, Medical Institute of Bioregulation, Kyushu University

In brain inflammation by ischemic stroke, multiple sclerosis, and Alzheimer's disease, acquired immune system and natural immune system interacts with brain cells, which is involved in repair of brain tissue and nerve system. In this study, we aim to clarify the developmental mechanism of brain-specific lymphocytes and repairing macrophages by analyzing such interactions in the brain, and further elucidate the contribution of such interactions to tissue repair and nerve regeneration.

Elucidation of cell interaction mechanism in suppression of chronic kidney disease progression through nervous and immune systems (*)

INOUE Tsuyoshi
Professor, Graduate School of Biomedical Sciences, Nagasaki University

It is known that there are many different cells in the kidney. We have found that the kidney is protected from injury through the nervous-immune systems. Therefore, in this study, I will focus on how immune cells activated by nerve stimulation protect the kidney (cell interaction) and whether there is a direct protective effect on the kidney through the nerve (organ interaction). I hope that this study reveals a new renal protection mechanism.

Study of the epithelial repair mechanism by the new bioactive peptide (*)

ODA Yukako
Associate Professor, Center for iPS Cell Research & Application, Kyoto University

Tight junctions (TJ) are cell–cell adhesion structures that function as a barrier between epithelial cells to avoid dehydration, regulate ion permeability and prevent invasion of bacteria and viruses. Despite the fact that restoration of TJ integrity is critical for a treatment of the diseases, coordinated mechanism that directly promotes TJ formation in vivo is unknown. We recently succeeded in identifying the new peptides that induce TJ formation. In this project, we will dissect the repairing mechanism of epithelia by the peptide in inflammation.

Covariation network analysis for neural differentiation in disease iPS cells (*)

KANO Fumi
Associate Professor, Institute of Innovative Research, Tokyo Institute of Technology

Alzheimer's disease (AD) is an irreversible neurodegenerative disorder, which usually progress slowly. To prevent the aggravation, detecting the symptoms of disease before the cells enter the severe irreversible pathological state would be effective. The aim of this study is to develop the innovative image-based covariation network analysis to reveal the key molecules and disease biomarkers at the early stage of disease progression. We apply this analysis to the neural differentiation of disease iPS cells derived from AD patients, elucidate the molecular mechanisms underlying the pathological phenotypes of AD-derived cells, and regulate the cell fate in neural differentiation.

Study on the crosstalk between stromal cells and immune cells in intestinal homeostasis (*)

KAYAMA Hisako
Associate Professor, Institute for Advanced Co-Creation Studies, Osaka University

In the intestinal mucosa, a refined balance is maintained between tolerance and inflammatory responses against multiple environmental factors. This is because aberrant inflammatory responses can cause tissue damage. In patients with inflammatory bowel diseases, composition of stromal cell subsets is altered. However, whether stromal cells are implicated in either the maintenance of gut homeostasis or the pathogenesis of IBD by interacting with immune cells remains unknown. Therefore, I will examine effects of interactions between stromal cells and immune cells on intestinal inflammation, tissue repair, and fibrosis, thereby promoting advances in diagnostic and therapeutic approaches for IBD.

Regulatory mechanism segregating blood and lymphatic vascular systems (*)

KUBOTA Yoshiaki
Professor, Keio University School of Medicine

Vascular and lymphatic systems are two major circulatory systems distributed throughout the body. The structures of these two are histologically very similar but anatomically never share the lumen with except for the "venous angle", the final junction of collecting lymph ducts and subclavian veins. In this research, we will uncover the fundamental mechanisms segregating blood and lymphatic vascular systems mainly using genetically modified mice. The resultant data may pave the way to treat the secondary lymphedema, which frequently occurs after extensive lymph node dissection associated with cancer surgery, and is currently a big social issue related to cancer survivors.

Exploring and exploiting regulatory T cell-dependent mechanisms of tissue homeostasis (*)

HORI Shohei
Professor, Graduate School of Pharmaceutical Sciences, The University of Tokyo

Regulatory T (Treg) cells exhibiting anti-inflammatory functions play an essential role in the maintenance of tissue homeostasis. We have hypothesized that impaired differentiation, homeostasis, and/or function of tissue-resident Treg cells contributes to pathological tissue remodeling (e.g., fibrosis) and that tissue Treg cell-dependent mechanisms of tissue homeostasis may be exploited for therapeutic conversion of pathological tissue repair into physiological tissue regeneration. This project aims at testing this hypothesis and thereby contributing to future development of therapeutic strategies to cure many fibrosis-associated diseases.

Removal repair of pre-cancerous cells by spatiotemporally sensing suboptimal cells (*)

MARUYAMA Takeshi
Associate Professor, Waseda Institute for Advanced Study, Waseda University

Spatiotemporal recognition of suboptimal cells triggers the elimination force of surrounding normal cells against transformed cells and induces the repair of the apportionment space. However, it was largely unknown how to recognize these transformed cells and evoke the eliminating force. We have found the alteration of antigen presentation on the transformed cells are recognized by surrounding normal cells. In this study, we will elucidate the whole mechanism of suboptimal cell recognition; elucidate the whole mechanism of multilateral and precise recognition mechanisms against suboptimal cell development.

Restoration of regenerative system in the aged central nervous system (*)

MURAMATSU Rieko
Director, National Institute of Neuroscience, National Center of Neurology and Psychiatry

The goal of this study is identification of molecular target for treating demyelinating diseases. White matter atrophy is a promising feature of many central nervous system diseases. White matter is composed by oligodendrocytes, which are generated from their precursor cells (oligodendrocyte precursor cells, OPCs). White matter atrophy in aging brain is caused by the impairment of OPC differentiation into the mature oligodendrocyte around the lesion; however, the mechanism of impairment of OPC differentiation in aged animal has not been clarified. This study unveils the molecular mechanism that restore the OPC differentiation potential to regenerate white matter in the aged brain.

PRIME Started in 2020 ····· 3rd period

Spatiotemporal-functional analysis of the enteric nervous system in tissue remodeling. (*)

ISHIGAME Harumichi
Associate Professor, Near InfraRed Photo-ImmunoTherapy Research Institute, Kansai Medical University

The enteric nervous system and immune system continuously sense luminal environmental changes to maintain tissue homeostasis. Their dysregulation is associated with human pathologies including defective motor function and chronic inflammation. This proposal will establish a genetic strategy that is capable of targeting a molecularly defined subtype of enteric neurons and manipulating its neuronal activity. The experiments proposed will incorporate the gene expression profiling of enteric neurons and immune cells as well as 4D intravital imaging techniques in order to identify specific neuronal cell types involved in intestinal tissue remodeling and elucidate their molecular mechanisms during intestinal inflammation.

Clarifying and Targeting Integrated Network of Hematopoiesis under Age-related Stress (*)

INOUE Daichi
Professor, Institute of Biomedical Research and Innovation, Foundation for Biomedical Research and Innovation at Kobe

In the bone marrow, hematopoietic stem cells (HSCs) utilize support from the microenvironment's niche cells. On the other hand, functionally impaired HSCs by aging or genetic alteration also adapt and repair themselves through the surrounding environment. Our study will mainly focus on the role of extracellular vesicles derived from HSCs in altering the multiple systems in and out of the bone marrow. We will seek to elucidate the complicated network changing the systemic organ functions as well as the hematopoiesis and create medical seeds by using single-cell omics and spatio-temporal imaging at the single-cell level.

Mechanisms of skeletal muscle regeneration mediated by increased macrophage diversity (*)

OISHI Yumiko
Professor, Graduate School of Medicine, Tokyo Medical and Dental University

Skeletal muscle, the dominant organ for locomotion and energy metabolism, has a remarkable capacity for repair and regeneration upon injury. Recent studies indicate that inflammation and regeneration processes are intricately linked in injured muscle, macrophages are crucial for both processes. In this study, I test the idea that increased macrophage diversity leads muscle regeneration and tissue restoration by rewiring intercellular communication networks and that macrophage diversity is driven by metabolic reprogramming. My long term aim is to contribute to our society by uncovering the mechanisms and providing novel therapeutic strategy for sarcopemia.

Enteric Mesenchymal-Neural Circuit for the Mucosal Regeneration and Fibrogenesis (*)

KURASHIMA Yosuke
Associate Professor, Chiba University Department of Innovative Medicine

Mesenchymal cells such as fibroblasts and myofibroblasts are deeply involved in tissue repair and fibrosis. However, in order to target these cells distributed in various organs and tissues of our body as therapeutic strategies for fibrotic diseases, it is necessary to find organ and disease specific traits and target molecules. In this research, we focus on the histological characteristics of mucosal tissues and elucidate the mechanisms of fibrogenesis caused by inflammatory bowel diseases and develop new treatment strategies from the viewpoint of enteric mesenchymal-neural circuits.

Study of the mechanism of lung repair in interstitial lung diseases by temporal cellular network analysis (*)

SHICHINO Shigeyuki
Lecturer, Research Institute of Biomedical Science, Tokyo University of Science

Impairment of lung resolution results in pulmonary fibrosis. However, little is known about the starting point of the cell-cell interaction (CCI) network which promote lung resolution. To address this question, we will evaluate the alterations of cellular composition/states in the resolution stage of various murine lung injury/fibrosis models by using our novel single-cell RNA-seq method—TAS-Seq. Next, we will establish novel analysis framework for re-construction of pseudotemporal CCI network based on the TAS-Seq data, and identify/validate the starting point of the network that highly propagates to the network structure of lung resolution. We believe resulting data will provide novel insights in lung fibrosis treatment and the framework for analyzing temporal changes of CCI network in various injured organs.

Spatiotemporal effects of a novel signaling molecule, bicarbonate, in neurovascular unit reconstruction (*)

JO-WATANABE Airi
Project Associate Professor, Juntendo University, Faculty of Medicine

The goal of this research proposal is to elucidate the cellular and molecular mechanisms of tissue adaptation and repair in brain ischemia-reperfusion injury from the viewpoint of the bicarbonate-induced intracellular signaling and intercellular communication within Neurovascular Unit (NVU). I am going to reveal the spatiotemporal effects of bicarbonate ion in the NVU after middle cerebral artery occlusion and reperfusion. The achievement of this research could lead to the development of novel therapeutic strategies for cerebrovascular diseases based on the molecular understanding of bicarbonate effects, and will allow us the identification of 'bicarbonate signaling defects' in acid-base imbalance in a variety of disorders.

Analysis of sparse and hidden tissue remodeling regions indicated by active astrocytes (*)

SUSAKI Etsuo A.
Professor, Juntendo University School of Medicine

This project aims to elucidate the hidden tissue damage and repair processes and their molecular mechanisms in the very early stages of disease that have been difficult to target in previous biomedical studies. In particular, we will investigate the function of the early activated astrocytic foci reported by the principal investigator and analyze their association with age and age-related diseases of the central nervous system. We will use advanced 3D tissue visualization and cellular perturbation techniques being developed by the principal investigator.

The roles of oxygen environment on the pathogenesis of cardiac fibrosis (*)

TAKEDA Norihiko
Visiting Researcher, Center for Molecular Medicine, Jichi Medical University

Excessive cardiac fibrosis elicits the development of heart failure with preserved ejection fraction (HFpEF), a form of congestive heart failure in which the fraction of blood ejected from the left ventricle is within normal thresholds. Therefore, elucidation of the molecular processes by which fibroblasts are activated or deactivated is critically important for the development of therapeutic approaches in the management of heart diseases.
In this project, we will identify the metabolic profiles of cardiac fibroblasts, which produces extracellular matrixes in hypoxic environment. These approaches will uncover a previously unidentified therapeutic target of cardiac fibrosis.

Modeling and studying cholestatic liver diseases using a novel hepato-biliary organoid system (*)

TANIMIZU Naoki
Assistant Professor, The Institute of Medical Science, The University of Tokyo

Neighboring epithelial tissues establish a functional connection for the transport of substances and metabolites. In the liver, bile canaliculi of hepatocytes and bile ducts consisting of cholangiocytes form the biliary system, whose destruction causes cholestasis resulting in fatal liver diseases. We recently established a novel hepatobiliary tubular organoid (HBTO) in which bile secreted from hepatocytes is transported to biliary tubules. In this project, we introduce hepatic stellate cells and Kupffer cells to HBTO and then induce cholestasis by disrupting the bile excretion system. We aim to identify molecular mechanisms modulating cellular communications at the onset of cholestasis-induced liver failure.

A challenge to reveal and regulate multi-cellular networks that remove abnormal cells and maintain tissue homeostasis (*)

MOROISHI Toshiro
Professor, Faculty of Life Sciences, Kumamoto University

Increasing amounts of abnormal cells, such as over-proliferating cells, will impair organ functions by destroying the tissue architecture. Those abnormal cells are removed by a multicellular network, mainly the immune system, to ensure tissue homeostasis, otherwise those cells contribute to chronic inflammation, organ fibrosis, and cancer progression. In this study, we aim to elucidate the molecular and cellular mechanisms of tissue adaptation by uncovering a multicellular network involved in the removal of abnormal cells. We also try to open up new avenues for future drug discovery for the prevention and treatment of diseases related to fibrosis and cancer.

