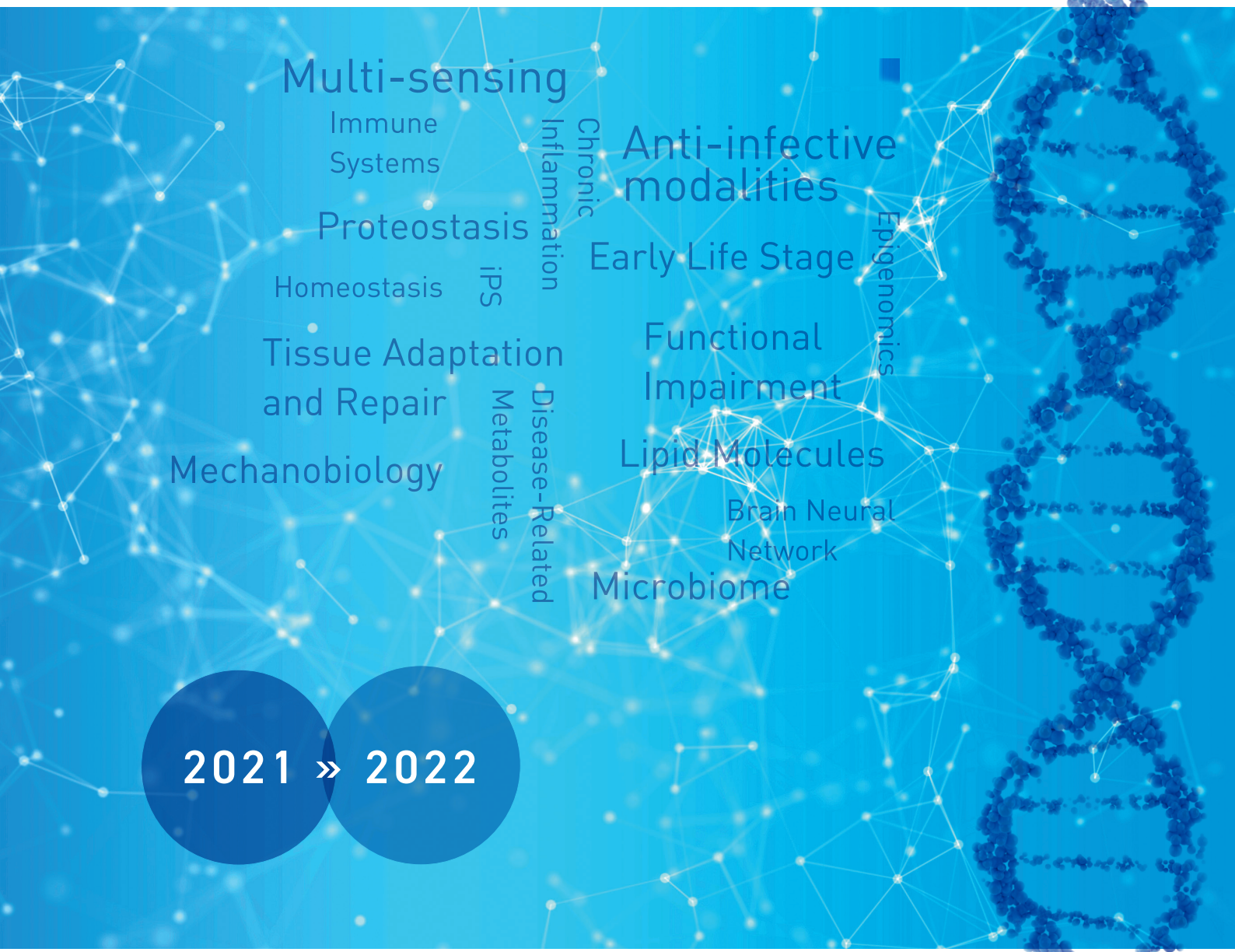
Advanced Research and Development Programs for Medical Innovation

AMED-CREST
PRIME
LEAP
FORCE



Japan Agency for Medical Research and Development
AMED

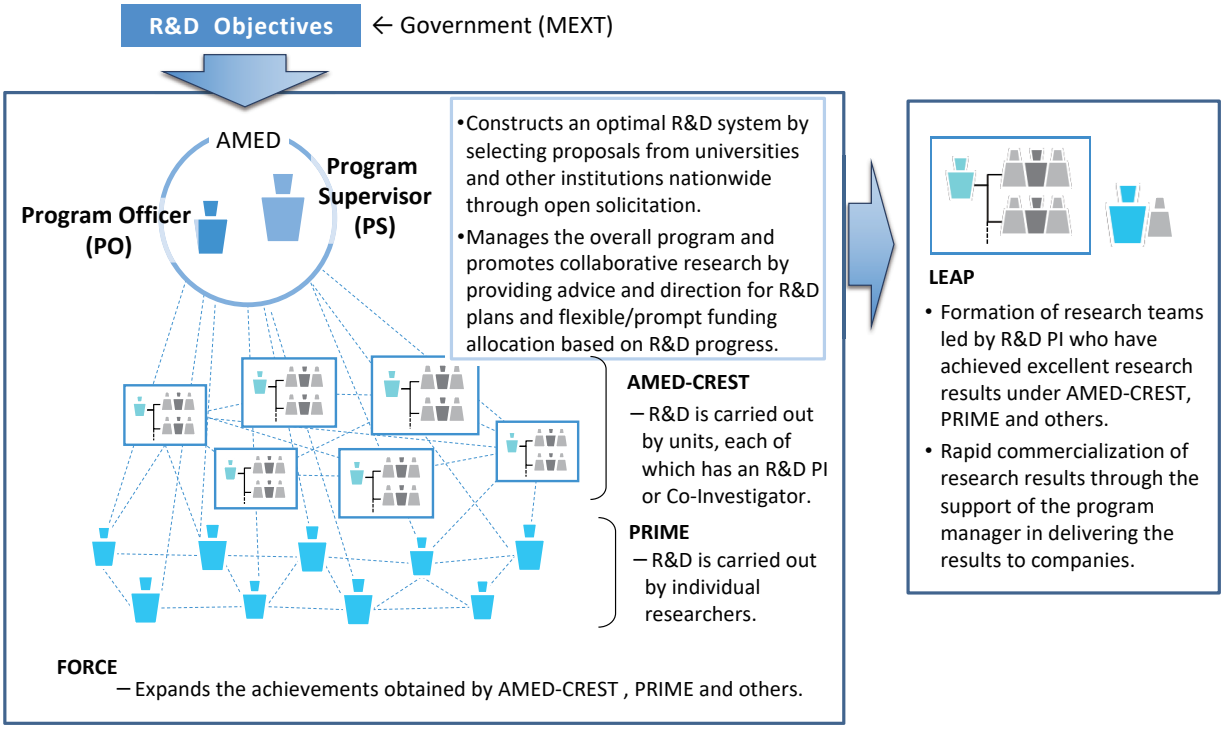
Contents

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 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.

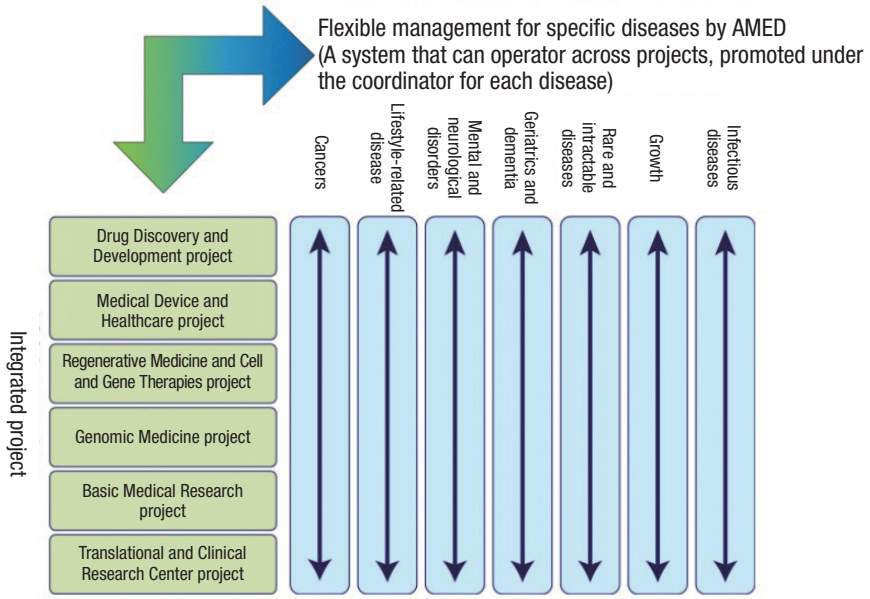
• FORCE program promotes prospective R&Ds which can lead to large developments, among research accomplishments obtained from terminated AMED-CREST and PRIME R&D projects. FORCE program aims to verify correlations between their achievements and target diseases and to validate generated analytical methods,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

• LEAP 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.



Program Director

SHIMIZU Takao, M.D., Ph.D.

Project Leader, Department of Lipid Signaling, Research Institute, National Center for Global Health and Medicine
Executive Director, Institute of Microbial Chemistry

POSITIONS

1973 Clinical research fellow, the University of Tokyo Hospital
1975 Research Assistant, Kyoto University School of Medicine
1982 Visiting Scientist, Department of Physiological Chemistry, Karolinska Institutet
1984 Associate Professor, Physiological Chemistry and Nutrition, Faculty of Medicine, The University of Tokyo
1991 Professor and Chair, Department of Biochemistry, Faculty of Medicine, The University of Tokyo
2007 Dean of Faculty of Medicine, The University of Tokyo
2011 Executive Vice President, The University of Tokyo
2012- present
Project Leader, Department of Lipid Signaling, National Center for Global Health and Medicine
2013 Director-General, Research Institute, National Center for Global Health and Medicine , Executive Director, National Center for Global Health and Medicine