(*) indicates completed R&D projects.
Institution names, affiliations, and titles are as of the final year.

Functional Impairment

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

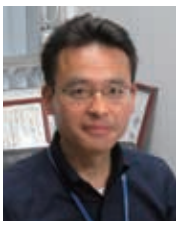
Research and Development Objectives

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)

NISHIDA Eisuke
Director, RIKEN Center for Biosystems Dynamics Research



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KURANAGA Erina
Professor, Graduate School of Life Sciences, Tohoku University

TAKEDA Kiyoshi
Professor, Graduate School of Medicine, Osaka University

MATSUZAKI Fumio
Professor, Graduate School of Medicine, Kyoto University

YANAGITA Motoko
Professor, Graduate School of Medicine, Kyoto University

AMED-CREST 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.

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.

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.

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.

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.

AMED-CREST 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.

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.

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.

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.

AMED-CREST Started in 2019 ····· 3rd period

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.

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.

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.

PRIME Started in 2017 ····· 1st period

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

PRIME Started in 2019 ····· 3rd period

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.

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'.

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.

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.

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.

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.

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.

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.

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.

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

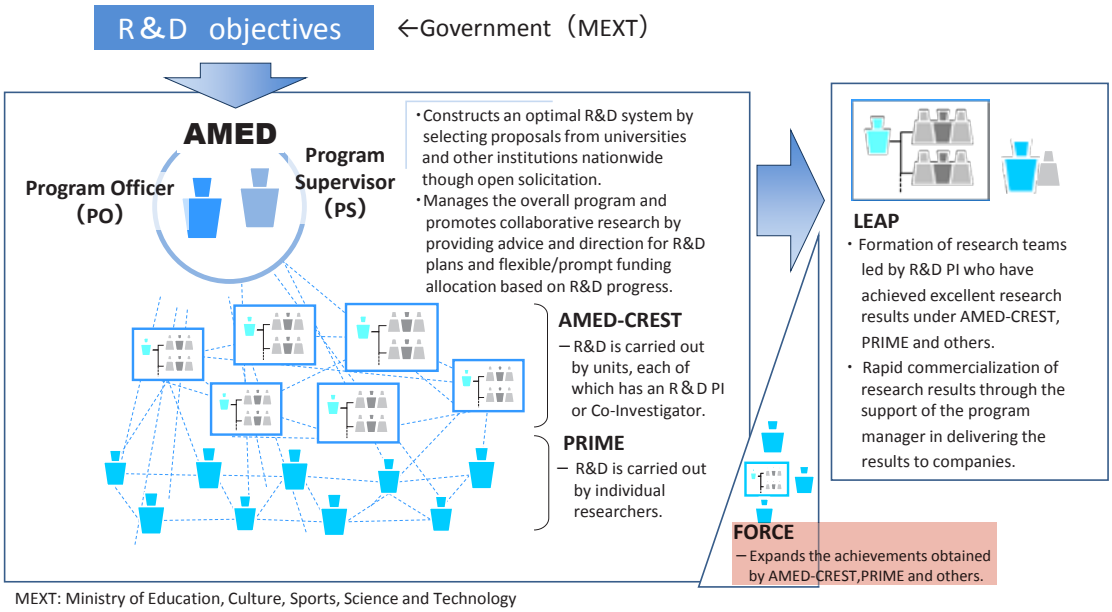
Among biological systems comprised with age is the decline of immune response, called immune senescence. One of the reasons for immune senescence is a decreased supply of naïve T and B lymphocytes, which results from the less growth of T- and B-precursors with age. In order to clarify the molecular mechanisms 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.
Institution names, affiliations, and titles are as of the final year.

FORCE

Objectives/Characteristics

- Step-type (Frontier Outstanding Research for Clinical Empowerment, FORCE) program promotes prospective R&Ds which can lead to large developments, among research accomplishments obtained from terminated AMED-CREST , PRIME and other projects. FORCE program aims to verify correlations between their achievements and target diseases and to validate generated analytical methods, devices, and instruments, by using human clinical samples.
- Purpose 1, Correlations with human diseases:
  - Elucidation of correlations between the object of R&Ds (e.g., proteins, genes, metabolites, biological phenomena) and specific diseases, and researches for their potentials toward medical treatments to narrow down target diseases.
  - Establishment of novel/improved model systems for target diseases.
- Purpose 2, Analytical methods, devices, and instruments:
  - Verification of versatility and effectiveness of analytical methods, devices, and instruments based on experimental results under various conditions including human clinical samples.
  - Improvement and optimization of analytical technologies and methods.



MEXT: Ministry of Education, Culture, Sports, Science and Technology

Program Supervisor (PS)

OHSHIMA Etsuo
Senior Fellow,
Kirin Holdings Co., Ltd.

Program Officer (PO)

ODA Yoshiya
Professor, Graduate School of Medicine,
The University of Tokyo.

KOHNO Takashi
Chief, Division of Genome Biology,
National Cancer Center Research Institute

MOTOHASHI Hozumi
Professor, Tohoku University
Graduate School of Medicine.

R&D Period and R&D Costs

Program	R&D Period	Annual R&D Costs (direct cost)
FORCE	Up to two years	Up to 20 million yen

FORCE Started in 2023 · 5th period

Pathological significance of cardiomyocyte DNA damage in human heart failure

KOMURO Issei
Project professor,
The University of Tokyo Hospital

Heart failure is a serious disease that, along with cancer, threatens the lives of many people worldwide. The disruption of the heart's response mechanism to mechanical stimuli is the essence of heart failure pathogenesis, and we have identified DNA damage as a central molecular mechanism. This study aims to elucidate the molecular mechanisms by which DNA damage causes heart failure and to develop a long-awaited pathogenesis-based therapeutic agent for heart failure.

Study on regulation of intestinal immunity and epithelial barrier in humans

TAKEDA Kiyoshi
Professor,
Osaka University Graduate School of Medicine

We have analyzed human intestinal microbiota and microbiota-derived metabolites to identify changes in patients with inflammatory bowel disease (IBD), and have analyzed the effects of these changes at the in vivo level using a mouse model of intestinal inflammation. In this project, we aim to elucidate the pathophysiology of human IBD by developing the pathophysiology of IBD clarified by the analysis of "human intestinal microbiota and metabolites – mouse model" into "human intestinal microbiota and metabolites - human intestinal mucosal cells".

Development of a microfluidic device system for analyzing the single immune cell function and its application to diagnosis of anti-tumor activity

TAMIYA Eiichi
Specially appointed professor,
SANKEN, Osaka University

Using biosensing and microfluidic device technology, we can identify the function of each cell, investigate the relationship between these cell function and various diseases, and characterize the genomic traits of individual cells by isolating each cell and linking each cell to genetic analysis. We aim to elucidate the relationship between cell function and disease. Using the developed chip, we seek to investigate whether single-cell GZMB activity evaluation can be used to predict the efficacy of ICT treatment in lung cancer. Our goal is to enhance the efficiency of cancer immunotherapy and contribute significantly to the comprehension of anti-tumor immune responses.

Development of innovative therapies for ischemic diseases targeting vascular endothelial stem cells

NAITO Hisamichi
Professor, Graduate School of Medical Sciences,
Kanazawa University

Regulation of angiogenesis is critical to overcome ischemic diseases. We priviously reported that vascular endothelial stem cells are important for angiogenesis and vascular repair. In this study, we analyze human samples to clarify the cellular heterogeneity of vascular endothelial cells, including vascular endothelial stem cells. In addition, we aims to develop new therapeutic targets by clarifying the correlation between endothelial cell heterogeneity and ischemic diseases.

FORCE Started in 2024 · 6th period

Autophagy activation by AUTACs for treatments of neurodegenerative diseases

ARIMOTO Hirokazu
Professor,
Tohoku University

Autophagy is an intracellular degradation mechanism that is also involved in the removal of debris that have accumulated in the cell. The AUTACs we are studying are compounds that selectively degrade specific harmful substances. We will work with clinicians to develop AUTACs effective in human-patient-derived cells, primarily for the remediation of neurodegenerative diseases.

Development of a new method for evaluating diagnostic and therapeutic efficacy using multi-parametric single-nanoparticle analysis

ISHII Ken
Professor,
The Institute of Medical Science, The University of Tokyo

We have invented a novel flow cytometry technology to develop high-resolution single nanoparticle analysis and sorting techniques for extracellular particles, such as exosomes and viruses, which have traditionally been analysed in bulk. By analysing microparticles in biological samples, including exhaled breath condensate, this study aims to develop new methods for disease diagnosis and treatment evaluation, ultimately proposing single-particle biology as an alternative to single-cell biology.

Mechanism of liver tumor-promoting microenvironment formation by gut microbial factors and its application to prognosis prediction, prevention, and treatment

OHTANI Naoko
Professor,
Graduate School of Medicine, Osaka Metropolitan University

Treatments for non-viral, metabolic dysfunction-associated liver diseases and hepatocellular carcinoma (HCC) are still underway, and even immune checkpoint inhibitors have shown limited efficacy for them. We focus on the gut-liver axis-mediated impact of gut microbiota and microbiota-related factors on the liver microenvironment. In this study, we aim to uncover mechanisms underlying the non-viral HCC progression and identify potential biomarkers and molecular targets. Additionally, we focus on improving the gut barrier function, which could contribute to preventing liver cancer progression.

Elucidation of correlations between lymphoma and dysfunction of inter-organelle lipid transport

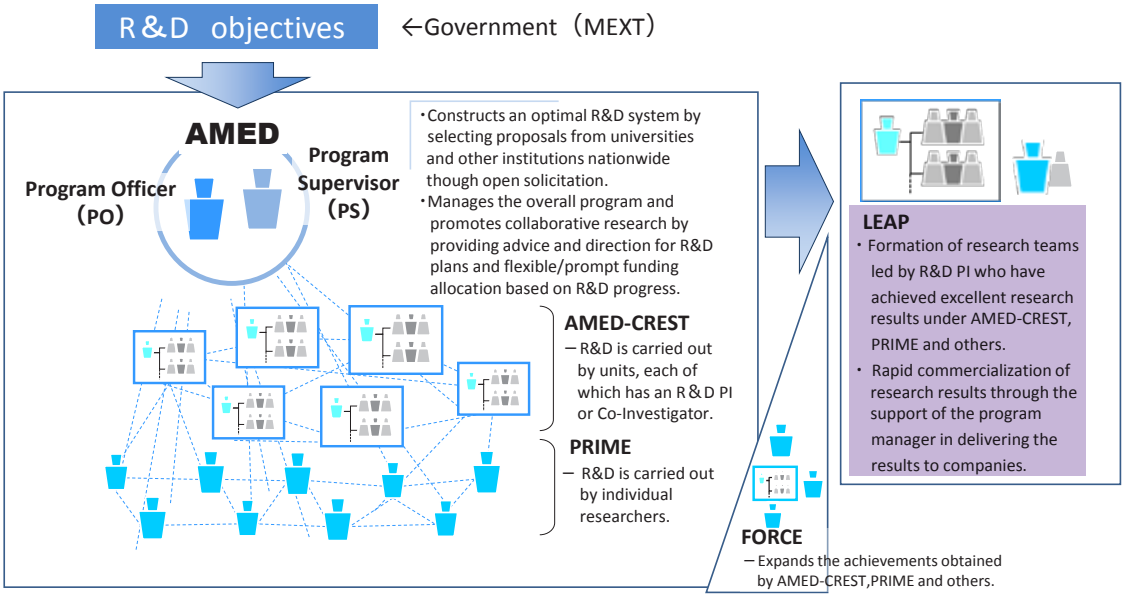
NAKATSU Fubito
Associate Professor, Graduate School of Medical and Dental Sciences, Niigata University

Lipids shape the structure of cellular membranes, including the plasma membrane and organelle membranes, and are responsible for numerous crucial physiological functions. We have studied the regulation and operational mechanisms of inter-organelle lipid transport at membrane contact sites, where cellular membranes are closely apposed. The goal of this research is to investigate whether the malfunction of inter-organelle lipid transport contributes to human malignant lymphoma pathology using clinical specimens, and to elucidate the pathogenesis using model mice and in vitro analyses.

LEAP

Objectives/Characteristics

LEAP (incubation-type, Leading Advanced Projects for medical innovation) is one of the programs promoted by the Advanced Research and Development Programs for Medical Innovation. The program aims to accelerate development of exceptional R&D results generated through unit-type (AMED-CREST) and solo-type (PRIME) projects implemented under the Advanced Research and Development Programs for Medical Innovation, passing on this follow of R&D to companies and venture businesses.
In concrete terms, the technical feasibility of world-leading exceptional R&D results are proven and presented, and rights to these R&D results are appropriately acquired, through the innovation-orientated R&D management of the Program Manager (PM). Through this, it is anticipated that the flow of R&D based on top scientific results will be turned towards medical applications and be passed on to companies, clinicians, and other programs, leading to the future development of innovative drugs, medical devices, and medical technologies, thereby giving birth to a tide of R&D that expands towards social change.



MEXT: Ministry of Education, Culture, Sports, Science and Technology

Program Supervisor (PS)

TAKIMOTO-KAMIMURA Midori

Director, The Chem-Bio Informatics Society, CBI Research Institute, Quantum-Structural life Science Laboratories

Program Officer (PO)

UCHIDA Takahiro

Founder and CEO, Sanamedi, Inc.

OGAWA Atsushi

General Manager of Japan, ICON plc

R&D Period and R&D Costs

The R&D period and costs for a single R&D project are basically as follows

Program	R&D Period	Annual R&D Costs (direct cost)
LEAP	Up to five years	Up to 300 million yen

Proposed R&D costs are examined as part of the selection process. Actual R&D budgets are determined after examination and approval of R&D project plans.

R&D Organization

The Program Manager (PM) works in cooperation with the R&D Principal Investigator (PI) to manage the overall R&D team, including other research collaborators, promoting R&D aimed at proving and presenting technical feasibility.

- R&D is implemented by the R&D PI.
- One PM is assigned to each R&D project. The R&D PI presents a PM candidate proposal at the time of R&D proposal submission.
- The R&D PI has responsibility for the R&D project overall, and promotes R&D necessary for proving and presenting technical feasibility as indicated by the PM. The PM works in cooperation with the R&D PI in carrying out management of the R&D projects for which they are responsible.
- The PM and R&D PI organize an appropriate R&D system that is necessary and sufficient for proving and presenting technical feasibility.
- Based on evaluations and advice provided by the Project Evaluation Committee, the PM proactively builds networks through dialogue with experts, mutual cooperation among participating researchers, and collaboration with individuals and institutions both in Japan and overseas while simultaneously utilizing these networks to promote R&D results with a view to developing them for medical application.

※ PS and PO participate in the preliminary evaluation as a program evaluation committee member and may be possible to participate in the mid-term and post-evaluations as observers.

Started in 2020 LEAP

Development of MuSK-activating drugs for the treatment of intractable neuromuscular diseases

SUGA Hiroaki
Professor, Graduate School of Science, The University of Tokyo

Program Manager KUBO Yuichi
Project Senior Specialist, Graduate School of Science, The University of Tokyo

This project develops drugs that apply to the medical treatment of intractable neuromuscular diseases including myasthenia gravis, amyotrophic lateral sclerosis, and sarcopenia via a mechanism of specific activation of the muscle specific receptor tyrosine kinase. We will develop two distinct modality molecules with unique pharmacological properties, aiming at to deliver either or both molecules to a preclinical phase.

Started in 2021 LEAP

Innovation in molecular design and production of mRNA based on chemistry and its application to vaccines

ABE Hiroshi
Professor, Graduate School of Science, Department of Chemistry, Nagoya University

Program Manager KIM Shokaku
Designated Professor, Graduate School of Science, Nagoya University

Current mRNA drugs have issues to be solved in terms of (1) manufacturing cost, (2) mass synthesis, (3) quality and purity, (4) storage management, (5) stability and sustainability, (6) translation efficiency, and (7) delivery. In this research, we will develop a unique platform technology for mRNA drug discovery to solve the above issues. In addition, in order to cope with current or future pandemics, we will establish a production technology for chemically modified mRNA and establish a base for stable supply in cooperation with pharmaceutical companies.

Started in 2022 LEAP

Seeds and modality development to enhance health and longevity from enhanced motor function

ASAHARA Hiroshi
Professor, Department of Systems Bio Medicine, Graduate School and Faculty of Medicine, Institute of Science Tokyo

Program Manager SHIMOKAWA Teruhiko
Professor, special, Center for Medical Innovation, Institute of Science Tokyo

In the super-aging society, the human locomotor function is linked to medical issues as a new group of diseases such as locomotive syndrome and frailty, as well as to the proposed concepts of "healthy life expectancy" and "healthy longevity society." For diseases, injuries, and aging of the locomotor organs that control this function, we will develop new seeds and modalities related to nucleic acid medicine, bioligament, and cell activation compounds for joint tissue diseases, leading to new treatment methods.

Started in 2023 LEAP

Development of immune system-humanized animal by design chromosome and the drug discovery application

KAZUKI Yasuhiro
Professor, Chromosome Engineering Research Center, Tottori University

Program Manager SAITO Hironobu
Specially appointed Professor, Chromosome Engineering Research Center, Tottori University

The difficulty in predicting human immune responses through in vitro tests and animal experiments is one of the major factors that reduces the probability of success in drug development. In this research, we will use our unique chromosome engineering technology to develop a variety of human immune system-transchromosomic (TC) mouse models that faithfully reproduces the foreign antigen-recognition system of human cellular and humoral immunity. The TC mouse group is useful as a platform that contributes to accelerating research and development of effective and safe biopharmaceuticals.

Started in 2024 LEAP

Therapeutic and diagnostic methods for kidney disease targeting tertiary lymphoid tissues

YANAGITA Motoko
Professor, Kyoto University Graduate School of Medicine

Program Manager SUZUKI Shinobu Innovation Design Expert, Program-Specific Professor, Kyoto University Office of Institutional Advancement and Communications

Chronic kidney disease (CKD) is a highly prevalent condition that progresses to end-stage kidney disease; however, current treatments do not completely prevent its progression. Through the AMED-CREST study, the Principal Investigator identified the formation of tertiary lymphoid structures (TLSs) in the kidney as CKD progressed. Furthermore, the inhibition of TLS formation has been observed to improve kidney function and ameliorate kidney injuries, thus presenting a promising novel therapeutic target. The objective of this research project is to develop therapeutic and diagnostic methodologies targeting TLSs for clinical applications.

Advanced Research and Development Programs for Medical Innovation Completed R&D Areas and Projects

Microbiome

Understanding the Interactions and Symbiosis between the Microbiome and the Host Organism, Leading to an Understanding of the Mechanisms of Disease Onset

AMED-CREST PRIME

【Research and Development Objectives】

Understanding the crosstalk and symbiosis between the microbiome and host, and the applications to health and healthcare

Program Supervisor (PS)

SASAKAWA Chihiro

Director and Professor, Medical Mycology Research Center, Chiba University

Program Officer (PO)

OHNO Hiroshi

Deputy Director, RIKEN Center for Integrative Medical Sciences

In this R&D area, we aim to achieve a better understanding of microbiome-host interactions and symbiosis and use these findings to elucidate the mechanisms involved in disease onset, thereby contributing to the development of new concepts for health and healthcare through the control of the human microbiome.
Various different microorganisms—bacteria, fungi, viruses—live in the parts of the human body that come into direct contact with the external environment, such as the digestive tract, skin, oral cavity, nasal cavity, respiratory organs, and reproductive organs. These microorganisms form microbiomes with different characteristics specific to each location. Research has started to show that the microbiomes of healthy individuals differ from those in diseased individuals in a wide range of diseases and conditions, suggesting that the microbiome plays an important role in health and disease. However, we still have a lot to learn about the mechanisms involved in host-microbiome interactions, symbiosis, and disease onset in terms of how these microbiomes form or change and how they affect human health, disease onset, or disease progression.
In this R&D area, we aim to gain a comprehensive understanding of the processes involved and develop new strategies for health promotion and healthcare technologies based on novel mechanisms for host-microbiome interactions.

R&D Area Advisors

KABASHIMA Kenji	Professor and Chairman, Kyoto University
KITANO Hiroaki	President,The Systems Biology Institute
KUMANOGOH Atsushi	Professor and Dean, Osaka University
KUROKAWA Ken	Vice-Director, National Institute of Genetics
SAKATA Tsuneaki	Specially Appointed Professor, Co-creation Bureau, Osaka University.
SHIRAHIGE Katsuhiko	Director Institute for Quantitative Biosciences, The University of Tokyo
DOHI Taeko	Visiting Professor, Faculty of Pharmacy, Keio University
HAYASHI Tetsuya	Professor, Kyushu University
FUKUSAKI Eiichiro	Professor, Osaka University
MATSUKI Takahiro	Manager, Gastrointestinal Symbiosis Research Laboratory, Basic Research Department Yakult Honsha Co., Ltd.

AMED-CREST

Started in 2016

Development of therapeutic strategies to inflammatory diseases based on comprehensive understanding on skin microbiome and host relationship

AMAGAI Masayuki
Professor and Chair, Department of Dermatology, Keio University School of Medicine

Started in 2016

Elucidation of causal association of intestinal dysbiosis in abnormal intestinal aggregation of alpha-synuclein in Parkinson's disease

OHNO Kinji
Professor, Nagoya University Graduate School of Medicine

Started in 2016

Understanding of disease mechanisms between microbiota and host intestinal epithelium

KANAI Takanori
Professor, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University School of Medicine

Started in 2016

Analysis on the mechanisms for commensalism and interplay of intestinal microbiota and the host

TAKEDA Kiyoshi
Professor, Graduate School of Medicine, Osaka University

Started in 2016

Clarifying the role of microbiome in cancer immunity for application into cancer therapy

NISHIKAWA Hiroyoshi
Chief, Division of Cancer Immunology, Research Institute/ EPOC, National Cancer Center

Started in 2017

Elucidation of host energy regulation by gut microbial metabolites and the development of preventive and therapeutic strategies for the related metabolic disorders

KIMURA Ikuo
Professor, Graduate School of Biostudies, Kyoto University

Started in 2017

Elucidation of molecular mechanisms of gut microbiota regulation by intestinal IgA

SHINKURA Reiko
Professor, Institute for Quantitative Biosciences, The University of Tokyo

Started in 2017

Development of metagenomics, metabolomics, and bioinformatics hub to promote human microbiome research and development

TOYODA Atsushi
Project Professor, Departnient of Genomics and Evolutionary Biology, National Institute of Genetics

Started in 2018

The mechanism and the regulation of liver diseases involved in gut-liver axis-mediated intestinal microbiota

OHTANI Naoko
Professor, Department of Pathophysiology, Osaka Metropolitan University, Graduate School of Medicine

Started in 2018

Exploring the molecular mechanisms of the systemic changes caused by the oral microbial dysbiosis in association with periodontal disease

MURAKAMI Shinya
Professor, Department of Periodontology, Osaka University Graduate School of Dentistry

Started in 2018

Study of microbiota-mediated modulation of neuroinflammation, neurodegeneration and neural development

YAMAMURA Takashi
Director, National Institute of Neuroscience, NCNP

PRIME

Started in 2016

Crosstalk among microbiome, host, disease, and drug discovery enhanced by statistical genetics

OKADA Yukinori
Professor, Graduate School of Medicine, Osaka University

Started in 2016

Tracking intercellular electrochemical interaction in human bacterial flora by gene expression mapping method

OKAMOTO Akihiro
Group leader, International Center for Materials Nanoarchitectonics, National Institute for Material Sciences

Started in 2016

High-resolution metagenomics for intra-species variations based on assembly of the comprehensive draft genomes

KAJITANI Rei
Assistant Professor, School of Life Science and Technology, Tokyo Institute of Technology

Started in 2016

Microbiota regulates IgE-mediated allergic responses

KIM Yun-Gi
Professor, Research Center for Drug Discovery, Faculty of Pharmacy, Keio University

Started in 2016

Regulation of intestinal microbiota through carbohydrate chain expressed on intestinal epithelial cells

GOTO Yoshiyuki
Associate Professor, Division of Molecular Immunology, Medical Mycology Research Center, Chiba University

Started in 2016

Development of metatranscriptome analysis method based on megagenome assembly and its application to metatranscriptome map of commom marmoset

SAKAKIBARA Yasubumi
Professor, Keio University

Started in 2016

Isolation of yet-uncultured microorganisms and elucidation of symbiosis mechanism between the microbe

SAKAMOTO Mitsuo
Senior Research Scientist, Japan Collection of Microorganisms, RIKEN BioResource Research Center

Started in 2016

Investigation of the mechanism for forming neonatal gut microbiota

SAWA Shinichiro
Professor, Medical Institute of Bioregulation, Kyushu University

Started in 2017

Developing mouse intestine infection model against enteric pathogens through the study of microbiota-bacterial pathogens interplay and its application

ASHIDA Hiroshi
Associate Professor, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University

Started in 2017

Elucidation of DOHaD mechanisms driven by gut microbiota

OBATA Fumiaki
Team Leader, Laboratory for Nutritional Biology, RIKEN center for Biosystems Dyamics Research

Started in 2017

Elucidation of the relationship between microbiota and enteroendocrine cells

KURAISHI Takayuki
Associate Professor, Kanazawa University

Started in 2017

Elucidation of crosstalk between the enteric nervous system and commensal microbiota for gut mucosal health and disease

KURASHIMA Yosuke
Associate Professor, Graduate School of Medicine, Department of Innovative Medicine, Chiba University

Started in 2017

Research for the mechanism of human gut microbiota mediated induction of immune cells and cancer immunity

TANOUE Takeshi
Assistant Professor, Department of Microbiology and Immunology, Keio University School of Medicine

Started in 2017

Elucidation of the inflammation regulating mechanism by skin resident commensals in the pathogenesis of inflammatory skin diseases