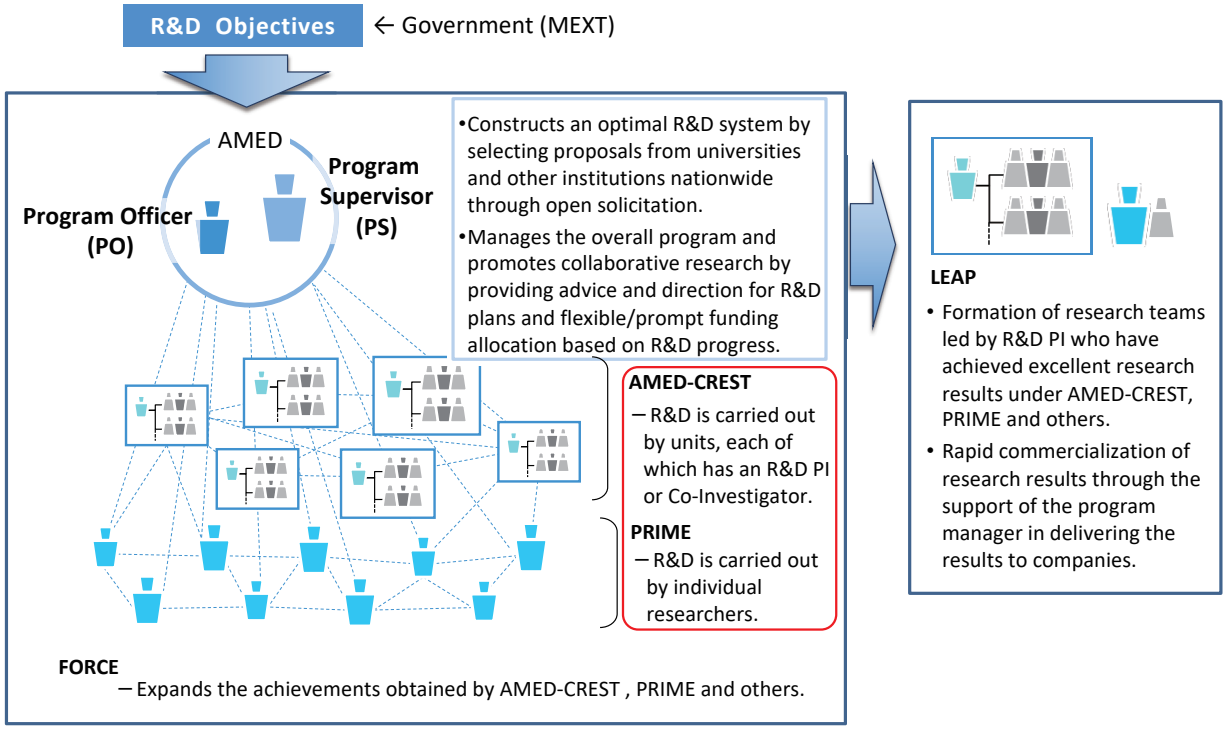
Throughout the 1st Medium- to Long-Term plan since AMED's inception in 2015, the division of Innovative Research and Development (former name: division of Emerging Research) has promoted the program for the purpose of creating and fostering the seeds of further practical application under the policy 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 of 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.

AMED-CREST PRIME

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	
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
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

Completed R&D Areas

Keyword	R&D Area	
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	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	Page
PS: NAGAI Ryozo PO: TAKEUCHI Shoji PO: NISHIDA Kohji	2021																9
PS: DOI Yohei PO: MATSUURA Yoshiharu	2021																13
PS: NAGATA Kazuhiro PO: ENDO Tamao	2020																15
PS: SASAKI Hiroyuki PO: TAKEDA Hiroyuki	2019																21
PS: YOSHIMURA Akihiko PO: YOKOMIZO Takehiko	2018																29
PS: NISHIDA Eisuke PO: HARA Eiji	2017																39
PS: SASAKAWA Chihiro PO: OHNO Hiroshi	2016																47
PS: SOKABE Masahiro PO: ANDO Joji	2015																55
PS: YOKOYAMA Shinji PO: IGARASHI Yasuyuki	2015																65

	R&D Period (FY)	Page
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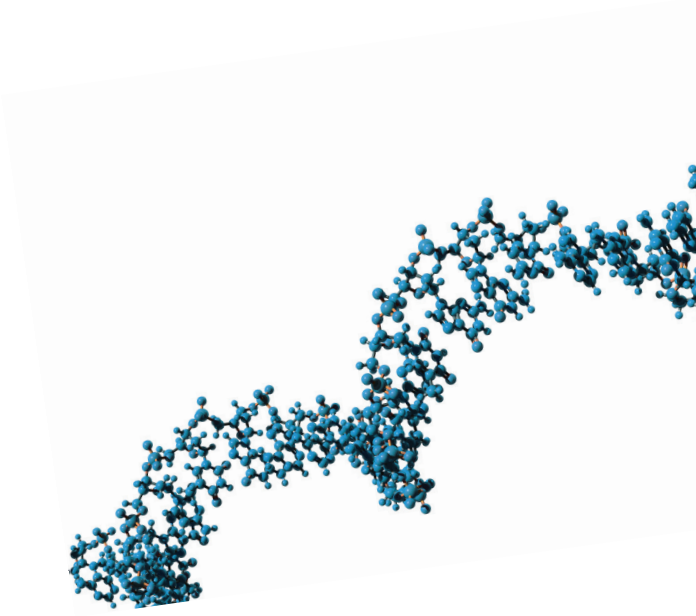
	2012 ~ 2019	83
	2011 ~ 2018	84
	2010 ~ 2017	85
	2009 ~ 2016	86
	2008 ~ 2015	87
	2008 ~ 2015	87



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

Program Supervisor (PS)

NAGAI Ryozo

President,
Jichi Medical University

Program Officer (PO)

TAKEUCHI Shoji

Professor, Graduate School of Information Science and Technology, the University of Tokyo

Program Officer (PO)

NISHIDA Kohji

Professor, Graduate School of Medicine, Osaka University

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

AMED-CREST
AMED-PRIME

R&D Area Advisors

OKADA Yukinori
Professor, Department of Statistical Genetics, Graduate School of Medicine, Osaka University

OKABE Shigeo
Professor, Graduate School of Medicine, Department of Cellular Neurobiology, The University of Tokyo

OGAWA Yoshihiro
Professor, Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University

SUNAGAWA Kenji
Director, Circulatory System Research Foundation

SEKITANI Tsuyoshi
Professor, SANKEN, Osaka University

TAKAI Madoka
Professor, School of Engineering, The University of Tokyo

TAKEDA Kiyoshi
Professor, Graduate School of Medicine, Osaka University

TAKEDA Noriaki
Professor, Graduate School of Biomedical Sciences, Tokushima University

TSUKADA Shingo
NTT Fellow, Multidisciplinary Materials Design and Science Laboratory, Molecular and Bio Science Research Group, Bio-Medical Informatics Research Center, Nippon Telegraph and Telephone Corporation, NTT Basic Research Laboratories

TOUHARA Kazushige
Professor, The University of Tokyo

NISHIZAWA Matsuhiko
Professor, Department of Finemechanics, Tohoku University

HIRAMATSU Ryuji
Visiting Director, Foundation for Biomedical Research and Innovation at Kobe

HOTTA Harumi
Theme Leader, Tokyo Metropolitan Institute of Gerontology

MANABE Ichiro
Professor, Chiba University

MITSUKURA Yasue
Professor, Keio University

YONEDA Yoshihiro
Director General, National Institutes of Biomedical Innovation, Health and Nutrition

Started in 2021

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.

Started in 2021

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.

Started in 2021

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.

Started in 2021

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.

Started in 2021

Theoretical basis for human clinical application of sensory medicine

KOBAYAKAWA Ko
Associate Professor,
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.

Started in 2021

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.

Started in 2021

PRIME

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.

Started in 2021

PRIME

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.

Started in 2021

PRIME

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.

Started in 2021

PRIME

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.

Started in 2021

PRIME

From vision to hippocampal cognitive map: underlying circuit mechanisms

KITANISHI Takuma
Lecturer, Graduate School of Medicine,
Osaka City University

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.

Started in 2021

PRIME

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.

Started in 2021

PRIME

Developing somatosensory system on a chip toward novel pain control method

Shimba Kenta
Assistant 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.

Started in 2021

PRIME

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

FUJIU Katsuhito
Associate Professor,
The University of Tokyo

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.

Started in 2021

PRIME

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.

Started in 2021

PRIME

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

TODA Chitoku
Assistant Professor, Department of Veterinary Medicine, Hokkaido University

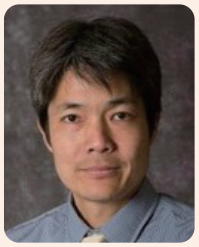
The brain monitors the amount of nutritional energy in the body and environmental food availability by multi-sensing systems. Animals change feeding behavior and energy utilization according to these internal and external situations. Obesity attenuates the function of multi-sensing systems and thus leads 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.

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



Program Supervisor (PS)

DOI Yohei

Professor, Departments of Microbiology and Infectious Diseases, Fujita Health University School of Medicine/ Professor, Division of Infectious Diseases, University of Pittsburgh School of Medicine

Program Officer (PO)

MATSUURA Yoshiharu

Director, Center for Infectious Diseases Education and Research (CiDER) and SA Professor, Laboratory of Virus Control, Research Institute for Microbial Diseases (RIMD), Osaka University

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.

AMED-CREST

R&D Area Advisors

IWASAKI Masaru
Vice-President, University of Yamanashi

SATO Junko
Office Director, Office of International Programs, Pharmaceutical and Medical Device Agency

SAWA Hirofumi
Professor, Division of Molecular Pathobiology, International Institute for Zoonosis Control, Hokkaido University

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

TAWARA Shuichi
Professor, Faculty of Veterinary Medicine, Okayama University of Science

TSUMOTO Kouhei
Professor, School of Engineering and The Institute of Medical Science, The University of Tokyo

HIRAI Keiji
Former Advisor, KYORIN Pharmaceutical Co., Ltd.

HONMA Teruki
Team Leader, Laboratory for Structure-based Molecular Design, Center for Biosystems Dynamics Research, RIKEN Yokohama Institute

HONMA Teruki
Team Leader, Laboratory for Structure-based Molecular Design, Center for Biosystems Dynamics Research, RIKEN Yokohama Institute

YAMANO Yoshinori
Chief Scientific Officer for Infectious Disease, Pharmaceutical Research Division, Shionogi & Co., Ltd.

YAMAMOTO Tomoko
Auditor, Chiba University

Started in 2021

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.

Started in 2021

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.

Started in 2021

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.

Started in 2021

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.

Started in 2021

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.

Started in 2021

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.

Proteostasis

Understanding proteostasis and discovering innovative medical applications

Research and Development Objectives

Understanding and medical application of proteostasis

Program Supervisor (PS)

NAGATA Kazuhiro

Director General,
JT Biohistory
Research Hall

Program Officer (PO)

ENDO Tamao

Senior Fellow, Tokyo
Metropolitan Institute
of Gerontology

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.

AMED-CREST
AMED-PRIME

R&D Area Advisors

ADACHI Takeshi
Professor, School of Medicine, National Defense Medical College

INADA Toshifumi
Professor, Graduate School of Pharmaceutical Sciences, Tohoku University

IWAI Kazuhiro
Dean, Professor, Graduate School of Medicine Kyoto University

KATO Koichi
Director, Exploratory Research Center on Life and Living Systems, National Institutes of Natural Sciences

KINOSHITA Taroh
Professor, Research Institute for Microbial Diseases, Osaka University

SHIMIZU Ritsuko
Professor, Tohoku University School of Medicine

SUZUKI Rami
President and Representative Director Moderna Japan KK

TANAKA Keiji
Board Chairperson, Tokyo Metropolitan Institute of Medical Science

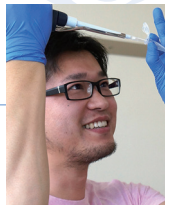
FUJIMOTO Toyoshi
Research Professor, Juntendo University School of Medicine

MIYOSHI Eiji
Professor, Graduate School of Medicine, Osaka University

YAMADA Hisafumi
Executive Vice President, Chugai Pharmaceutical Co., LTD.

Started in 2020

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.

Started in 2020

Study on organelle homeostasis by post-translational modifications

MATSUDA Noriyuki
Project Leader, Ubiquitin Project,
Department of Basic Medical Sciences,
Tokyo Metropolitan Institute of Medical Science

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.

Started in 2020

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.

Started in 2020

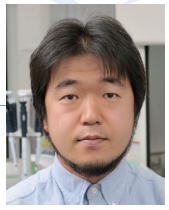
Study on understanding of the molecular mechanisms of tissue-specific unfolded protein responses for radical cure of human chronic diseases

MORI Kazutoshi
Professor, Department of Biophysics,
Graduate School of Science, Kyoto University

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.

Started in 2020

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.

Started in 2021

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

INABA Kenji
Professor, Tohoku University, Institute of
Multidisciplinary Research for Advanced Materials

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.

Started in 2021

CREST

The neo-ubiquitin code for improving proteostasis dysregulation

OHTAKE Fumiaki

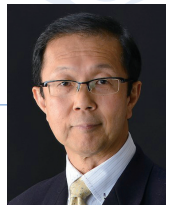
Associate Professor Hoshi University, Institute for Advanced Life Sciences,

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.

Started in 2021

CREST

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



FUKAMIZU Akiyoshi

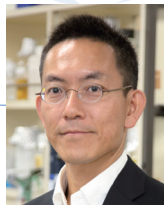
Professor, Life Science Center for Survival Dynamics, Tsukuba Advanced Research Alliance, University of Tsukuba

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.

Started in 2021

CREST

Comprehensive study of in vivo protein folding in proteostasis network



TAGUCHI Hideki

Professor, Cell Biology Center, Institute of Innovative Research, Tokyo Institute of Technology

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.

Started in 2020

PRIME

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.

Started in 2021

CREST

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

TANAKA Motomasa

RIKEN Center for Brain Science, Team Leader

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.

Started in 2020

PRIME

The quality control mechanisms of nascent organellar proteins

IZAWA Toshiaki

Assistant Professor, Faculty of Pharmaceutical Sciences, Tohoku University

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.

Started in 2020

PRIME

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

IWASAKI Mio
Assistant 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.

Started in 2020

PRIME

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.

Started in 2020

PRIME

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.

Started in 2020

PRIME

Study of cellular proteostasis dynamics by imaging or manipulation of proteasome activity

HAMAZAKI Jun
Assistant professor, 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.

Started in 2020

PRIME

Proteostatic regulation for maintaining the function of adult neural stem cells

KOBAYASHI Taeko
Associate Professor, Graduate School of Biostudies, Kyoto University

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.

Started in 2020

PRIME

Mechanism of autophagy driven by liquid-liquid phase separation

FUJIOKA Yuko
Researcher, Institute of Microbial Chemistry, Microbial Chemistry Research Foundation

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.

Started in 2020

PRIME

Study for physiological regulation and cancer metastasis through modification with glycerol phosphate as a glycosylation termination factor of 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.

Started in 2021

PRIME

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

OIKAWA Daisuke
Associate Professor,
Department of Pathobiochemistry,
Graduate School of Medicine, Osaka City 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.

Started in 2021

PRIME

Understanding and control of cytotoxic TDP-43 phase transition

ASAKAWA Kazuhide
Associate professor,
School of Medicine, Tokyo Medical University

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.

Started in 2021

PRIME

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

JOHMURA Yoshikazu
Assistant Professor, Institute of Medical Science, University of Tokyo

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.

Started in 2021

PRIME

Ubiquitin-dependent proteasome phase separation for maintaining proteostasis

ENDO Akinori
Assistant 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.

Started in 2021

PRIME

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

SHIRAKAWA Ryutaro
Assistant professor, 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.

Started in 2021

PRIME

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 Innovative Research, Tokyo Institute of Technology

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.

Started in 2021

PRIME

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

MORISHITA Hideaki
Lecturer, Department of Physiology, Juntendo University School of Medicine

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.

Started in 2021

PRIME

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.

Started in 2021

PRIME

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.

Started in 2021

PRIME

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

MATSUMOTO Akinobu
Associate Professor, Department of Molecular and Cellular Biology, Kyushu 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.

Started in 2021

PRIME

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

YABUKI Yasushi
Assistant 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.

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

Program Supervisor (PS)

SASAKI Hiroyuki

Distinguished Professor,
Medical Institute of Bioregulation,
Kyushu University

Program Officer (PO)

TAKEDA Hiroyuki

Professor,
Graduate School of Science,
The University of Tokyo

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.

AMED-CREST
PRIME

R&D Area Advisors

ISHII Shunsuke
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RIKEN,
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MATSUMOTO Mitsuru
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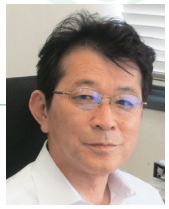
Institute for Enzyme Research,
Tokushima University

YOSHIDA Tomokazu
Senior Executive Officer, Executive
Vice President, Central Research
Laboratories Sysmex Corporation

Started in 2019

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.

Started in 2019

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.

Started in 2019

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.

Started in 2019

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.

Started in 2019

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.

Started in 2020

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

USHIJIMA Toshikazu
Chief, National Cancer Center Research Institute

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.

Started in 2020

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.

Started in 2021

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.

Started in 2020

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.

Started in 2021

Creating innovative human embryology using stem cells

TAKASHIMA Yasuhiro

Junior Associated 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.

Started in 2020

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.

Started in 2021

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.

Started in 2019

PRIME

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.

Started in 2019

PRIME

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.

Started in 2019

PRIME

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

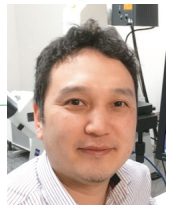
UEMATSU Akira
Assistant Professor, International Research Center for Neurointelligence (IRCN), The University of Tokyo

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.

Started in 2019

PRIME

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.

Started in 2019

PRIME

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.

Started in 2019

PRIME

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.

Started in 2019

PRIME

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

TAKAHASHI Nobuaki
Associate Professor,
The Hakubi Center, 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.

Started in 2019

PRIME

Study of the establishment of DNA methylation during primate germ cell development

WATANABE Toshiaki
Researcher,
Central Institute For Experimental Animals,
Department of Marmoset Biology and Medicine

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.

Started in 2019

PRIME

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

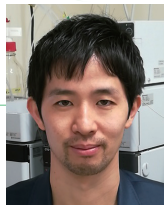
NISHIYAMA Masaaki
Professor, Department of Histology and Cell Biology, Kanazawa University

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.

Started in 2020

PRIME

Regulatory mechanism of longevity through developmental environment



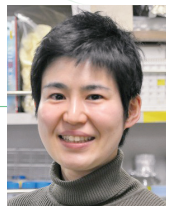
OBATA Fumiaki
Team Leader, RIKEN Center for Biosystems Dynamics Research

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.

Started in 2019

PRIME

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.

Started in 2020

PRIME

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

NAKATO Ryuichiro
Lecturer, 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.

Started in 2020

PRIME

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.

Started in 2020

PRIME

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

MASUDA Takahiro
Associate Professor, Graduate School of Pharmaceutical Sciences, 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.

Started in 2020

PRIME

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

NONOMURA Keiko
Assistant Professor, Division of Embryology, National Institute for Basic Biology

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.

Started in 2020

PRIME

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

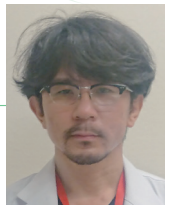
MISHIMA Yuichiro
Associate Professor, Faculty of Life Sciences, Kyoto Sangyo University

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.

Started in 2020

PRIME

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.

Started in 2020

PRIME

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

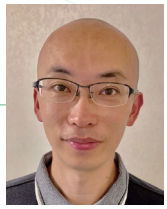
YANAGIDA Keisuke
Senior Research Fellow, National Center for Global Health and Medicine

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.

Started in 2020

PRIME

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.

Started in 2021

PRIME

Mechanisms of disease predisposition by transgenerational histone modifications

INOUE Azusa
Young Chief Investigator, RIEKN 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.

Started in 2020

PRIME

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.

Started in 2021

PRIME

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.

Started in 2021

PRIME

Study on reproductive life span using infertile model animals

ISHIGRO 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.

Started in 2021

PRIME

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.

Started in 2021

PRIME

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

KUSUYAMA Joji
Assistant Professor, Frontier Research Institute for Interdisciplinary Sciences (FRIS), Tohoku University

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.

Started in 2021

PRIME

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.

Started in 2021

PRIME

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.

Started in 2021

PRIME

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

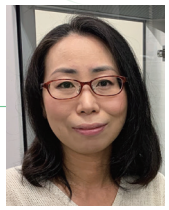
TSUKASAKI Masayuki
Project Assistant Professor,
Graduate School of Medicine and Faculty of Medicine, The University of Tokyo

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.

Started in 2021

PRIME

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



SATOH-TAKAYAMA Naoko
Senior Research Scientist,
RIEKN 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.

Started in 2021

PRIME

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.

Tissue Adaptation and Repair

AMED-CREST
AMED-PRIME

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, Keio University School of Mediceine

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.

R&D Area Advisors

ISHII Masaru
Professor, Graduate School of Medicine, Osaka University

IMAI Yumiko
Project Leader, National Institutes of Biomedical Innovation, Health and Nutrition

KATAGIRI Hideki
Professor, Tohoku University Graduate School of Medicine

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

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

TAMURA Kouichi
Executive Officer, Research, Head of Kobe Research Institute, Healios 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

Started in 2018

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.

Started in 2018

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).

Started in 2018

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.