NAKAJIMA Saeko
Program-Specific Associate Professor, Graduate School of Medicine, Kyoto University

Started in 2017

The role of gastric dysbiosis in gastrointestinal diseases and its relationship to nerve-dependent regulation of gastrointestinal stem cells

HAYAKAWA Yoku
Assistant Professor, Department of Gastroenterology, The University of Tokyo

Started in 2017

Identification of the mechanism responsible for the evolutionary changes of *S. aureus*-genome controlled by normal skin microbiome

MATSUOKA-NAKAMURA Yuumi
Associate Professor, Immunology Frontier Research Center, Osaka University

Started in 2018

Mucosal immunity developed by microbe-host interaction through D-amino acids and its pathological role in the immunological diseases

SASABE Jumpei
Assistant Professor, Keio University School of Medicine

Started in 2018

Comprehensive analysis of microbiome by single cell glycomics

TATENO Hiroaki
Group Leader, Cellular and Moleclar Biotechnology Research Institute, National Institute of Advanced Industrial Science and Technology (AIST)

Started in 2018

The occurrence and control of diabetes and obesity: exploring the multidimensional interaction between host, antagonist bacteria, and protagonist viruses

TAMAKI Hideyuki
Group Leader, Bioproduction Research Institute, National Institute of Advanced Industrial Science and Technology (AIST)

Started in 2018

Mechanism for acceleration of T cell senescence and transformation by intestinal flora

NAKATSUKASA Hiroko
Associate Professor, Laboratory of Microbiology and Immunology, Graduate School of Pharmaceutical Sciences, Chiba University

Started in 2018

Elucidation of inhibitory receptor-microbiome interaction in health and disease

HIRAYASU Kouyuki
Associate Professor, Kanazawa University Advanced Preventive Medical Sciences Research Center

Started in 2018

Elucidation of mechanism of pancreatic cancer initiation based on the interaction between microbial flora and host

FUKUDA Akihisa
Lecturer, Department of Gastroenterology and Hepatology, Graduate School of Medicine, Kyoto University

Started in 2018

Understanding of immunity and metabolism network through nutrient-specific intestinal microbial control and bacterial metabolites

FUJISAKA Shiho
Associate Professor, Faculty of Medicine, Academic Assembly, University of Toyama

Started in 2018

Unraveling the anti-inflammatory mechanisms of human 2 *Bacteroides* species and their application for treating chronic inflammatory diseases

YAMASHITA Tomoya
Professor, Advanced Medical Science, Graduate School of Science, Technolgy and Innovation, Kobe University

※ The names of the position, institution and organization are as of the end of the R&D pursuit area year.

Mechanobiology

Mechanobiology Elucidation of Mechanobiological Mechanisms and Their Application to the Development of Innovative Medical Instruments and Technologies

AMED-CREST PRIME

【Research and Development Objectives】

Elucidation of mechanobiological mechanisms leading to the development of innovative medical instruments and technologies

Program Supervisor (PS)

SOKABE Masahiro

Professor, Human Information Systems Laboratories,Kanazawa Institute of Technology

Program Officer (PO)

ANDO Joji

Professor, Laboratory of Biomedical Engineering, Dokkyo Medical University School of Medicine

In this R&D area, the main objective is to understand the body's systems for sensing, transduction, and response to physical stimuli and to create platform technologies with healthcare applications.
When the cells making up the body are exposed to different physical stimuli, such as skeletal muscle/organ functioning, blood flow, gravity, or signals originating from neighboring cells and substrates, they use these stimuli to self-regulate replication, differentiation, death, morphogenesis, or movement. We do not yet have a detailed understanding of how the cells perceive physical stimuli or how these stimuli elicit physiological or pathological responses after the stimuli have been converted into intracellular signals. Mechanobiology is a new R&D area that combines physics, engineering, medical science, and biology to investigate such questions and clarify the role of physical stimuli in regulating the structure and function of cells, tissues, organs, and the body as a whole.
A better understanding of the mechanisms involved in perception of and response to physical stimuli is expected to open up new avenues of research in the quest to understand currently unresolved issues like how the body develops, grows, and forms tissues; how a failure of these mechanisms leads to disease; or how to develop regenerative medicine techniques for tissues and organs. We also expect to develop devices that can quantitatively apply and control physical stimuli or platform technologies for the precise measurement of biological responses to physical stimuli.

R&D Area Advisors

KOTERA Hidetoshi	Professor Emeritus,Kyoto University
SATO Masaaki	Professor Emeritus, Tohoku University
SHIGEMATSU Takashi	Bio Science & Engineering Laboratory,Research & Development Management Headquarters, FUJIFILM Corporation
TAKEDA Shinichi	Honorary director general, National Institute of Neuroscience, National Center of Neurology and Psychiatry (NCNP)
NARUSE Keiji	Professor, Okayama University
NISHIMOTO Takahiro	General Manager, Technology Research Laboratory, Shimadzu Corporation
MIZUMURA Kazue	Professor Emeritus, Nagoya University

AMED-CREST

Started in 2015

Exploration of molecular mechanisms of nucleo-cytoplasmic mechano-transduction and its medical application

OGURA Toshihiko
Professor, Institute of Development, Aging and Cancer, Tohoku University

Started in 2015

Development of mechanobio-materials for quality keeping culture of stem cells

KIDOAKI Satoru
Professor, Institute for Materials Chemistry and Engineering, Kyushu University

Started in 2015

Elucidation of mechano-cascade by osteocyte for bone homeostasis

NAKASHIMA Tomoki
Professor, Department of Cell Signaling, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University

Started in 2015

Analyses of the mechanism nderlying nano-scale mechanoresponses of the inner ear and its application to medical therapies for deafness

HIBINO Hiroshi
Professor, Department of Molecular Physiology, Niigata University School of Medicine

Started in 2015

Development of a comprehensive analysis technique for mechanotransduction through tissue-cell-nucleus pathway toward the elucidation of mechanisms of disease development in blood vessels

MATSUMOTO Takeo
Professor, Department of Mechanical Systems Engineering, Graduate School of Engineering, Nagoya University

Started in 2015

Vascular mechanobiology: Molecular mechanisms of blood flow sensing and cerebral aneurysm development

YAMAMOTO Kimiko
Associate Professor, Graduate School of Medicine, The University of Tokyo

Started in 2016

Analysis of mechano signal cascade regulating tendon/ligament homeostasis and regeneration

ASAHARA Hiroshi
Professor, Department of Systems Bio Medicine, Graduate School and Faculty of Medicine, Tokyo Medical and Dental University

Started in 2016

Elucidation of membrane and sugar chain environment required for mechano-sensing/ response and its application to the development of therapeutic strategy for muscle diseases

KANAGAWA Motoi
Professor,Ehime University Graduate School of Medicine

Started in 2016

Mechanobiology in cancer and stroma cells

HAGA Hisashi
Professor, Faculty of Advanced Life Science, Hokkaido University

Started in 2016

Mitochondrial mechanobiology to unravel its role in muscular atrophy

HIGASHITANI Atsushi
Professor, Tohoku University Graduate School of Life Sciences

Started in 2017

Molecular mechanobiological and pathological analyses of cell migration and neuronal network formation based on the force interaction between cells and adhesive substreates

INAGAKI Naoyuki
Professor, Graduate School of Biological Sciences, Nara Institute of Science and Technology

Started in 2017

Analysis of angiogenesis-related signaling pathways regulated by cyclic compression force-for developing wound treatment devices by non-contact ultrasound-

OGAWA Rei
Professor and Chief, Department of Plastic, Reconstructive and Regenerative Surgery, Graduate School of Medicine, Nippon Medical School

Started in 2017

Development of novel therapeutic approaches for heart failure by dissecting the mechanisms of cardiomyocyte mechanobiology

KOMURO Issei
Professor, Graduate School of Medicine, The University of Tokyo

PRIME

Started in 2015

Thermal control of cellular functions using the technology to create organelle-size heat spots

ARAI Satoshi
Associate Professor, NanoLSI, Kanazawa University

Started in 2015

Cardiac reprogramming and heart regeneration via mechano-transduction

IEDA Masaki
Professor and Chair, Department of Cardiology, Faculty of Medicine, University of Tsukuba

Started in 2015

Elucidation of the molecular mechanisms and physiological role of mechanotransduction and establishment of innovative targets for medicine

KATANOSAKA Yuki
Lecturer, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University

Started in 2015

Mechanobiology of baroreceptor afferent nerves and a development of nerve engineering-based medical therapy

KAMIYA Atsunori
Professor, Department of Cellular Physiology, Graduate School of Medicine, Okama University

Started in 2015

Stress intensity-dependent mechano-responses of articular chondrocytes

SAITO Taku
Associate Professor, Orthopaedic Surgery, Graduate School of Medicine, The University of Tokyo

Started in 2015

Nuclear micromechanics and mechano-transduction mechanisms

SHIMAMOTO Yuta
Associate Professor, Center for Frontier Research, National Institute of Genetics

Started in 2015

Elucidation of plasma membrane tension dependent signal transduction in cancer cell invasion and metastasis

TSUJITA Kazuya
Lecturer, Biosignal Research Center,Kobe University

Started in 2015

Development of biomimetic microdevices to recapitulate physiological mechanical stimulation to model hematopoietic function

TORISAWA Yu-suke
Associate Professor, The Hakubi Center for Advanced Research, Kyoto University

Started in 2015

Non-invasive force measurement using fluctuation for organelle transport in neurons

HAYASHI Kumiko
Associate Professor, Graduate School of Engineering, Tohoku University

Started in 2015

Elucidating the mechanisms of mechanotransduction in angiogenesis

FUKUHARA Shigetomo
Professor, Dept. of Mol. Pathophysiol., Inst. of Adv. Med. Sci., Nippon Medical School

Started in 2015

Innovation of novel medical technology against cardiac mechano-sensor, pannexin

FURUKAWA Tetsushi
Professor, Department of Bio-informational Pharmacology, Medical Research Institute, Tokyo Medical and Dental University

Started in 2015

Mechanobiological understanding of the mechanism of selective gene expression regulated by extracellular nano-topographical cues, and the application to external control of the stem cell differentiation

MIYOSHI Hiromi
Associate Professor, Faculty of System Design, Tokyo Metropolitan University

Started in 2015

Study on the autonomous regulation of ciliary motility through mechanical feedback system

YOSHIMURA Kenjiro
Professor,Shibaura Institute of Technology

Started in 2016

Light-responsive dynamically manipulatable cell culture platforms for revealing the mechanism of cellular mechanostructural memory

UTO Koichiro
Independent Scientist, MANA, National Institute for Materials Science (NIMS)

Started in 2016

Identification and functional analysis of mechanosensor proteins involoved in actin cytoskeleton remodeling

OHASHI Kazumasa
Professor, Graduate School of Life Sciences, Tohoku University

Started in 2016

Molecular mechanisms of mechano-feedback from epithelial architecture in organogenesis

KONDO Takefumi
Program-Specific Assistant Professor, Graduate school of Biostudies, Kyoto University

Started in 2016

Single molecule imaging; on the mechanism behind the tension sensing by actin filaments

TATSUMI Hitoshi
Professor, Kanazawa Institute of Technology

Started in 2016

Elucidation of mechanobiology of renal glomerular podocytes and development of innovative evaluation method of intraglomerular pressure

NAGASE Miki
Professor, Department of Anatomy, Kyorin University Faculty of Medicine

Started in 2016

The role of phospholipid flippase-mediated mechanosensing machinery in myotube formation

HARA Yuji
Associate Professor, Graduate School of Engineering, Kyoto University

Started in 2016

Studies on the mechanism and physiology of brain sensors for osmolality and Na^+ level

HIYAMA Takeshi
Senior assistant professor, Graduate school of medicine denistry and pharmaceutical sciences, Okayama University

Started in 2016

Elucidating the mechanism of cellular force-sensing and -generating systems by using live-cell, low invasive imaging technique

YOSHIMURA Shige H.
Associate Professor, Division of Integrated Life Science, Graduate School of Biostudies, Kyoto University

Started in 2017

Imaging and optical control of force-field in cardiomyocyte using DNA nano-bio device

IWAKI Mitsuhiro
Deputy Team Leader, Center for Biosystems Dynamics Research,RIKEN

Started in 2017

Mechanobiology of stem cell tissues under adhesion-modulated microenvironment

OKEYO Kennedy Omondi
Senior Lecturer, Institute for Frontier Life and Medical Sciences, Kyoto University

Started in 2017

Isolation of novel temperature-sensing proteins and development of applied-technology using these molecules

KUHARA Atsushi
Professor, Department of Biology, Faculty of Science and Engineering, Konan University

Started in 2017

Quantification of stress/deformation/ signal fields and data assimilation to understand and predict mechanics of a growing epithelial tissue

SUGIMURA Kaoru
Associate Professor, Department of Biological Sciences, Graduate School of Science, The University of Tokyo

Started in 2017

Elucidation of invasion mechanism of glioma stem cell-derived population response induced by interstitial flow

SUDO Ryo
Professor Department of System Design Engineering,Keio University

Started in 2017

Identifying and manipulating molecules responsible for insufficient transcriptional activation of HSF1 and mitochondrial adaptabilities in aged skeletal muscle

TAMURA Yuki
Assistant Professor, Department of Physical Education, Faculty of Sport Science, Nippon Sport Science University

Started in 2017

The function and regulation of mechanosensors in skin metabolism

TOYOSHIMA Fumiko
Professor, Institute for Frontier Life and Medical Science, Kyoto University

Started in 2017

Functional analysis of a transcriptional co-activator that senses mechanical stimulation and promotes tissue fibrosis for developing a new fibrotic treatment method

NAKAYA Michio
Associate Professor, Graduate School of Pharmaceutical Sciences, Kyushu University

Started in 2017

Elucidation of the role of mechanosensation for proper circulation of lymph

NONOMURA Keiko
Assistant Professor, Division of Embryology, National Institute Basic Biology

※ The names of the position, institution and organization are as of the end of the R&D pursuit area year.