Started in 2018

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.

Started in 2018

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.

Started in 2019

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.

Started in 2019

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.

Started in 2020

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

SHICHITA Takashi
Project Leader, Stroke Renaissance Project, Tokyo Metropolitan Institute of Medical Science

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.

Started in 2019

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.

Started in 2020

Metabolic reprogramming driving hematological aging

TAKUBO Keiyo
Project director, National Center for Global Health and Medicine Research Institute

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.

Started in 2019

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.

Started in 2020

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

TAKEBE Takanori
Professor, Institute of research, Tokyo Medical and Dental 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.

Started in 2020

AMED-CREST

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.

Started in 2018

PRIME

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.

Started in 2018

PRIME

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.

Started in 2018

PRIME

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

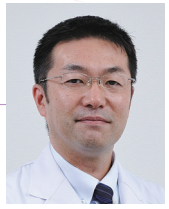
KADOYA Ken
Associate Professor, Faculty of Medicine and Graduate School of Medicine, Hokkaido University

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.

Started in 2018

PRIME

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.

Started in 2018

PRIME

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.

Started in 2018

PRIME

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.

Started in 2018

PRIME

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.

Started in 2018

PRIME

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.

Started in 2018

PRIME

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.

Started in 2018

PRIME

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.

Started in 2019

PRIME

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

IKEDA Kenji

Junior 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.

Started in 2019

PRIME

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.

Started in 2019

PRIME

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.

Started in 2019

PRIME

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.

Started in 2019

PRIME

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.

Started in 2019

PRIME

Study of the epithelial repair mechanism by the new bioactive peptide

ODA Yukako
Assistant Professor, Institute for Frontier Life and Medical Sciences, 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.

Started in 2019

PRIME

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.

Started in 2019

PRIME

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.

Started in 2020

PRIME

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

ISHIGAME Harumichi

Senior Research Associate, RIKEN Center for Integrative Medical Science

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.

Started in 2019

PRIME

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.

Started in 2020

PRIME

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.

Started in 2019

PRIME

Restoration of regenerative system in the aged central nervous system

MURAMATSU Rieko

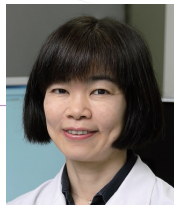
Director, National Institute of Neuroscience, National Center of Neurology and Psychiatry

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.

Started in 2020

PRIME

Mechanisms of skeletal muscle regeneration mediated by increased macrophage diversity



OISHI Yumiko

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

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 sarcopenia.

Started in 2020

PRIME

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.

Started in 2020

PRIME

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.

Started in 2020

PRIME

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

SHICHINO Shigeyuki
Assistant Professor, Institute of Biomedical Sciences, 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.

Started in 2020

PRIME

The roles of oxygen environment on the pathogenesis of cardiac fibrosis

TAKEDA Norihiko
Professor, 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.

Started in 2020

PRIME

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

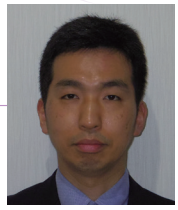
JO-WATANABE Airi
Assistant Professor, Juntendo University
School of Medicine

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.

Started in 2020

PRIME

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



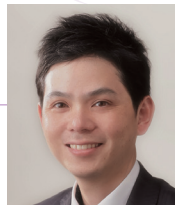
TANIMIZU Naoki
Assistant Professor, The Institute of Medical Science, The University of Tokyo

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.

Started in 2020

PRIME

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.

Functional Impairment

AMED-CREST
PRIME

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

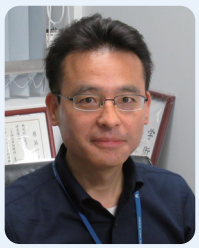
Research and Development Objectives

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

Program Supervisor (PS)

NISHIDA Eisuke

Director, RIKEN Center for Biosystems Dynamics Research



Program Officer (PO)

HARA Eiji

Professor, Research Institute for Microbial Diseases, Osaka University

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.

R&D Area Advisors

ICHIJO Hidenori
Professor, Graduate School of Pharmaceutical Sciences, The University of Tokyo

IMAI Toshio
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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
Team Leader, RIKEN Center for Biosystems Dynamics Research

YANAGITA Motoko
Professor, Graduate School of Medicine, Kyoto University

YOKOTE Koutaro
Professor, Graduate School of Medicine, Chiba University

Started in 2017

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

UEMURA Tadashi
Professor, Graduate School of Biostudies, Kyoto University

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

Started in 2017

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

YAMADA Yasuhiro
Professor, The Institute of Medical Science, The University of Tokyo

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

Started in 2017

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

KAGEYAMA Ryoichiro
Professor, Institute for Frontier Life and Medical Sciences, Kyoto University

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

Started in 2017

Stem cell homeostasis and functional impairment in spermatogenesis

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

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

Started in 2017

Strategy for extending healthy lifespan by the proteasome

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

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

Started in 2018

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

ISHIHARA Naotada
Professor, Graduate School of Science, Osaka University

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

Started in 2018

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

TAKEDA Hiroyuki

Professor, Graduate School of Science, The University of Tokyo

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

Started in 2019

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

INADA Toshifumi

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

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

Started in 2018

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

HAYASHI Yu

Professor, Graduate School of Medicine, Kyoto University

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

Started in 2019

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

OGAWA Seishi

Professor, Graduate School of Medicine, Kyoto University

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

Started in 2018

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

YOSHIMURA Akihiko

Professor, Keio University School of Medicine

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

Started in 2019

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

MINAMINO Tohru

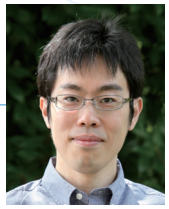
Professor, Juntendo University Graduate School of Medicine

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

Started in 2017

PRIME

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



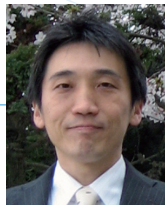
KIMURA Wataru
Team Leader, RIKEN Center for Biosystems Dynamics Research

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

Started in 2017

PRIME

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



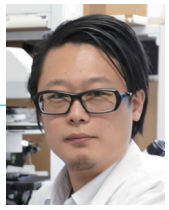
BABA Yoshihiro
Professor, Medical Institute of Bioregulation, Kyushu University

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

Started in 2017

PRIME

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



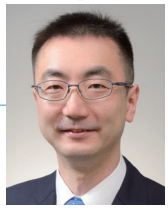
SATOH Takashi
Professor, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University

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

Started in 2017

PRIME

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



HIRAHARA Kiyoshi
Associate Professor, Graduate School of Medicine, Chiba University

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

Started in 2017

PRIME

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

NAKAMURA Shuhei
Associate Professor, Institute for Advanced Co-Creation Studies, Osaka University

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

Started in 2017

PRIME

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

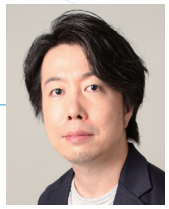
FUJIU Katsuhito
Associate Professor, Graduate School of Medicine, The University of Tokyo

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

Started in 2017

PRIME

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



YACHIE Nozomu

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

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

Started in 2017

PRIME

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

YOSHITANE Hikari

Project Leader, Tokyo Metropolitan Institute of Medical Science

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

Started in 2017

PRIME

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

YANAI Hideyuki

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

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

Started in 2018

PRIME

Revealing and treating of stress-experience related body dysfunctions

ABE Kentaro

Professor, Graduate School of Life Sciences, Tohoku University

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

Started in 2017

PRIME

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

YOO Sa Kan

Chief Scientist, RIKEN

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

Started in 2018

PRIME

Understanding the mechanism of maternal epigenetic inheritance of metabolic disorders

INOUE Azusa

Young Chief Investigator, RIEKN Center for Integrative Medical Sciences,

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

Started in 2018

PRIME

Roles of mitophagy in prevention of hypofunction in whole body

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

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

Started in 2018

PRIME

Elucidating the cellular and molecular mechanisms of epithelial stem cell aging

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

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

Started in 2018

PRIME

Elucidation of mechanisms how social environment regulates the functional impairment

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

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

Started in 2018

PRIME

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

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

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

Started in 2018

PRIME

Comprehensive analysis of ageing-related decreases in mental-body functions

SASAKI Takuya
Professor, Graduate School of Pharmaceutical Sciences, Tohoku University

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

Started in 2018

PRIME

Age-associated changes in the neural plasticity gene expression profile

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

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

Started in 2018

PRIME

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

MIYAJIMA Michio
Senior Research Scientist, RIKEN Center for Integrative Medical Sciences (IMS)

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

Started in 2019

PRIME

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

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

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

Started in 2018

PRIME

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

MIYANISHI Masanori
Senior Research Scientist, RIKEN Center for Biosystems Dynamics Research

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

Started in 2019

PRIME

Clarification of the heterogeneity of cellular senescence in functional impairment

TAKAHASHI Akiko
Project Leader, Cancer Institute, Japanese Foundation for Cancer Research

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

Started in 2019

PRIME

Comprehensive identification of enhancers in developmental and aging process of in vivo neurons

KISHI Yusuke
Senior Lecturer, Graduate School of Pharmaceutical Sciences, The University of Tokyo

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

Started in 2019

PRIME

Mechanism of memory impairment through age-related metabolic change

TONOKI Ayako
Lecturer, Graduate School of Pharmaceutical Sciences, Chiba University

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

Started in 2019

PRIME

Investigating mechanisms of rejuvenation in basal metazoans and their potential applications

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

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

Started in 2019

PRIME

Individual's functional impairment and age-related disorders in organs by cytosolic dsDNA of mitochondrial origin

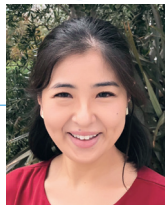
MATSUI Hideaki
Professor, Brain Research Institute, Niigata University

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

Started in 2019

PRIME

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



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

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

Started in 2019

PRIME

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

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

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

Started in 2019

PRIME

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

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

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

Started in 2019

PRIME

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

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

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

(＊) indicates completed R&D projects.

Microbiome

Understanding the Interactions and Symbiosis between the Microbiome and the Host Organism, Leading to an Understanding of the Mechanisms of Disease Onset

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

Team Leader and Chief Scientist, Laboratory for Intestinal Ecosystem, 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.

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

Our team will clarify how skin microbiome affects immune system in a healthy condition, and how dysbiosis is involved in the cause of skin inflammation, such as atopic dermatitis in mice and human. Furthermore, we will clarify the homeostatic mechanism of stratum corneum, which is highly regulated to maintain 10-15 layers of dead keratinocytes and provides niche for skin microbiome. The goal of our study is to develop a novel therapeutic strategy to inflammatory and allergic skin diseases by regulating skin microbiome through manipulating the microenvironment of stratum corneum.

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

The mechanisms by which commensal microorganisms colonize in the intestine and thereby influence our health condition remain unknown. In this research project, we will analyze the mechanism by which human microbiota and mycobiota help each other to colonize in the intestine. Will also analyze the mechanisms how commensal microorganisms influence our health condition by identifying their metabolites, which act on the host cells.

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

Accumulating knowledge indicates that abnormally aggregated α-synuclein in the intestine behaves like a prion and causes Parkinson's disease (PD). It is subsequently inferred that intestinal microbiota is causally associated with the development of PD. Specific aims of our current studies are to obtain temporal profiles of clinical features, biomarkers, and intestinal microbiota in patients with PD and dementia with Lewy bodies (DLB), and to perform cross-sectional and longitudinal analyses using machine learning techniques to elucidate the possible roles of intestinal dysbiosis in the development of PD and DLB.

Started in 2016

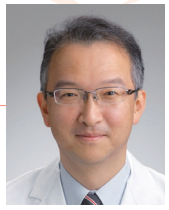
Clarifying the role of microbiome in cancer immunity for application into cancer therapy

NISHIKAWA Hiroyoshi
Chief, Division of Cancer Immunology, Research Institute/ EPOC, National Cancer Center

Immune checkpoint blockade provides clinical success in various types of cancers. Yet, more than half of treated patients do not respond to immune checkpoint blockade therapy, even in combination. It is therefore required to define biomarkers to properly evaluate phenotypes of both immune responses and cancer cells in cancer patients for detecting responders. In this study, we focus on the diversity of metabolism and microbiome of cancer tissues in each cancer patient, clarifying their contribution to cancer immunity. Moreover, the role of the microbiome in immune tolerance and surveillance is addressed from the view of cancer immunity.

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

Previous studies have revealed the intestinal microbiota is implicated in numerous aspects of health and disease based on their interaction with host epithelium. In this project, we use both an gnotobiotic mouse model using human patients-derived feces and a novel ex vivo intestinal epithelium culture system to understand the mechanism of communication between gut microbes and host intestinal epithelium. The goal of our study will establish basic roles of the effect of microbes for entire body of human thought gut-liver-brain axis that could have implications for therapy and generate new drugs of diseases such as cancer and inflammation of gut or liver that demonstrate poor healing.

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

Gut microbiota has emerged as a pivotal, multifactorial mediator in metabolic disorders as it remarkably regulates host energy acquisition and metabolism while being modified by diet. Short-chain fatty acids represent an essential subset of gut microbial metabolites derived from the fermentation of the otherwise indigestible dietary fiber. This research aims at elucidating the molecular interplay between host energy metabolism and these metabolites of gut microbiota that underlies the pathogenesis of metabolic disorders with further exploration of novel interventions including drugs and functional foods.

Started in 2017

AMED-CREST

Elucidation of molecular mechanisms of gut microbiota regulation by intestinal IgA

SHINKURA Reiko

Professor, Institute for Quantitative Biosciences, The University of Tokyo

As a modulator of the intestinal microbiota, we isolated a mouse monoclonal IgA antibody (clone W27) with high affinities for multiple commensal bacteria, but not for beneficial bacteria such as *Lactobacillus casei*. By modulating the gut microbiota *in vivo*, oral administration of W27 IgA effectively prevented development of colitis in several mouse models. In this research, we will clarify how intestinal IgA interacts and regulates human gut microbiota. The elucidation of precise molecular mechanism of IgA function leads to a new solution for treatment of dysbiosis.

Started in 2018

AMED-CREST

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

Periodontal disease is a condition in which periodontal tissues supporting the teeth are destroyed by bacteria in the oral cavity. Our study examines the deterioration of the oral bacterial flora that accompanies the progression of periodontal disease and includes a detailed analysis of the resulting changes in intestinal bacterial flora and metabolites produced through host-bacteria interactions. Thereby, our study aimed to clarify the etiopathology of periodontal disease from a new perspective and to elucidate the molecular mechanisms involved in the altering effects of periodontal disease on the overall physical condition of the patient.

Started in 2017

AMED-CREST

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

We aim to establish a new research and development facility to enhance metagenomics, metabolomics, and bioinformatics approaches for human microbiome research in this project. Our missions are to (i) support sequencing and bioinformatics analyses for shotgun metagenomics and amplicon sequencing, (ii) develop advanced technologies by taking advantage of achievements in human microbiome, (iii) propose ethical guidelines for human microbiome research and the recommended protocols for both experiments and bioinformatics analyses (iv) build a human metagenomics data sharing system and (v) create a new integrated metagenomics and metabolomics database including search/browse information and comparative analysis results.

Started in 2018

AMED-CREST

Study of microbiota-mediated modulation of neuroinflammation, neurodegeneration and neural development

YAMAMURA Takashi

Director, National Institute of Neuroscience, NCNP

As recent study has indicated, chronic inflammation accompanied by activated glia cells may play a critical role in neurodegenerative and neurodevelopmental disorders. Given the recent concept on gut-brain axis, we explore the role of gut microbiota in neurodegenerative and neural development disorders. We will analyze the microbiota and gut immunity in new animal models relevant for study of such disorders, and further conduct translational research dependent on human fecal samples. Our unique approaches will lead us to obtain new insights into the pathogenesis and new possible therapeutic strategies.

Started in 2018

AMED-CREST

The mechanism and the regulation of liver diseases involved in gut-liver axis-mediated intestinal microbiota

OHTANI Naoko

Professor, Department of Pathophysiology, Osaka City University, Graduate School of Medicine

The gut and the liver are anatomically and physiologically connected and this “gut-liver axis” exert various influences on liver pathology. Gut microbiota normally co-exist in the gut and have a role of maintaining the homeostasis of the host. However, once the homeostasis is unbalanced, metabolites and components derived from the gut microbiota are absorbed and transferred to the liver and elicit pathological stresses on the liver. Therefore, the liver is continuously susceptible to the influence of gut microbiota. We will elucidate the unknown mechanism of liver diseases involving the gut microbiota via "gut-liver axis", and clarify gut microbiota and their metabolites useful for prevention of liver diseases including cancer.

Started in 2016

PRIME

Crosstalk among microbiome, host, disease, and drug discovery enhanced by statistical genetics (*)

OKADA Yukinori

Professor, Graduate School of Medicine, Osaka University

Statistical genetics is a research field that evaluates causality of human genetic variations on diseases, using statistical and bioinformatics approaches. In this project, we integrate high-throughput omics data related to human microbiome generated by next generation sequencer. We focus on variations in human genome and metagenome sequences, and their relationships in host-microbiome interaction. Based on the newly developed statistical genetic approaches, our project aims elucidation of novel disease biology and identification of drug discovery seeds.

Started in 2016

PRIME

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

In the natural environment, certain bacterial consortia live on electricity by transporting respiratory electrons though biofilm and sharing energy. Such “electric symbiosis” has not been known in human or disease-related microbiome. We recently revealed by electrochemical assay that some pathogenic strains have the potential for the electronic symbiosis. In this project, we study the intercellular electrical interaction in in-vivo biofilms by tracking gene expression level of individual bacteria, and challenge to develop technologies to control the activity of human bacterial flora.

Started in 2016

PRIME

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

Numerous numbers of microorganisms colonize in our intestine. Epithelial cells covering the intestinal tract directly face to these microorganisms and create a symbiotic environment with microorganisms by expressing α1, 2-fucose, a kind of sugar chain, on their cell surface. In this project, we aim to clarify regulation mechanism of the homeostasis of commensal microbiota by symbiotic and immunological factors including carbohydrate chain produced by epithelial cells in each intestinal tract. We further investigate mechanism of the development of inflammatory bowel disease and metabolic disorders caused by dysbiosis.

Started in 2016

PRIME

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

To investigate genomic composition of microbiomes, the methods based on marker sequences such as 16S rRNAs are widely utilized and the valuable knowledge associated with health and disease have been accumulated. However, it was also reported that the fine-scale mutations critically changed the characteristics of the microbes, including resistances for medicines, as the results of studies of isolated microbes for decades. In this study, the whole sequence of each microbe genome in a microbiome is thoroughly analyzed and I intend to elucidate the nature of microbiomes that are not targeted in marker sequences-based analysis, mainly developing the informatics methods.

Started in 2016

PRIME

Development of metatranscriptome analysis method based on megagenome assembly and its application to metatranscriptome map of commom marmoset (*)

SAKAKIBARA Yasubumi
Professor,
Keio University

We develop a bioinformatics method for high-precision meta-transcriptome analysis that can deeply detect bacteria species with high sensitivity and low abundance by applying the MetaVelvet, an assembler specialized for metagenomes developed in our laboratory. Next, we construct the meta-transcriptome map in the intestine including rectal and vermiform that forms the common bacterial flora using common marmoset as a target preclinical primate model of human.

Started in 2016

PRIME

Microbiota regulates IgE-mediated allergic responses (*)

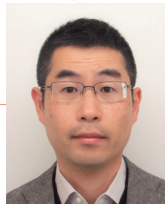
KIM Yun-Gi
Professor, Research Center for Drug Discovery, Faculty of Pharmacy, Keio University

Prenatal or early-life antibiotic exposures are known to increase the risk of allergic diseases, suggesting that exposure to environmental microorganisms in this period is important event to develop and maintain balanced immune systems. Several mouse studies have shown that germ free and antibiotic-treated mice have increased serum IgE level and enhanced disease severity such as allergic airway inflammation and food antigen-induced anaphylaxis. In this study, I try to find gut bacteria which have an ability to reduce serum IgE level. Also, I will elucidate the mechanisms by which the bacteria reduce serum IgE level.

Started in 2016

PRIME

Isolation of yet-uncultured microorganisms and elucidation of symbiosis mechanism between the microbe (*)



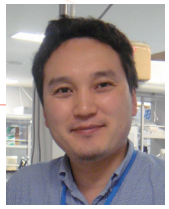
SAKAMOTO Mitsuo
Senior Research Scientist, Japan Collection of Microorganisms, RIKEN BioResource Research Center

Human intestinal microbiota is composed of a wide variety of species, many of which have been found to be yet-uncultured or unclassified bacteria. In this study, we aim to establish a new culture system and co-cultivation system by multiple species in order to isolate yet-uncultured microorganisms. Furthermore, by clarifying the characteristics of the isolates and co-culturing them with multiple species based on the obtained information, it is possible to clarify the mechanisms of the interaction between the microbiota and the host.