Lipid Molecules

Studies on Specific Activities and Functions of Lipid Molecules to Develop Innovative Medical Technologies

AMED-CREST PRIME

【Research and Development Objectives】

Comprehensive elucidation of functional lipid which contributes to breakthrough medicines

Program Supervisor (PS)

YOKOYAMA Shinji

Visiting Professor,
Research Institute for Biological Functions, Chubu University

Program Officer (PO)

IGARASHI Yasuyuki

Professor, Faculty of Advanced Life Science,
Hokkaido University

Lipids carry fundamental functions in living organisms as major components of biomembranes and energy-storage molecules. Numbers of their derivatives also play specific roles in regulating metabolism, immunity/inflammation, reproduction, circulation, neural network, etc, and are involved in pathogenesis of various disorders and diseases related to these systems. The objective of this research and development R&D area is to investigate novel biological functions of lipids and develop new technologies for their analysis, to elucidate molecular mechanism of lipid-associated various diseases, and finally to exploit novel developmental seeds for compounds and technologies to overcome these diseases, i.e. chemical compounds relevant to pre-clinical stage, target materials and reactions promising medical application in near future, or innovative diagnostic methods that may construct new clinical benefits, etc.

Lipid research has advanced along with numbers of discovery of new biological activities and exploitation of new analytic technologies. Therefore, more innovative research and exploitation should also be necessary in order to accomplish the goal of this program and initiatively dispatch the novel results toward the world. It should be also important to gather ideas of researchers in various different fields and disciplines, such as the scientists in clinical medicine, pharmaceutical sciences, synthetic chemistry, biophysics and bioengineering, and information engineering, as well as those in lipid biology and biochemistry who have carried mainstream of lipid research. Broad viewpoints based on our interdisciplinary research team works will be indispensable for advancement of research and development in lipid research field to strengthen our international competitiveness.

We would like the program members to conduct their researches with practical translational outputs always in their mind. However, it does not necessarily mean that all the members are obliged to produce practical seeds within the term. We consider it is also important to promote fundamental basic studies that would possibly become the basis for generation of innovative technologies, diagnostics, and medicines only in not-remote future, for development and enforcement of international competitiveness of our lipid research. The research field of biological activities of lipids is continuously expanding, and this R&D area is expected to lead the world in innovative and explorative research in this field.

Because of expected medical application, target lipids are primarily set as the molecules originating in mammalian cells. However, the molecules closely related to human disorders and of nutritional importance may be included, such as omega-3 fatty acids and ceramide.

R&D Area Advisors

ISHII Ken	Professor, The University of Tokyo
UESUGI Motonari	Professor, Kyoto University
OKADA Yasushi	Team Leader, RIKEN Center for Biosystems Dynamics Research
OGAWA Yoshihiro	Professor, Kyushu University
CHIBA Kenji	Fellow, Mitsubishi Tanabe Pharma Corporation
NISHIJIMA Masahiro	Professor Emeritus, Showa Pharmaceutical University
HANDA Tetsurou	Auditor, Kyoto Pharmaceutical University
FUKAMI Kiyoko	Professor, Tokyo University of Pharmacy and Life Sciences
FUKUSHIMA Daikichi	Director, Ono Medical Research Foundation, Foundation Chairman
NISHIMAKI-MOGAMI Tomoko	National Institute of Health Sciences

AMED-CREST

Started in 2015

Development of MULTUM-PALM and its application to cell membrane biology

UEDA Masahiro
Professor, Graduate School of Frontier Biosciences, Osaka University

Started in 2015

Elucidation of molecular mechanism of body surface barrier formation by lipids

KIHARA Akio
Professor, Faculty of Pharmaceutical Sciences, Hokkaido University

Started in 2015

Chain length of fatty acids, elucidation of mechanisms of disease control and development of fundamentals toward medical evolution

SHIMANO Hitoshi
Professor, Internal Medicine (Endocrinology and Metabolism), Faculty of Medicine, University of Tsukuba

Started in 2015

Creation of a novel technology "Optolipidomics" to identify, control and observe functional lipids using light

SETOU Mitsutoshi
Director, International Mass Imaging Center, Hamamatsu University School of Medicine

Started in 2015

Elucidation of the mechanism of the hijacking of host lipids by pathogens and its application to pharmaceutical development

HANADA Kentaro
Director, Department of Biochemistry & Cell Biology, National Institute of Infectious Diseases

Started in 2016

Understanding disease mechanisms based on glucosylated lipid functions

KAMIGUCHI Hiroyuki
Deputy Director,RIKEN Center for Brain Science

Started in 2016

Development of innovative technology for structure-based drug design targeting prostanoid receptor

KOBAYASHI-SHIMIZU Takuya
Professor, Department of Medical Chemistry, Kansai Medical University

Started in 2016

Elucidation of metabolic control by oxysterols and disease molecular mechanism

SATO Ryuichiro
Professor, Graduate School of Agricultural and Life Sciences, The University of Tokyo

Started in 2016

Creation of a novel approach for drug development by elucidation of the regulation mechanism of cell migration with S1P transporters

NISHI Tsuyoshi
Associate Professor, ISIR, Osaka University

Started in 2016

Development of novel anti-infective drugs targeting lipid metabolism

YAMASAKI Sho
Professor, Research Institute for Microbial Diseases, Osaka University

Started in 2017

Innovative research by control and visualization of cellular membrane phospholipids

SHINDOU Hideo
Vice Project Leader, National Center for Global Health and Medicine (NCGM)

Started in 2017

Elucidation of roles and functions of bioactive lipids underlying stress-related dysfunctions and foundation of novel technology platforms for bioactive lipid-targeting clinical applications

FURUYASHIKI Tomoyuki
Professor, Graduate School of Medicine, Kobe University

Started in 2017

Elucidation of disease mechanism and study of drug discovery targeted for oxidized lipids

YAMADA Kenichi
Professor, Faculty of Pharmaceutical Sciences, Kyushu University

PRIME

Started in 2015

Development of milieu-lipidomics platform for grasping metabolic crosstalk between host and intestinal bacteria

IKEDA Kazutaka
Deputy Team Leader, Laboratory for Metabolomics, RIKEN Center for Integrative Medical Sciences (IMS)

Started in 2015

Elucidation of roles of lipids in the epithelial-mesenchymal transition

IKENOUCHI Junichi
Professor, Faculty of Sciences, Kyushu University

Started in 2015

Control of functional lipids using optogenetics

UEDA Yoshibumi
Specially Appointed Researcher, Department of General Systems Studies, Graduate School of Arts and Sciences, The University of Tokyo

Started in 2015

The role of lipid in the exosome derived from the inflammatory cancer

KOTANI Ai
Professor, Institute of Medical Science, Tokai University

Started in 2015

Development of basic technologies for medical application based on oxidized phospholipid-derived bioactive fatty acids

KONO Nozomu
Associate Professor, Graduate School of Pharmaceutical Sciences, The University of Tokyo

Started in 2015

Mechanisms of lipid dynamics on plasma membranes and their application

SUZUKI Jun
Professor, Institute for Integrated Cell-Material Sciences (iCeMS), Kyoto University

Started in 2015

Unraveling a novel metabolic system orchestrated by a metabolic sensor toward development of therapeutics

SEKIYA Motohiro
Associate Professor, Department of Internal Medicine, Endocrinology and Metabolism, Tsukuba University

Started in 2015

Development of vibrational microspectroscopy to determine lipid species in live tissues derived from patients

NAGASHIMA Yu
Assistant Professor, Department of Neurology, School of Medicine, The University of Tokyo

Started in 2015

Palmitoylation-dependent regulations of membrane receptors in synapses

HAYASHI Takashi
Section Chief, National Institute of Neuroscience, National Center of Neurology and Psychiatry (NCNP)

Started in 2015

Identification of lipid metabolites controlling physiological function of the uterus

HIROTA Yasushi
Lecturer, Department of Obstetrics and Gynecology, Graduate School of Medicine, The University of Tokyo

Started in 2015

Physiological and pathological roles of cholesterol in primary cilia

MIYAMOTO Tatsuo
Associate Professor, Research Institute for Radiation Biology and Medicine, Hiroshima University

Started in 2015

Functional elucidation of bioactive alkenyl-type lysophospholipids

YAMAMOTO Kei
Associate Professor, Graduate School of Technology, Industrial and Social Science, Tokushima University

Started in 2016

Understanding lipid-related orphan G protein-coupled receptors using activating GPCR mutations

INOUE Asuka
Associate Professor, Graduate School of Pharmaceutical Sciences, Tohoku University

Started in 2016

Development of novel treatment strategies by regulating functional lipids involved in the pathogenesis of pulmonary hypertension

ENDO Jin
Assistant Professor, Department of Cardiology, Keio University School of Medicine

Started in 2016

Functional analysis on cholesterol metabolizing enzyme that defines a novel T cell subset and the clinical application for disease control

TAKAHASHI Hayato
Assistant Professor, Department of Dermatology, Keio University School of Medicine

Started in 2016

Molecular mechanism and physiological role of PI4P-driven lipid countertransport system

NAKATSU Fubito
Associate Professor, Department of Neurochemistry and Molecular Cell Biology, Graduate School of Medical and Dental Sciences, Niigata University

Started in 2016

Understanding pathogenic mechanisms of skin diseases by focusing on polyphosphoinositide metabolism

NAKAMURA Yoshikazu
Associate Professor, Faculty of Science and Technology, Tokyo University of Science

Started in 2016

Development of molecular tools for the clarification of metabolism and molecular interaction of glycolipids

HIRAI Go
Professor, Graduate School of Pharmaceutical Science, Kyushu University

Started in 2016

Identification of functional lipid metabolites to control purinergic chemical transmission, and the molecular mechanism-based drug discovery research

MIYAJI Takaaki
Research Professor, Advanced Science Research Center, Okayama University

Started in 2016

Development of novel microsystems for highly sensitive analysis of lipid transport proteins

WATANABE Rikiya
Chief Scientist, Molecular Physiology Laboratory, RIKEN

Started in 2017

Elucidation of the immune-metabolic-regeneration systems network linked by fatty acids

OISHI Yumiko
Professor, Department of Biochemistry & Molecular Biology, Nippon Medical School

Started in 2017

Characterization of the early steps of high-density lipoprotein (HDL) formation

KIMURA Yasuhisa
Assistant Professor, Graduate School of Agriculture, Kyoto University

Started in 2017

The clarification of lipid-mediated mechanisms in the inflammatory and repairing process after stroke

SHICHITA Takashi
Project Leader, Stroke Renaissance Project, Tokyo Metropolitan Institute of Medical Science

Started in 2017

Development and application of the phosphatidylinositol-specific nucleic acid drug

SUIZU Futoshi
Associate Professor, Institute for Genetic Medicine, Hokkaido University

Started in 2017

The molecular mechanism that regulates cellular signaling pathways through organelle-specific lipid domains

TAGUCHI Tomohiko
Professor, Graduate School of Life Sciences, Tohoku University

Started in 2017

Dissecting intracellular phospholipid traffic for understanding mitochondrial functional integrity

TAMURA Yasushi
Professor, Faculty of Science, Yamagata University

Started in 2017

Development of enzymatic fluorometric assays for quantifying phospholipids, sphingolipids and acylglycerols and for evaluating asymmetrical distribution of membrane lipids

MORITA Shin-ya
Associate Professor, Shiga University of Medical Science

Started in 2017

Elucidation of the molecular mechanism of dietary lipids-mediated reproductive dysfunction to develop novel drugs and treatments for infertility

YAMANASHI Yoshihide
Assistant Professor, Department of Pharmacy, the University of Tokyo Hospital

※ The names of the position, institution and organization are as of the end of the R&D pursuit area year.