Started in 2016

PRIME

Investigation of the mechanism for forming neonatal gut microbiota (*)



SAWA Shinichiro
Professor, Medical Institute of Bioregulation, Kyushu University

Neonate is a critical period for colonizing bacteria in mammals. However, it has been unclear by which mechanism particular species of bacteria colonize in the neonatal gut. In this project, I am investigating mechanism for forming intestinal microbiota and for shaping immune system, particularly focusing on the newly identified lymphoid population termed innate lymphoid cells. This study will bring us a new knowledge that helps us to understand relationship between the dysbiosis and the necrotizing colitis (NEC) that occur in neonates. Moreover, this study might help us to develop new strategy to prevent dysbiosis occasionally observed in adult patients suffering from obesity and inflammatory bowel disease.

Started in 2017

PRIME

Elucidation of the relationship between microbiota and enteroendocrine cells (*)

KURAISHI Takayuki
Associate Professor, Kanazawa University

Intestinal enteroendocrine cells are specialized minority cells of the gastrointestinal tract with endocrine function. They produce peptide hormones in response to various stimuli, such as amino acids and lipids of ingested foods, in order to modulate host metabolism. In a sense, enteroendocrine cells are considered as chemosensors for host internal environment that are responsible for the control of host physiology. We hypothesized that enteroendocrine cells could recognized bacterial metabolites derived from intestinal microbes so as to adjust their production of peptide hormones. In this study, we try to identify bacterial subsets that induce the expression of the intestinal peptide hormones, and clarify its molecular mechanisms.

Started in 2017

PRIME

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

Enteric infectious diseases caused by enteric bacterial pathogens are one of the leading infectious killers. Furthermore, since many enteric pathogens are highly human adapted and unable to colonize mice intestine, lack of appropriate animal infection models are becoming bottleneck for in vivo pathogenic analysis and developing vaccine and novel drugs. Therefore I am trying to develop mouse intestinal infection model that would be suitable to in vivo pathogenic analysis and develop vaccine and novel drug through the analysis of microbiota-bacterial pathogens interplay.

Started in 2017

PRIME

Elucidation of crosstalk between the enteric nervous system and commensal microbiota for gut mucosal health and disease (*)

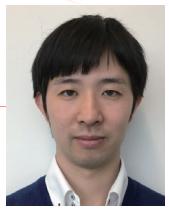
KURASHIMA Yosuke
Associate Professor, Graduate School of Medicine, Department of Innovative Medicine, Chiba University

The enteric nervous system is comprised of two separate plexuses, the Meissner's and Auerbach's plexuses. The Meissner's plexus is in the intestinal submucosa while the Auerbach's plexus is located between the longitudinal and circular intestinal muscle layers. Both plexuses promote peristalsis and digestive activity through myenteron stimulation. The plexuses, particularly Meissner's plexus, have also been shown to alter epithelial cell function such as hormone and mucous secretion; however, the precise mechanisms are not well elucidated. We aim to detail mechanisms of gut mucosal health and disease, to elucidate the body's environmental maintenance mechanisms.

Started in 2017

PRIME

Elucidation of DOHaD mechanisms driven by gut microbiota (*)



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

Early-life environment can influence the adult health throughout life. However, mechanism(s) of this phenomenon known as “The Developmental Origins of Health and Disease (DOHaD)” is poorly understood. The present study elucidates the mechanism of DOHaD driven by gut microbiota, based on a hypothesis that developmental environment triggers irreversible reprogramming of gut microbiome to affect the organismal healthspan. Taking advantages of shorter lifespans of fruit flies *Drosophila melanogaster* enables to promote the rapid progress of the unique research.

Started in 2017

PRIME

Research for the mechanism of human gut microbiota mediated induction of immune cells and cancer immunity (*)

TANOUE Takeshi
Assistant Professor, School of Medicine, Department of Microbiology and Immunology, Keio University

There are mounting evidences showing that gut microbiota affects various physiological responses of the host. A control or reproduce of these effects is promising strategies for disease control and health maintenance in clinical fields. In this study. I focus on the immunological effect and try to investigate the molecular mechanism of human gut microbiota mediated induction of immune cells, mainly search for bacteria-derived antigen that can drive the activation of immune cells. And I also try to address the effect of microbiota on cancer immunity.

Started in 2017

PRIME

Elucidation of the inflammation regulating mechanism by skin resident commensals in the pathogenesis of inflammatory skin diseases (*)

NAKAJIMA Saeko
Lecturer, Department of Dermatology, Graduate School of Medicine, Kyoto University

Shifts in skin microbiota composition have been shown in the context of skin inflammatory disorders, however, the precise role of cutaneous commensals in the control or promotion of skin inflammatory states remains unclear.
I will identify the skin commensals which regulate the inflammation and will evaluate local immune responses in inflammatory skin diseases such as psoriasis vulgaris and atopic dermatitis. I will clarify the molecular mechanism which is regulated by skin commensals. I will use microbiological and immunological approaches to assess these questions by using human skin models and murine dermatitis models.

Started in 2018

PRIME

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

While microbiota is increasingly associated with the host physiology and pathology, molecular mechanisms that link between microbiota and its host are less understood. In this project, we focus on D-amino acids, chiral forms of L-amino acids, originated in bacteria as interkingdom signaling molecules. We aim to understand the immunological and pathological significance of microbe-host relationship through D-amino acids and a host metabolic enzyme, D-amino acid oxidase.

Started in 2017

PRIME

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

Changes in gastric microbiome during gastritis and gastric cancer progression have been recently reported, but the details and mechanisms of gastric dysbiosis remain unclear. In this proposal, we focus on gastric dysbiosis during gastric disease progression, and their role in gastritis, intestinal metaplasia, and gastric cancer. We will investigate the possible relationship between gastric microbiome and small intestinal and colon diseases. We will also explore how gastric microbiome affects gastrointestinal stem cell activity and influences nerve-dependent regulation of gastrointestinal homeostasis. This proposal would contribute to provide new insights for understanding the pathogenesis of gastrointestinal diseases, and help to establish novel therapeutic approaches such as probiotics treatment.

Started in 2018

PRIME

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)

Not only mammalian cells, but also microorganisms are also coated with glycans at the outermost cell surface, which play roles as “starting point” of the crosstalk with host cells. However, there has been no method to analyze the glycome of microbiome and its roles have not been understood at all. In this study, I will develop a novel technology to analyze the glycome of microbiome in a high-throughput manner and pioneer a new breakthrough in microbiome researches.

Started in 2017

PRIME

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

Atopic dermatitis (AD) and CA-MRSA infection are associated with the skin colonization with *Staphylococcus aureus*. In this study, we will analyze the mechanism responsible for this evolutionary change of *S. aureus*-genome that regulates *S. aureus* adaptation to the skin by using whole genomic analysis of *S. aureus* and skin microbiome analysis. This study can contribute a more detailed understanding of the role of *S. aureus* in skin disease pathogenesis and provide the new therapeutic target for AD and *S. aureus*-associated cutaneous infections.

Started in 2018

PRIME

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)

In this work, we aim to investigate the interaction between uncultured intestinal flora and two widespread health conditions of major concern-diabetes and obesity. In particular, we will cultivate and identify diabetes and obesity causing bacteira (DIB) and DIB-targeting viruses (DIB-V), and perform a concerted investigation of the three-way interaction between the host, DIB, and DIB-V to address the main questions at hand: cause, mechanism, and solution. This work will provide major steps forward in our comprehension of the relationship between human diseases, GIT microbiota, and even viruses and, most importantly, essential insight into unprecedented microbiology-based bottom-up development of innovative disease prevention and treatment.

Started in 2018

PRIME

Mechanism for acceleration of T cell senescence and transformation by intestinal flora

NAKATSUKASA Hiroko

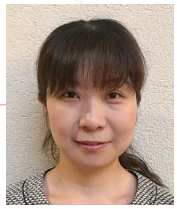
Assistant Professor, Department of Microbiology and Immunology, Keio University School of Medicine

Aging-dependent dysbiosis is related to susceptibility to infection and cancer and contributes to the development of various diseases, such as chronic inflammation, autoimmune diseases, diabetes, and cardiovascular diseases, through T cell senescence and dysfunction of immune systems. In this study, we will clarify the effect of intestinal bacteria-dependent epigenetic modification on T cell homeostasis including senescence and tumorigenesis. We will also try to identify the intestinal bacteria species or their metabolites responsible for T cell senescence and tumorigenesis, and to develop therapeutic strategy for aging-related diseases.

Started in 2018

PRIME

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

Diet is the major driver that controls the gut microbiota which is known to be involved in the onset of various diseases such as obesity and type 2 diabetes. Microbiota produces various metabolites from dietary nutrients. However, it is poorly understood what nutrients affect bacterial composition that produces biologically active metabolites and how they affect the host metabolism. The aim of this study is to elucidate the crosstalk between nutrient-specific microbiota control and bacterial metabolites, and clarify the relation with host metabolism and immunity.

Started in 2018

PRIME

Elucidation of inhibitory receptor-microbiome interaction in health and disease

HIRAYASU Kouyuki

Associate Professor, Kanazawa University Advanced Preventive Medical Sciences Research Center

Host-commensal bacteria relationships can impact host immunity, the mechanism of which is not fully understood. Considering that not only microbial pathogens but also tumor cells exploit host inhibitory receptors to act on host immune system, the host microbiome is also likely to interact with immune inhibitory receptors to establish the host-microbe symbiosis. Therefore, this study aims to elucidate the host-microbiome interaction in health and disease by focusing on the immune inhibitory receptors.

Started in 2018

PRIME

Unraveling the anti-inflammatory mechanisms of human 2 *Bacteroides* species and their application for treating chronic inflammatory diseases

YAMASHITA Tomoya

Associate Professor, Division of Cardiovascular Medicine, Kobe University

Our clinical studies demonstrated *Bacteroides vulgatus* and *Bacteroides dorei* were decreased in coronary artery disease patients compared with controls. Further, oral administration of the *Bacteroides* 2 species were shown to reduce the cytokine and chemokine production *in vivo*, and to inhibit the progression of atherosclerotic lesion formation in atherosclerosis-mouse model. The aims of this research are to clarify the anti-inflammatory mechanisms of *Bacteroides* 2 species *in vivo* (1), to verify the effects of them on several inflammation-related disease mouse models (2), and finally to establish the basis for clinical application of them as microbial drugs.

Started in 2018

PRIME

Elucidation of mechanism of pancreatic cancer initiation based on the interaction between microbial flora and host

FUKUDA Akihisa

Lecturer, Department of Gastroenterology and Hapatology, Graduate School of Medicine, Kyoto University

This study aims to investigate the mechanism by which pancreatic ductal adenocarcinoma (PDAC) is developed in the context of the interaction between microbial flora and host. We will investigate how innate immune response to intestinal microbial flora affects inflammation, dedifferentiation of pancreatic epithelial cells, formation of pancreatic precancerous lesions and PDAC, and pancreatic cancer stem cells. To this end, we will use genetically engineered mouse models of PDAC and ex vivo 3D culture system of PDAC spheroids of mouse and human.

(*) indicates completed R&D projects.

Mechanobiology

Mechanobiology Elucidation of Mechanobiological Mechanisms and Their Application to the Development of Innovative Medical Instruments and Technologies

Research and Development Objectives

Elucidation of mechanobiological mechanisms leading to the development of innovative medical instruments and technologies

Program Supervisor (PS)

SOKABE Masahiro

Professor, Mechanobiology Laboratory, Nagoya University Graduate School of Medicin

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.

AMED-CREST
AMED-PRIME

R&D Area Advisors

OSADA Yoshihito
Senior Visiting Scientist, RIKEN

KOTERA Hidetoshi
Executive Director, RIKEN

SATO Masaaki
Professor Emeritus, Tohoku University

SHIGEMATSU Takashi
R&D Management Division, 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
Senior Manager, Global Strategy Planning Unit Corporate Strategy Planning Department, Shimadzu Corporation

MIZUMURA Kazue
Professor Emeritus, Nagoya University

Started in 2015

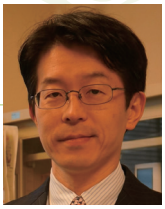
Exploration of molecular mechanisms of nucleo-cytoplasmic mechano-transduction and its medical application (*)

OGURA Toshihiko
Professor, Institute of Development, Aging and Cancer, Tohoku University

We will uncover the molecular mechanisms that transduce mechanical stimuli from cytoplasm to nucleus in living organs and tissues to control gene expression profiles. Based upon our findings, we will develop novel techniques to manipulate cells mechanically in a microscale level. In addition, we will discover new therapeutic ways, namely, exercise mimetics and exercise pill, to combat with diseases, such as metabolic syndrome, disuse atrophy and cardiovascular diseases.

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

Hearing is essential for human life. This sensation is triggered by transduction of nano-scale vibrations induced by acoustic stimuli to electrical signals in the 'cochlea' of the inner ear. Deafness, which afflicts 10% of the global population, emerges primarily from disruption of the cochlea; the causes of this disease remain largely uncertain. In this study, we will focus highly sensitive and tuned mechanical response of the cochlea and investigate the underlying mechanisms and their pathological significance by interdisciplinary approaches. Furthermore, on the basis of the results we will develop a next-generation device to assist hearing for patients with deafness.

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

Mesenchymal stem cells (MSCs), one of the most useful cell sources for regenerative medicine in these days, tend to deteriorate its stemness depending on the mechanical conditions of culture substrate. Therefore, special cares are required to maintain its quality from the view of stem cell mechanobiology. For this issue, we have fabricated microelastically-patterned hydrogel, applied it for MSC culture, and discovered a phenomenon of "frustrated differentiation" which enables to inhibit lineage specification of MSCs. In this project, we elucidate the mechanism of the frustrated differentiation as well as development of the culture substrate that ensures to keep high quality stemness of MSCs.

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

As one of the mechanotransduction pathways that convert mechanical stimuli into biochemical activities, it is recently suggested that load applied to a tissue may deform cells in the tissue, causing the deformation of their nuclei, and nuclear deformation may affect the distribution of chromatin, and finally stimulate mRNA transcription. In this project, we take artery walls as the test model, and aim to study in detail and quantitatively how the deformation applied to artery wall is transferred to cells, then nuclei, and finally chromatin, and how the change in chromatin distribution causes mRNA transcription by combining multi-scale experiments and computer simulations.

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

The weight-bearing exercises help to build bones and to maintain them strength. On the other hand, bone loss with bedridden and space flight are well known as essential problems. Bone is constantly renewed by the balanced action of osteoblastic bone formation and osteoclastic bone resorption both of which mainly occur at the bone surface. This restructuring process called "bone remodeling" is important not only for normal bone mass and strength, but also for mineral homeostasis. However, the molecular basis for the regulatory mechanisms underlying bone remodeling in response to mechanical stimuli has not been sufficiently elucidated. Based on this novel concept of a regulatory mechanisms mediated by osteocytes in response to mechanical stimuli (the "osteomechano-cascade"), we plan to investigate the biological systems of osteocytes through approach combined with comprehensive analysis and sophisticated genetically modified mouse system.

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

We study mechanobiology dealing with mechanical phenomena in the human body, especially focusing on cellular sensing and mechanotransduction mechanisms underlying the responses to mechanical stimuli. The main theme of our study is to elucidate how vascular endothelial cells sense hemodynamic forces (i.e., shear stress and stretch) generated by blood flow and blood pressure. This would be of benefit not only for understanding the blood flow-mediated regulation of vascular functions, angiogenesis and vascular remodeling, but also for the elucidation of clinically important problems, such as the development of cerebral aneurysms and atherosclerosis.

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

Tendons and ligaments are tissues that exert their functions by linking muscles and bones accurately and tightly, and their disorders and diseases cause the patient to dramatically lower daily life. In this study, we will examine molecular mechanisms of tendons/ligaments development and homeostasis via a mechano signal cascade and apply the finding to tendon regenerative medicine.

Started in 2016

Mitochondrial mechanobiology to unravel its role in muscular atrophy

HIGASHITANI Atsushi
Professor, Tohoku University Graduate School of Life Sciences

Skeletal muscle has the ability to respond to mechanical stress, suggesting that skeletal muscle has mechanosensor that sense and convert mechanical signals into biochemical signals. However the details of those sensors or signals remain unclear. Recently it has been reported that mitochondrial dysfunction causes various diseases including muscle atrophy. In addition, mitochondria have been demonstrated to activate several intracellular signaling pathways upon mechanical stress. Therefore, we hypothesize that mitochondria can feel and respond to mechanical stress as mechanosensors, and that mitochondrial responses against the excess or deficiency of mechanical stress may collapse skeletal muscle homeostasis. In this project, we try to verify our hypothesis and to investigate the mitochondrial signaling pathways that regulate skeletal muscle atrophy or hypertrophy.

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

Sugar chain is an important biomolecule that coordinates cellular membrane environment. Changes in its quality or quantity affect mechanical response in muscle cells, sometimes leading to human diseases. In this study, we will investigate membrane molecular environment essential for appropriate mechano-sensing/response that includes sugar chains and proteins either directly or indirectly interacting with mechano-sensor proteins. We will also clarify mechanism how muscle cells maintain the cellular homeostasis utilizing mechanical stress and the pathogenesis associated with disrupted mechano-sensing/response. Finally, we will develop therapeutic strategies for mechano-fragile muscular dystrophy/muscle atrophy or mechano-adaptive myalgia.

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

Neurons extend axons and form elaborate networks in the brain. In this study, we will elucidate the molecular mechanics underlying cell migration and axon guidance (chemotaxis + haptotaxis + durotaxis), and formulate a mathematical model to describe them. This study also analyzes a mechanosensor system responsible for axonal haptotaxis. In addition, we will elucidate the molecular pathology of L1-CAM syndrome, with characteristic symptoms corpus callosum hypoplasia, mental retardation, dysphasia, spastic paraplegia and hydrocephalus, and the molecular mechanisms of malignant glioma cell invasion. We also analyze the molecular mechanics underlying dendritic spine formation, by expanding the model of axon guidance.

Started in 2016

Mechanobiology in cancer and stroma cells

HAGA Hisashi
Professor, Faculty of Advanced Life Science, Hokkaido University

Abnormally stiff substrates have been shown to trigger cancer progression. Our main goal in this research and development program is to elucidate the detailed molecular mechanisms underlying this trigger. We focus on the influence of cancer-associated fibroblasts (CAFs) on the progression of cancer. Moreover, we examine the involvement of lipid rafts regulated by the stiffness of the extracellular matrix in cancer cell migration. We are also developing a new screening system to observe the effects of substrate stiffness on malignancy, aiming to find a possible therapeutic target for tissue stiffening causing cancer.

Started in 2017

Analysis of angiogenesis-related signaling pathways regulated by cyclic compression force -for developing wound treatment devices by non-contact ultrasound-

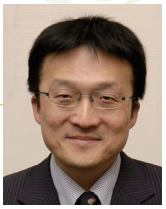
OGAWA Rei
Professor and Chief, Department of Plastic, Reconstructive and Regenerative Surgery, Graduate School of Medicine, Nippon Medical School

The main aim of this research is to elucidate the mechanism of acceleration of wound healing by compression force applied by our original non-contact airborne ultrasound device. Cyclic compression by our device accelerated wound healing in mice models. This accelerated healing was accompanied by the increased epithelization and the granulation tissue formation facilitating contraction of the collagen matrix and wound closure. We also focus on activation of Notch signaling pathway and high-frequency calcium oscillation of human microvascular endothelial cells which have been compressed from the apical surface. We expect to construct a fundamental technology of mechanotherapy using the ultrasound device.

Started in 2017

AMED-CREST

Development of novel therapeutic approaches for heart failure by dissecting the mechanisms of cardiomyocyte mechanobiology



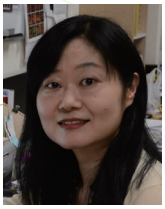
KOMURO Issei
Professor, Graduate School of Medicine, The University of Tokyo

Heart failure is a leading cause of death worldwide. It has been thought that disruption of cardiac response to mechanical stress is essential for heart failure, but the central molecular mechanisms remain elusive and there is no effective treatment targeting the pathogenesis. In this study, we focus on cardiomyocyte mechanosignaling molecules to elucidate the nature of heart failure. This study would lead to the comprehensive understanding of pathogenesis of heart failure and the development of novel therapeutic approaches.

Started in 2015

PRIME

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

We have previously reported that TRP vanilloid family type 2 channels (TRPV2) can be activated by hypotonicity- and stretch-induced mechanical stimulation. In this project, we aimed to understand the roles of TRPV2 in mechanical-signal-dependent remodeling of physiological function and structure in a wide variety of tissues using several types of tissue-specific TRPV2 knockout (KO) mice. We also clarify the mechano-feedback mechanisms required for the maintenance of cellular structure and function in several tissues. These studies will elucidate the molecular bases of mechanotransduction and their physiological role for maintaining homeostasis. In addition, we will propose the effective therapeutic targets for the diseases caused by defects in mechano-feedback signal transmitted via TRPV2.