Disease-Related Metabolites

Creation of Innovative Technology for Medical Applications Based on the Global Analyses and Regulation of Disease-Related Metabolites

AMED-CREST

【Research and Development Objectives】

Creation of core technologies for early-stage drug discovery through the investigation of disease-specific profiles of biomolecules

Program Supervisor (PS)

SHIMIZU Takao

Project Leader, Department of Lipid Signaling, National Center for Global Health and Medicine

The aim of this R&D area is to create breakthrough technology platforms based on biomolecular dynamics analysis, the outcomes of which will contribute to medical applications such as drug discovery, disease diagnosis, and prevention. The technology platforms should increase the capacity of current systems to find, identify, and quantify disease-related metabolites and their associated factors as potential target molecules for disease control and broader medical applications.
In particular, metabolomics and other "omics" approaches are in great demand for the identification of disease-associated factors; therefore, these need to be developed. Further, we need the technology to identify proteins and other biomolecules related to these factors so they are within the scope. By combining biomedical research projects with the newly developing technology platforms, this R&D area aims to deliver proofs of concept for human disease control by taking full advantage of information obtained about core biomolecules as potential targets for medical applications.
The technical goals specified by the R&D area should be shared among individual research projects. Therefore, the management strongly encourages them to collaborate with others within this so-called virtual-network-type institute as well as with projects in the corresponding Precursory Research for Embryonic Science and Technology (PRESTO) Research Area (of the Japan Science and Technology Agency (JST)), both aiming for the establishment and sophistication of technologies in a team-oriented manner. The management also prioritizes smooth translations to clinical applications; therefore, it considers further efforts allied with other drug discovery programs.

R&D Area Advisors

ABE Keiko	Professor, Graduate School of Agricultural and Life Sciences, The University of Tokyo
UEMURA Daisuke	Distinguished Professor, Kanagawa University
ODA Yoshiya	Professor, Graduate School of Medicine Lipidomics, The University of Tokyo
SATO Taka-aki	Fellow, Director of Life Science Research Center, Shimadzu Corporation
SUZUKI Rami	Vice President Head, Medical Affairs Division, Janssen Pharmaceutical K.K.
TAKAI Yoshimi	Professor, Graduate School of Medicine, Kobe University
TAKAGI Toshihisa	President, Toyama University of International Studies
NAGANO Tetsuo	Visiting Professor / Emeritus Professor, Drug Discovery Initiative, The University of Tokyo
NARUMIYA Shuh	Professor and Director, The Medical Innovation Center Graduate School of Medicine, Kyoto University
NISHIJIMA Masahiro	Professor emeritus, Showa Pharmaceutical University
MATSUZAWA Yuji	Director Emeritus. Supreme Adviser, Sumitomo Hospital

Started in 2013

Identification of disease-related lysophospholipid and its application to medical science

AOKI Junken
Professor, Graduate School of Pharmaceutical Science, Tohoku University

Started in 2013

Development of fundamental technologies for medical applications based on membrane phospholipids

ARAI Hiroyuki
Professor, Graduate School of Pharmaceutical Science, The University of Tokyo

Started in 2013

Formulation of a hub for metabolome analysis and development of medical basic technologies based on cancer specific metabolism

SOGA Tomoyoshi
Professor, Institute for Advanced Biosciences, Keio University

Started in 2013

Development of basic technology for identification of bioactive metabolites and target proteins

SODEOKA Mikiko
Chief Scientist, Synthetic Organic Chemistry Laboratory, RIKEN

Started in 2013

Development of user-friendly metabolomics technology for application to lifestyle-related diseases research

FUKUSAKI Eiichiro
Professor, Graduate School of Engineering, Osaka University

Started in 2013

PLA2 metabolome-based identification of novel lipid-metabolic maps linked to diseases from bench to clinic

MURAKAMI Makoto
Professor, Faculty of Medicine, Center for Disease Biology and Integrative Medicine, The University of Tokyo

Started in 2014

Creation of search techniques for disease-related metabolic activities based on live imaging of clinical specimen and its application to drug developments

UESUGI Motonari
Professor, Institute for Chemical Research, Kyoto University

Started in 2014

Creation of search techniques for disease-related metabolic activities based on live imaging of clinical specimen and its application to drug developments

URANO Yasuteru
Professor, Graduate School of Pharmaceutial Sciences, The University of Tokyo

Started in 2014

Establishment of the platform for the control and prevention of allergy by omics-based understanding of its pathogenesis

OHNO Hiroshi
Team Leader, Center for Integrative Medical Science, RIKEN

Started in 2014

Development of a novel medical application by systematic mining of metabolism regulator molecules

KABE Yasuaki
Associate Professor, School of Medicine, Keio University

Started in 2014

Development of metabolite biomarkers of Parkinson's disease and identification of drug seeds from chemical screening based on the biomarkers

HATTORI Nobutaka
Professor and Chairperson, Graduate School of Medicine, Juntendo University

Started in 2014

How gut microbiota shifts metabolites leading to neuro-endocrine disorders in mouse and man

FAGARASAN Sidonia
Team Leader, Center for Integrative Medical Science, RIKEN

Started in 2014

Cancer diagnosis/drug efficiency evaluation biomarker research by comprehensive metabolomics/targeted proteomics and establishment of innovative integrated clinical diagnosis network

YOSHIDA Masaru
Associate Professor, Graduate School of Medicine, Kobe University

※ The names of the position, institution and organization are as of the end of the R&D pursuit area year.

Homeostasis

Innovation for Ideal Medical Treatment Based on the Understanding of Maintenance, Change and Breakdown Mechanisms of Homeostasis among Interacting Organ Systems

AMED-CREST

【Research and Development Objectives】

Integrated clarification of the maintenance and change mechanisms of dynamic homeostasis in the body and creation of technology to understand and regulate complex dynamic homeostasis to achieve preventive medicine, appropriate diagnosis and treatment

Program Supervisor (PS)

NAGAI Ryozo
President, Jichi Medical University

The objective of this R&D area is to comprehend the process from birth to demise, which takes place in the individual, from the view of a dynamic homeostatic mechanism and to elucidate the mechanisms as to how the individual adapts and changes in reaction to internal and external stresses in a spatio-temporal and cross-sectional manner. The dynamic homeostatic mechanism is operated via a high-order network consisting of the nervous, immune, endocrine, circulatory, and other systems. Furthermore, we aim to understand various diseases, including lifestyle diseases, as deviations from or breakdown of a "homeodynamic" state, constituting a ground for the development of preventive technologies that predict and control such deviation.
Particularly in recent years, technologies such as development of cell-specific genetically modified animals and cell separation technologies have made great progress and they have triggered major changes in life science and medicine. Expectations are to gain a better understanding of mechanisms of homeostasis and adaptations to various stressors, which function through interactions between different cells, systems, and organs. Furthermore, advances in life science and clinical medicine that control these mechanisms are needed. Specifically:
1. How complex functional networks behave interdependently in order to maintain homeostasis in response to external and internal stresses will be elucidated. These networks correlate among multiple organs, such as between parenchyma cells and interstitial cells, among organs as well as among the systems like the nervous, immune, endocrine, circulatory and others. In particular, humoral factors, neurotransmission, immunocytes, and interstitial cells that are involved in the maintenance and dysfunction of homeostasis need to be identified. These findings are needed to develop technologies that can be used to control homeostasis.
2. Researchers are expected to elucidate the phases of sequential and dynamic changes that take place in an individual's homeostatic mechanism during the life stages through birth, growth, development, and aging. Technologies that enable early detection of the subtle symptoms of these phases, as well as those to control them, are to be developed.
3. This R&D area involves research aiming at elucidation of the mechanisms in onset and progression of organ dysfunction resulting from internal and external factors, the biological defense mechanisms against stresses and injuries and healing mechanisms. Furthermore, we aim to develop technologies that will assist in the diagnosis and treatment of human patients. We will apply results of basic research for examination in clinical cases as much as possible, and investigate the potential of medical care where multiple medical departments cooperate based on new concepts of pathology.
4. We aim at the establishment of highly reliable methods to control these networks, based on multilateral understanding of the dynamic interactions between these complex networks. To achieve this goal, we will work to promote simulation technologies and theoretical computational science research that would make these technologies possible.
Through this research, we will elucidate previously unknown molecular, cellular, and networking mechanisms and develop new medical technologies based on these understandings.

R&D Area Advisors

IRIKI Atsushi	Team Leader, RIKEN Center for Biosystems Dynamics Research
OHSHIMA Etsuo	Representative Director and President & CEO, Kyowa Pharma Chemical Co., Ltd.
KANGAWA Kenji	Emeritus Director General, National Cerebral and Cardiovascular Center Research Institute
KOJIMA Itaru	Professor, Gunma University
SAKAGUCHI Shimon	Professor, Osaka University
SAKATA Tsuneaki	Senior Fellow, Shionogi & Co., Ltd.
SUNAGAWA Kenji	Director, Circulatory System Research Foundation
NAKAO Kazuwa	Professor (Special Appointment), Kyoto University
NAGASE Miki	Professor, Kyorin University
NABESHIMA Yo-ichi	Director, IBRI, Foundation for Biomedical Research and Innovation at Kobe
MOCHIZUKI Atsushi	Professor, Institute for Frontier Life and Medical Sciences, Kyoto University

Started in 2012

Holistic investigation of the inter-organ communication systems responsible for metabolic homeostasis and disorders

KATAGIRI Hideki
Professor, Tohoku University Graduate School of Medicine

Started in 2012

Elucidating the pathophysiology of senescence-associated homeostatic disorders and its control

HARA Eiji
Professor, Research Institute for Microbial Diseases, Osaka University

Started in 2012

Discovering therapies for intractable diseases through the identification and characterization of gut microbiota

HONDA Kenya
Professor, Keio University School of Medicine

Started in 2012

Mechanisms of homeostatic maintenance by quorum control of the tissue in whole body

MIURA Masayuki
Professor, Graduate School of Pharmaceutical Sciences, The University of Tokyo

Started in 2012

Study of autophagy toward development of therapy for disorders caused by hypernutrition

YOSHIMORI Tamotsu
Professor, Graduate School of Frontier Biosciences, Osaka University

Started in 2013

A challenge to reveal dynamic properties in circadian sleep-wake homeostasis

UEDA Hiroki
Professor, Graduate school of Medicine, The University of Tokyo

Started in 2013

Clarifying and controlling the pathology of lifestyle diseases caused by alteration of homeostatic maintenance based on tissue repair

OIKE Yuichi
Professor, Graduate School of Medical Sciences, Kumamoto University

Started in 2013

Homeostatic regulation by bones through the inter-organ metabolic network

SATO Shingo
Junior Associate Professor, Tokyo Medical and Dental University, Graduate School of Medical and Dental Sciences

Started in 2013

Identification of novel scavenging system in organisms and its therapeutic application

MIYAZAKI Toru
Professor, Faculty of Medicine, The University of Tokyo

Started in 2013

Understanding homeostatic mechanisms maintained by the cardio-osteo-renal network and interconnecting blood vessels

MOCHIZUKI Naoki
Director General, National Cerebral and Cardiovascular Center Research Institute

Started in 2014

Regulatory mechanism underlying tissue fibrosis induced through local cell-cell interaction and systemic organ network and its medical applications

OGAWA Yoshihiro
Professor, Graduate School of Medical Sciences, Kyushu University

Started in 2014

Phosphatostasis and phosphatopathy: pathophysiology of the inter-organ network maintaining phosphate homeostasis

KURO-O Makoto
Professor, Center for Molecular Medicine, Jichi Medical University

Started in 2014

Homeostatic regulation and dysregulation of neural stem cells under physiological and pathological challenges

GOTOH Yukiko
Professor, Graduate School of Pharmaceutical Sciences, The University of Tokyo / Principal Investigator, International Research Center for Neurointelligence (IRCN), The University of Tokyo

Started in 2014

A novel approach to drug discovery through receptor activity modification

SHINDO Takayuki
Professor, Faculty of Medicine, Shinshu University

Started in 2014

Understanding the autonomic nervous system underlying the gut-brain axis: with a view to exploring higher-order homeostatic mechanisms

TAKAHASHI Yoshiko
Deputy Executive Vice-President, Professor, Graduate School of Science, Kyoto University

Started in 2014

Investigation of energy metabolism and immune system based on the association with autonomic nerve and peptides

NAKAZATO Masamitsu
Professor, Department of Internal Medicine, University of Miyazaki

Started in 2014

Signal transduction systems responsible for tissue, organismal and transgenerational homeostasis

NISHIDA Eisuke
Director, RIKEN Center for Biosystems Dynamics Research

※ The names of the position, institution and organization are as of the end of the R&D pursuit area year.

Epigenomics

Development of Fundamental Technologies for Diagnosis and Therapy Based upon Epigenome Analysis

AMED-CREST

【Research and Development Objectives】

Creation of the basic technologies for disease analysis and elucidation of stem cell differentiation mechanisms by using epigenomic comparison toward the realization of treatments and regenerative medicine used to prevent, diagnose, and treat diseases

Program Supervisor (PS)

YAMAMOTO Masayuki
Professor, Tohoku University Graduate School of Medicine

Program Officer (PO)

USHIJIMA Toshikazu
Chief, Division of Epigenomics,
National Cancer Center Research Institute

For healthy life and development of novel strategies for disease prevention, diagnosis, and therapy, this R&D area focuses on discovery of new principles and establishment of fundamental medical technologies based on epigenome analyses accompanied by biological analyses.
Specifically, this R&D area invites proposals that identify epigenome alterations useful for identification of etiologies or those critically involved in development and progression of cancers or other chronic disorders, such as arteriosclerosis, diabetes, neurological diseases, and autoimmune diseases. The findings should lead to identification of novel mechanisms for induction of epigenome alteration or maintenance of epigenomes or to innovative strategies for disease prevention, diagnosis, and therapy. This area also invites proposals that, by comparing epigenome profiles during stem cell differentiation, reveal mechanisms of cellular differentiation and establish technologies for robust directed differentiation of various cells to specific lineages. Furthermore, this area invites proposals that develop key technologies for more efficient analysis of methylomes and histone modifications, and for control of epigenomes.
In this R&D area, AMED cooperates with the International Human Epigenome Consortium (IHEC) through some proposals.

R&D Area Advisors

TAKAGI Toshihisa	Professor, Graduate School of Science, The University of Tokyo
TAKAHASHI Masayo	Project Leader, RIKEN Center for Biosystems Dynamics Research
TAJIMA Shoji	Professor Emeritus, Osaka University
CHIBA Tsutomu	Director, Kansai Electric Power Hospital
NISHIJIMA Kazumi	Fellow, Clinical Development Planning and Management, Mochida Pharmaceutical Co., Ltd.
FUKAMIZU Akiyoshi	Professor, Life Science Center Survival Dynamics, TARA, University of Tsukuba
MOTOHASHI Hozumi	Professor, Institute of Development, Aging and Cancer (IDAC), Tohoku University
MOROHASHI Ken-ichirou	Distinguished Professor, Faculty of Medical Sciences, Kyushu University
YOSHIDA Minoru	Group Director, RIKEN Center for Sustainable Resource Science

Started in 2011

Elucidating epigenomeloops of cell differentiation using quantitative ChIP-Seq method

IGARASHI Kazuhiko
Professor,
Tohoku University Graduate School of Medicine

Started in 2011

Epigenome analysis of mental disorders using advanced technologies

KATO Tadafumi
Team Leader, RIKEN Brain Science Institute

Started in 2011

Reference epigenome analysis in normal epithelial cells of human digestive system and development of analysis technology

KANAI Yae
Professor, Keio University School of Medicine

Started in 2011

Study of the molecular mechanism in the pluripotency maintenance of stem cells and three-dimensional mapping of the epigenome structure

SHIRAKAWA Masahiro
Professor, Graduate School of Engineering,
Kyoto University

Started in 2011

Development of genomic technologies to explore human epigenetic regulation

SHIRAHIGE Katsuhiko
Professor/Director, The Institute of Molecular and Cellular Biosciences (IMCB), The University of Tokyo

Started in 2011

Molecular mechanisms underlying direct reprogramming of fibroblasts to hepatocytes and applications thereof

SUZUKI Atsushi
Professor, Medical Institute of Bioregulation, Kyushu University

Started in 2011

Mechanism of higher-order epigenome regulation and its medical significance

NAKAO Mitsuyoshi
Professor, Institute of Molecular Embryology and Genetics, Kumamoto University

Started in 2011

Epigenetic drug development to prevent pervasive developmental disorders

HAGIWARA Masatoshi
Professor, Graduate School of Medicine,
Kyoto University

Started in 2011

New diagnostic and therapeutic tools targeting epigenetic modulation for lifestyle-related disease

FUJITA Toshiro
Emeritus Professor, Research Center for Advanced Science and Technology, The University of Tokyo

Started in 2012

Identification of factors to modify and resist epigenomic alteration induction

KANEDA Atsushi
Professor, Graduate School of Medicine,
Chiba University

Started in 2012

Epigenome analysis of cells in the placenta and endometrium forming the fetal-maternal interface

SASAKI Hiroyuki
Distinguished Professor, Medical Institute of Bioregulation, Kyushu University

Started in 2012

Basic studies aimed for an epigenome-based therapy: proof of concept in brain function

SHINKAI Yoichi
Chief Scientist, Cellular Memory Laboratory, RIKEN

Started in 2012

Molecular regulation and analysis of the establishment of epigenome

NAKANO Toru
Professor, Graduate School of Frontier Biosciences, Osaka University

Started in 2012

Understanding the epigenetic modifications related to cancer development and regression

NAKAHATA Tatsutoshi
Professor, Center for iPS Cell Research and Application, Kyoto University

Started in 2013

Epigenome changes by environmental factors and diseases

ISHII Shunsuke
Deputy Director,
RIKEN Center for Pioneering Research

Started in 2013

Analysis and application for regulation of cell function on linked mechanisms of enhancer dynamics and transcription regulation by epigenetic control

KOSEKI Haruhiko
Team Leader, RIKEN Center for Integrative Medical Sciences

Started in 2013

Mechanisism of transgenerational epigenetic regulation in germ cells

MATSUI Yasuhisa
Professor, Institute of Development, Aging and Cancer (IDAC), Tohoku University

Started in 2013

Epigenetic analysis of the mechanisms of metabolic control and their disruption in type 2 diabetes and obesity

YAMAUCHI Toshimasa
Professor, Graduate School of Medicine,
The University of Tokyo

Started in 2013

Regulation of immunological disorders by modification of epigenetics of T cells

YOSHIMURA Akihiko
Professor, Keio University School of Medicine

※ The names of the position, institution and organization are as of the end of the R&D pursuit area year.

Chronic Inflammation

Creation of Basic Medical Technologies to Clarify and Control the Mechanisms Underlying Chronic Inflammation

AMED-CREST

【Research and Development Objectives】

Creation of basic medical technologies for the prevention, diagnosis and treatment of cancer, arteriosclerotic diseases, and autoimmune disorders by the elucidation of the mechanisms underlying chronic inflammation

Program Supervisor (PS)

MIYASAKA Masayuki
Professor Emeritus, Osaka University;
FiDiPro Professor, Academy of Finland

The purpose of this R&D area is to elucidate the mechanisms through which inflammation becomes chronic, and to create basic technologies for the early detection, control, resolution, and reparation of chronic inflammation.

More specifically, this involves research aimed at: (1) identifying factors that induce and maintain the chronicity of inflammation by determining failure mechanisms of inflammation control; (2) clarifying the mechanisms through which specific diseases (including cancer, degenerative neurological disorders, and arteriosclerotic diseases) develop as a result of chronic inflammation, and to create basic technologies to control them; and (3) creating basic technologies that allow for the early detection and quantitative assessment of chronic inflammation. This not only involves established basic and clinical research, but also emphasizes research that sufficiently sublimes evidence-based findings for understanding higher order inflammation control mechanisms, and leads to the development of new preemptive basic medical technologies.

R&D Area Advisors

INAGAKI Nobuya	Professor, Kyoto University
IMAMURA Takeshi	Professor, Ehime University
UEMATSU Satoshi	Professor, Chiba University
OHSUGI Yoshiyuki	Chairman&CEO, Ohsugi BioPharma Consulting Co., Ltd.
KOH Shosei	Director, Shironishi Hospital; Professor Emeritus, Shinshu University
TAKATSU Kiyoshi	Director, Toyama Prefectural Institute of Pharmaceutical Research
TAKAYANAGI Hiroshi	Professor, The University of Tokyo
YAMAUCHI-TAKIHARA Keiko	Professor, Osaka University
MURAKAMI Masaaki	Director, Hokkaido University
YOKOMIZO Takehiko	Professor, Juntendo University
YOSHIMURA Akihiko	Professor, Keio University

Started in 2010

Regulation of inflammation time axis at RNA level

ASAHARA Hiroshi
Professor, Tokyo Medical and Dental University

Started in 2010

Next-generation imaging technology to ascertain the *in vivo* mode of action of chronic inflammatory macrophages

ISHII Masaru
Professor, Osaka University

Started in 2010

The research for the mechanism of chronically intractable pain based on the functions of microglia as brain immunocompetent cell

INOUE Kazuhide
Professor, Kyushu University

Started in 2010

Understanding of chronic inflammation for the development of new therapeutic strategies for intestinal inflammatory diseases

KIYONO Hiroshi
Professor, The University of Tokyo

Started in 2010

The role of microenvironmental niches for hematopoiesis in chronic inflammation

NAGASAWA Takashi
Professor, Osaka University

Started in 2010

Prostaglandin-mediated mechanisms of initiation and progression of chronic inflammation

NARUMIYA Shuh
Professor, Kyoto University

Started in 2010

Molecular and cellular bases of chronic inflammation associated-organ fibrosis

MATSUSHIMA Kouji
Professor, The University of Tokyo

Started in 2011

Pathophysiological role of chronic inflammation in aging-associated diseases

AKAZAWA Hiroshi
Lecturer, The University of Tokyo

Started in 2011

Regulation of chronic inflammation and the development of new strategies for treating airway inflammatory diseases

NAKAYAMA Toshinori
Professor, Chiba University

Started in 2011

Structural basis for the pathogenic disease mechanisms caused by chronic inflammation

NUREKI Osamu
Professor, The University of Tokyo

Started in 2011

Control of chronic inflammation through elucidation of organ-specific autoimmune disease mechanisms

MATSUMOTO Mitsuru
Professor, Tokushima University

Started in 2011

Identification of critical genes involved in the pathogenesis of human chronic inflammatory diseases

YASUTOMO Koji
Professor, Tokushima University

Started in 2011

Protective mechanisms against environmental stresses leading to therapeutic strategies for chronic inflammation

YAMAMOTO Masayuki
Professor, Tohoku University

Started in 2012

The role of chronic inflammation in promotion and malignant progression of cancers

OSHIMA Masanobu
Professor, Kanazawa University

Started in 2012

Investigation of pathological implications of guidance molecules in chronic inflammation

KUMANOGOH Atsushi
Professor, Osaka University

Started in 2012

Devising novel methods to control chronic inflammation via regulatory T cells

SAKAGUCHI Shimon
Professor, Osaka University

Started in 2012

Analysis of mechanisms suppressing chronic inflammation via posttranscriptional regulation in innate immunity

TAKEUCHI Osamu
Professor, Kyoto University

※ The names of the position, institution and organization are as of the end of the R&D pursuit area year.

Brain Neural Network

Elucidation of the Principles of Formation and Function of the Brain Neural Network and Creation of Control Technologies

AMED-CREST

【Research and Development Objectives】

Clarification of the control mechanisms of neural circuit operation and its formation

Program Supervisor (PS)

OZAWA Seiji
Professor, Takasaki University of Health and Welfare

This R&D area aims to elucidate the molecular and cellular mechanisms of the generation, development, and regeneration of the brain neural network; to investigate how neural networks composed of a variety of elements in individual brain areas work and express their specific functions; and to clarify how the brain works as a coherent system by integrating the activities of these local networks. On the basis of such research, it also aims to create technologies for controlling the process of formation and activities of the brain neural network.

Specific approaches may include elucidation of the molecular mechanisms of development, differentiation, regeneration, target recognition, and migration of neurons (components of neural networks) and glial cells that significantly influence neural network formation and functions; elucidation of the mode of neural network activities by combining new technologies, such as visualization of specific neurons with the use of specific expression molecules and fluorescent proteins, simultaneous recording of activities of many neurons, and local stimulation with a caged compound; research to clarify the relationship of higher order brain functions with synaptic events through the combination of research at the network and system levels in model animals and research on the regulatory mechanism of synaptic transmission at the molecular and cellular levels; elucidation of the mechanism of neural network reorganization at the critical period or after brain damage; and creation of technologies for intervention in its process.

R&D Area Advisors

ISA Tadashi	Professor, Kyoto University
OHMORI Harunori	Professor, Kyoto University
OKABE Shigeo	Professor, The University of Tokyo
KIMURA Minoru	Professor, Brain Science Institute Tamagawa University
KUDO Yoshihisa	Professor Emeritus, Tokyo University of Pharmacy and Life Sciences
KUBA Kenji	Professor Emeritus, Nagoya University
TSUDA Ichiro	Professor, Hokkaido University
NISHIZAWA Masatoyo	Professor Emeritus, Niigata University Fellow, Brain Research Institute
HONMA Sato	Professor, Hokkaido University
WADA Keiji	Director, National Center of Neurology and Psychiatry

Started in 2010

System analysis of the structure and function of higher order neural circuits integrating sensory information

ITO Kei
Associate Professor, The University of Tokyo

Started in 2010

Architecture of functional neural circuits in the cerebral cortex

OHKI Ken-ichi
Professor, The University of Tokyo

Started in 2010

Elucidation of working principles within neural networks controlling language

SAKAI L.Kuniyoshi
Professor, The University of Tokyo

Started in 2010

Roles of cell adhesion molecules in the formation of hippocampal neuronal circuitry

TAKAI Yoshimi
Professor, Kobe University

Started in 2010

Elucidation of the molecular basis of signaling cascades underlying plastic neuronal circuits via development of new probing and control technologies

BITO Haruhiko
Professor, The University of Tokyo

Started in 2010

Elucidation of mechanisms of neural network reorganization and functional recovery after brain injury

YAMASHITA Toshihide
Professor, Osaka University

Started in 2011

Neuron-glia interaction in long-term remodeling of synapses in vivo

NABEKURA Junichi
Professor, National Institute for Physiological Sciences

Started in 2011

Modes of motor information processing in primate cerebro-cerebello-basal ganglia networks

HOSHI Eiji
Project Leader, Tokyo Metropolitan Institute of Medical Science

Started in 2011

Neurophysiological investigation of mechanisms of cognitive memory network in the cerebral cortex of macaques

MIYASHITA Yasushi
Project Professor, Juntendo University

Started in 2011

Neuronal individuality providing neural circuit formation and cell assembly

YAGI Takeshi
Professor, Osaka University

※ The names of the position, institution and organization are as of the end of the R&D pursuit area year.

iPS

Fundamental Technologies for Medicine Concerning the Generation and Regulation of Induced Pluripotent Stem (iPS) Cells

AMED-CREST

【Research and Development Objectives】

Creating fundamental technologies for advanced medicine through generation and regulation of stem cells, based on cellular reprogramming

Program Supervisor (PS)

SUDA Toshio

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

The objective of this R&D area is to establish fundamental technologies contributing to advanced medicine through the development of cellular reprogramming technology. Remarkable progress has been made in this field recently, especially the generation of iPS cells. The research objectives include the advancement and simplification of this technology, the elucidation of pathological mechanisms through the development of model cells, the formulation of new therapy strategies, and novel methods for the early discovery of diseases.
Specifically, included is research on cellular reprogramming and differentiation mechanisms using genomics, chromosome structure and epigenetic analysis; research on gene transfer regulation; high-throughput screening of reprogramming-inducing compounds; and research using iPS cells generated from patients with congenital diseases for the elucidation of pathological mechanisms. Moreover, the research also covers an area that may lead to the pioneering of new therapy methods and preventive medicine through the integration of stem cell research and pathological studies.

R&D Area Advisors

SASAKI Hiroyuki	Professor, Kyushu University
SHIOMI Mikiko	Professor, The University of Tokyo
TAKAI Yoshimi	Professor, Kobe University
TAKEICHI Masatoshi	Team Leader, RIKEN
NAKANO Toru	Professor, Osaka University
HAYASHIZAKI Yoshihide	Director, RIKEN
MIYAZONO Kohei	Professor, The University of Tokyo

Started in 2010

Direct reprogramming of fibroblasts into cardiomyocytes by defined factors and its application to potential regenerative therapies

IEDA Masaki
Project Assistant Professor, Keio University

Started in 2010

Search for pathogenesis and novel therapeutics of hematological malignancies based on generation of iPS cells from primary tumor cells

KUROKAWA Mineo
Professor, The University of Tokyo

Started in 2010

The generation of high-quality human iPS cells and their characterization

HANAZONO Yutaka
Professor, Jichi Medical University

Started in 2010

Construction of functional liver tissues using iPS cells

MIYAJIMA Atsushi
Professor, The University of Tokyo

Started in 2010

Establishment of the mouse model with human liver derived from iPS cells and its use for experimental therapy

YAMAMURA Ken-ichi
Professor, Kumamoto University

Started in 2010

Chemical regulation of nuclear epigenome and mitochondrial genome

YOSHIDA Minoru
Chief Scientist, RIKEN

※ The names of the position, institution and organization are as of the end of the R&D pursuit area year.

Immune Systems

Etiological Basics of and Techniques for Treatment of Allergic and Autoimmune Diseases

AMED-CREST

【Research and Development Objectives】

Development of medical technology using immunoregulation to overcome allergic and autoimmune diseases including pollinosis

Program Supervisor (PS)

SUGAMURA Kazuo

Chief Director, Miyagi Prefectural Hospital Organization

This R&D area aims to improve prevention, diagnosis, and treatment of human immunological diseases, centered on allergic and autoimmune diseases, and includes research for development of basic technologies for improvement of appropriate functioning of the immune system.
Diseases centered on allergic responses and autoimmune systems vary from those that may lower the quality of life (QOL) of patients to those leading to death in serious cases. Deepened understanding of the immune mechanism and control of such diseases at levels of molecules, cells, organs, and tissues will be evolved into understanding of a higher-level control immune network system at individual levels, leading to clinical application.
Specific examples of research projects include immunoregulatory mechanisms by regulatory cells, construction mechanisms of the mucous membrane immune system, autoimmune system, acquired immune system, and natural immune system and their control, etiological mechanisms of autoimmune and allergic diseases, immune and infection control mechanisms, development of drugs and vaccines against diseases and measurement of their effects, establishment of methods for diagnosis and treatment of diseases, and so forth.

R&D Area Advisors

SAITO Takashi	Group Director, RIKEN Yokohama Institute
SAKAGUCHI Shimon	Professor, Osaka University
SHIBUYA Kazuko	Associate Professor, University of Tsukuba
TAKATSU Kiyoshi	President Professor, University of Toyama
TOKUHISA Takeshi	Professor, Chiba University
NOSE Masato	Professor Emeritus, Ehime University
HANAI Nobuo	President, Kyowa Hakko Kirin Co., LTD.
MIYASAKA Nobuyuki	Professor, Tokyo Medical and Dental University
YAMAMOTO Kazuhiko	Professor, The University of Tokyo

Started in 2010

Control of allergic diseases by regulation of human mast cell activation

SHIBUYA Akira
Professor, University of Tsukuba

Started in 2010

Development of a new strategy targeting innate immunity for treatment of intestinal immune disorders

TAKEDA Kiyoshi
Professor, Osaka University

※ The names of the position, institution and organization are as of the end of the R&D pursuit area year.

FORCE

Started in 2019

Neuronal disease caused by defects in lipid dynamics on disease and strategy for its treatment

SUZUKI Jun
Professor, Institute for Integrated Cell-Material Sciences, Kyoto University

Started in 2019

Analysis of the involvement of RNA-binding proteins (RBPs) in human inflammatory diseases and development of methods to control the RBPs

TAKEUCHI Osamu
Professor Graduate School of Medicine, Kyoto University

Started in 2019

Development of cancer navigation strategy based on RNA pathophysiology in endocrine therapy-resistant breast cancer

NAKAO Mitsuyoshi
Professor, Institute of Molecular Embryology and Genetics, Kumamoto University

Started in 2019

Protein modification at excitatory synapses in brain diseases

HAYASHI Takashi
Researcher, National Institute of Neuroscience, National Center of Neurology and Psychiatry (NCNP)

Started in 2019

Exploration of disease-associated lipid maps by PLA2 metabolome and their human relevance

MURAKAMI Makoto
Professor, Graduate School of Medicine, The University of Tokyo

Started in 2020

Elucidation of disease-specific microbiota and personalized medicine by metagenome-wide association studies

OKADA Yukinori
Professor, Osaka University Graduate School of Medicine

Started in 2020

Investigating the relationship between detrimental neutrophil activation and anti-tumor immunity by using lung cancer patient samples

KUMANOGOH Atsushi
Professor, Department of Respiratory Medicine and Clinical Immunology, Osaka University Graduate School of Medicine

Started in 2020

Identification of cell clusters exerting EP2/EP4-dependent immune-evasion in human tumors

NARUMIYA Shuh
Professor, Kyoto University Graduate School of Medicine

Started in 2020

Identification of biomarkers for the diagnosis of implantation failure

HIROTA Yasushi
Associate Professor, Department of Obstetrics and Gynecology, Graduate School of Medicine, The University of Tokyo

Started in 2020

Psychiatric symptoms associated with autoimmune diseases: The metabolic link

FAGARASAN Sidonia
Team Leader, RIKEN Center for Integrative Medical Sciences

Started in 2021

Verification of qualitative changes in cell membranes in human invasive cancer and development of therapeutic methods targeting cell membranes

IKENOUCHI Junichi
Professor, Department of Biology, Faculty of Science, Kyushu University

Started in 2021

Polyclonal metastasis mechanism of human colon cancer

OSHIMA Masanobu
Professor, Cancer Research Institute, Kanazawa University

Started in 2021

Comprehensive evaluation of pseudo exonic splicing mutations for drug development

HAGIWARA Masatoshi
Professor, Department of Anatomy and Developmental Biology, Kyoto University

Started in 2021

Development of Treatment Targeting NFIA for Obesity in Humans

YAMAUCHI Toshimasa
Professor, Graduate School of Medicine, the University of Tokyo

Started in 2021

Molecular Mechanism and Therapy in AHR and NRF2-mediated Atopic Dermatitis

YAMAMOTO Masayuki
Professor, Department of Medical Biochemistry, Graduate School of Medicine, Tohoku University

Started in 2022

Establishment of an activity-based diagnosis platform based on protein functional analysis at proteoform level

KOMATSU Toru
Assistant Professor,Graduate School of Pharmaceutical Sciences, The University of Tokyo

Started in 2022

Prodrug strategy triggered by cancer-specific acrolein

TANAKA Katsunori
Chief Scientist, RIKEN Cluster for Pioneering Research

Started in 2022

Development of novel therapeutic and diagnostic strategies for pulmonary hypertension targeting gut microbiome

NAKAOKA Yoshikazu
Director,National Cerebral and Cardiovascular Center Research Institute

Started in 2022

Screening of biomarkers for the clock aging in human

YOSHITANE Hikari
Project Leader, Tokyo Metropolitan Institute of Medical Science

※ The names of the position, institution and organization are as of the end of the R&D pursuit area year.

LEAP

Started in 2014

Research and discovery of innovative ways to treat and prevent influenza virus

	KAWAOKA Yoshihiro	Professor, Institute of Medical Science, The University of Tokyo
Program Manager :	YAMASHITA Makoto	Professor, Institute of Medical Science, The University of Tokyo

Started in 2014

Project for exploration of cancer therapeutic targets

	MANO Hiroyuki	Chief, Division of Cellular Signaling, Research Institute, National Cancer Center
Program Manager :	AIKAWA Katsuji	Chief, Seeds Development Support Section Translational Research Management Division, National Cancer Center Hospital East

Started in 2015

Innovative drug development based on the physiological functions and mechanistic basis of DOCK family proteins

	FUKUI Yoshinori	Professor, Medical Institute of Bioregulation, Kyushu University
Program Manager :	KOBAYASHI Masakazu	Medical Institute of Bioregulation, Kyushu UniversityCenter Hospital East

Started in 2015

Generation of functional organs using developmental niche

esearch and development representative	NAKAUCHI Hiromitsu	Distinguished Professor, IMSUT Distinguished Professor Unit, Division of Stem Cell Therapy, The University of Tokyo
Program Manager :	WATANABE Motoo	Senior Research Advisor, IMSUT Distinguished Professor Unit, Division of Stem Cell Therapy, The University of Tokyo

Started in 2016

Development of therapeutic cocktails of bacteria isolated from the gut microbiota

	HONDA Kenya	Professor, Keio University School of Medicine
Program Manager :	SHIOTA Atsushi	Professor, Keio University School of Medicine

Started in 2017

Lysophospholipid mediators and their application to medical science

	AOKI Junken	Professor, Graduate School of Pharmaceutical Sciences, The University of Tokyo
Program Manager :	KISHIKAWA Katsuya	Researcher, Graduate School of Pharmaceutical Sciences, The University of Tokyo

Started in 2018

Development of new immunosuppressive technology targeting regulatory T cells

	SAKAGUCHI Shimon	Distinguished Professor, Immunology Frontier Research Center, Osaka University
Program Manager :	MIKAMI Norihisa	Visiting Academic Staff, Immunology Frontier Research Center, Osaka University

Started in 2019

Mechnikov-based drug development by AIM

	MIYAZAKI Toru	Director, The Institute for AIM Medicine
Program Manager :	KUROKAWA Kiyoshi	Honorary Director, The Institute for AIM Medicine

※ The names of the position, institution and organization are as of the end of the R&D pursuit area year.

Individual Differences

Stress

Aging

Immunological Memory

Multi-sensing

Anti-infectives

Proteostasis

Early Life Stage

Tissue Adaptation and Repair

Functional Impairment

FORCE

LEAP

Microbiome

Mechanobiology

Lipid Molecules

Disease-Related Metabolites

Homeostasis

Epigenomics

Chronic Inflammation

Brain Neural Network

iPS

Immune Systems

AMED-CREST PRIME LEAP FORCE

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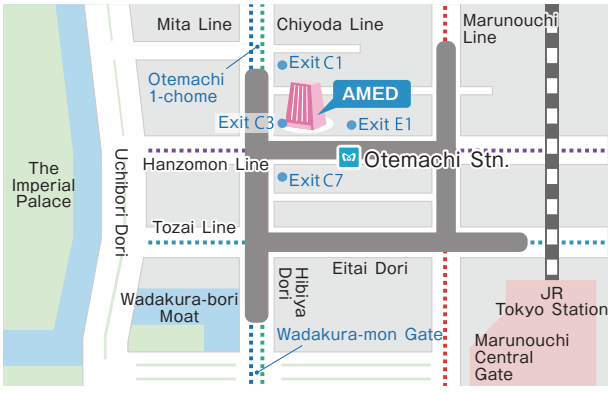

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