Started in 2015

PRIME

Thermal control of cellular functions using the technology to create organelle-size heat spots (*)

ARAI Satoshi
Associate Professor, NanoLSI, Kanazawa University

Heat therapy, typified by hyperthermia for cancer treatment, has not been established as a standardized way in medical field. As a reason, it is pointed out that the underlying mechanism of how heat stress affects cellular activities still remains elusive at the single-cell level. In this project, we propose a method whereby nano/micro-sized heat spots can be generated at targeted places inside cells. Using the method, we perform systematic studies to unveil the correlation between heat stress and cellular functions. The deeper understanding of its correlation would expand possibilities of heat therapy and bring innovation for next-generation medical treatment.

Started in 2015

PRIME

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

Baroreceptor afferent nerves locally locating at cervical arteries and aorta sense blood pressure as mechanical stress and systemically regulate autonomic nerves and cardiovascular organs (heart, kidney, vessel) to maintain homeostasis and life. In the present study, I will examine at single-cell resolution where and how these afferent nerves sense and respond to blood pressure in baroreceptor regions of living animals by using two-photon imaging and system identification and engineering technology, and develop a platform for near future medical therapy by engineering of nerve functions.

Started in 2015

PRIME

Cardiac reprogramming and heart regeneration via mechano-transduction (*)

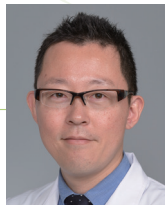
IEDA Masaki
Professor and Chair, Department of Cardiology, Faculty of Medicine, University of Tsukuba

The heart is always exposed to mechanical stimulation, and mechanical stress is necessary for proper cardiac development and cardiomyocyte maturation. However, it remains unknown whether the cell fate of cardiomyocytes is determined by mechanical stimulation. We previously reported that cardiac-specific transcription factors, including Gata4, Mef2c, and Tbx5, reprogrammed fibroblasts into induced cardiomyocyte-like cells (iCMs) in vitro and in vivo. Moreover, in vivo cardiac reprogramming can regenerate injured hearts and improve cardiac function. In these experiments, we found that the quality of cardiac reprogramming was better under in vivo than under in vitro conditions. In this study, we will elucidate the link between mechanical stimulation and cardiac reprogramming, identify the underlying molecular mechanisms, and apply the findings to regenerative medicine.

Started in 2015

PRIME

Stress intensity-dependent mechano-responses of articular chondrocytes (*)



SAITO Taku
Associate Professor, Orthopaedic Surgery, Graduate School of Medicine, The University of Tokyo

Proper mechanical loading is essential for maintenance of bone and cartilage, meanwhile exposure of articular cartilage to excessive mechanical loading is deeply involved in the pathogenesis of osteoarthritis. In this project, we examine molecular mechanisms underlying cartilage anabolism by proper mechanical loading and cartilage degeneration by excessive mechanical loading. We further aim to develop novel therapeutics by applying the findings of chondrocyte mechano-responses.

Started in 2015

PRIME

Nuclear micromechanics and mechano-transduction mechanisms (*)

SHIMAMOTO Yuta

Associate Professor, Center for Frontier Research, National Institute of Genetics

It has long been recognized that the cell nucleus, the site for diverse genomic events such as DNA replication and transcription, senses and responds to mechanical force that cell are exposed to. Its malfunction is linked to tumorigenesis and apoptosis; however, the underlying mechanisms remain largely unknown. We will use quantitative force measurement, high-resolution imaging, and biochemical perturbation to examine the mechanical response of the cell nucleus and its relationship to nuclear architecture and function. By establishing the physical and molecular basis of nuclear mechanics and mechano-chemistry, our study will help develop novel strategies to control cell fate and cure related diseases.

Started in 2015

PRIME

Non-invasive force measurement using fluctuation for organelle transport in neurons (*)

HAYASHI Kumiko

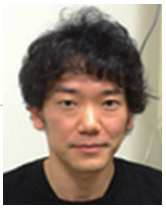
Associate Professor, Graduate School of Engineering, Tohoku University

Organelles are transported by motor proteins, as if cargos are carried by couriers. Because of this transport, substances necessary for life activity spread everywhere in a cell. We develop a non-invasive force measurement method using fluctuation in the motion of an organelle observed by fluorescence microscopy. Using the method, we investigate the role of motor proteins on axonal transport and neuronal diseases caused by the deficit of the transport.

Started in 2015

PRIME

Elucidation of plasma membrane tension dependent signal transduction in cancer cell invasion and metastasis (*)



TSUJITA Kazuya

Lecturer, Biosignal Research Center, Kobe University

Recent advanced biophysical techniques have found that while tumors are stiffer than normal tissue, malignant cells themselves are much softer than their normal counterparts. However, molecular mechanisms by which cell stiffness controls cancer cell invasion and metastasis are largely unclear. In this project, I focus on the mechanical tension of the plasma membrane (PM) and membrane-bending BAR proteins, and attempt to reveal how PM tension dependent signaling pathways govern cancer cell invasion and metastasis. I also explore whether breast cancer metastasis could be prevented by the manipulation of PM tension or by genetic targeting of membrane-bending proteins.

Started in 2015

PRIME

Elucidating the mechanisms of mechanotransduction in angiogenesis (*)

FUKUHARA Shigetomo

Professor, Dept. of Mol. Pathophysiol., Inst. of Adv. Med. Sci., Nippon Medical School

Angiogenesis, the growth of new blood vessels from pre-existing vessels, plays an important role not only in regulating physiological functions but also in development and progression of various diseases. In this research project, we try to elucidate the mechanisms of mechanotransduction in angiogenesis to develop effective vascular regeneration therapy for ischemic diseases and novel treatment of pathological angiogenesis-related diseases. To this end, we investigate the following two issues by performing fluorescence-based bioimaging using zebrafish as a model animal; (1) the molecular mechanisms by which mechanotransduction mediated by cell adhesion apparatus regulates endothelial cell dynamics during angiogenesis and (2) the regulatory mechanisms of angiogenesis by mechanical stresses such as shear stress and intravascular pressure.

Started in 2015

PRIME

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

This study aims to develop a novel in vitro platform to simulate hematopoietic function by recapitulating physiological microenvironment using microengineering techniques. We reconstitute embryonic endothelium to generate hematopoietic stem cells (HSCs) from induced pluripotent stem (iPS) cells by recapitulating the mechanical microenvironment. Since HSCs arise at arterial sites of the embryonic vasculature after the initiation of heartbeat, mechanical forces based on heartbeat are linked to hematopoietic development. By controlling mechanical microenvironment, we try to understand mechanobiology of hematopoietic development and blood physiology. Our goal is to model hematopoietic function in vitro using the biomimetic microdevices with iPS-derived cells.

Started in 2015

PRIME

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

Heart is a unique organ which is under the control mechanical stress for 24 hours per day and 7 days per week. Therefore, in the heart sensing system against mechanical stimuli, mechano-sensor, is extremely important. We recently found that pannexin, a family of gap-junction channel, is one of the mechano-sensor in the heart. In response not only to mechanical stress but also to ischemic stress activates pannexin and induces the release of ATP. ATP-release provides the protection against mechanical and ischemic stresses. Our aims are to clarify the underlying mechanism of pannexin-mediated protection, and to search low-molecular chemicals activating pannexin.

Started in 2015

PRIME

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 (*)

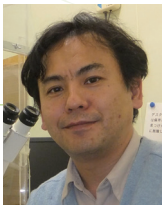
MIYOSHI Hiromi
Associate Professor, Faculty of System Design, Tokyo Metropolitan University

Although all cells in a multicellular organism contain the same genome in DNA, they look different and perform different functions. The difference is caused by the difference in gene expression pattern occurring during differentiation. This study aims to clarify the mechanism how mechanical and structural properties of the microenvironment where the cells reside affect the intracellular mechanical forces transmitted to DNA, and further modulate cell fate determination and differentiation. The finding will be a basis to develop tissue engineering that creates various tissues and organs by utilizing mechanical and structural cues provided by the artificial microenvironments.

Started in 2016

PRIME

Identification and functional analysis of mechanosensor proteins involoved in actin cytoskeleton remodeling (*)



OHASHI Kazumasa
Professor, Graduate School of Life Sciences, Tohoku University

The cells constituting our bodies sense and respond to various mechanical forces. The mechanoresponses are crucial for many important physiological processes including the maintenance of homeostasis in body and morphogenesis in development. In this study, we focus on cytoskeletal reorganization in response to mechanical stimuli, and search for mechanosensory proteins and investigate the molecular mechanisms of sensing of mechanical stresses and the intracellular processes of mechanotranduction. The findings of our research will contribute to elucidate the pathogenic mechanisms of cardiovascular diseases and cancers caused by abnormalities in these molecular mechanisms.

Started in 2015

PRIME

Study on the autonomous regulation of ciliary motility through mechanical feedback system (*)

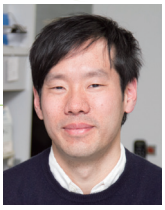
YOSHIMURA Kenjiro
Professor,
Shibaura Institute of Technology

The motility of cilia and flagella including transport of body fluid, mucous, and signaling molecules has an essential role in the maintenance of life. This project aims at unveiling the mechanical feedback system in cilia and flagella such as an increase or reversal in the motility upon rise in mechanical load. The obtained outcome would help to unravel ciliopathy and to develop drugs acting on the factors regulating the motility of cilia and flagella.

Started in 2016

PRIME

Molecular mechanisms of mechano-feedback from epithelial architecture in organogenesis (*)



KONDO Takefumi
Program-Specific Assistant Professor,
Graduate school of Biostudies, yoto University

In morphogenesis, each organ in our bodies acquires appropriate shape and composition of cell types to function properly. In this project, by using Drosophila genetics and imaging techniques, I am trying to uncover molecular and cellular mechanisms that ensure the robustness of organogenesis. Especially, I am focusing on mechano-sensing mechanisms by which cells adjust their gene expression to the change of epithelial tissue architecture during epithelial morphogenesis. In the end, I aim at uncovering the novel mechano-feedback system to harmonize tissue architecture with cell differentiation precisely at molecular levels.

Started in 2016

PRIME

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)

In this project, I'm aiming to reveal cellular memory phenomena in response to environmental mechanostructural factors, such as topography and elasticity of substrates, and its mechanism. Specifically, I will develop a dynamic cell culture platform enabling spatiotemporal control of substrate topography and elasticity in order to investigate the effect of the culture history of an extracellular mechanostructural environment on stem cell behaviors. Understanding the spatiotemporal role of mechanostructural information of cellular surrounding through this project leads to further an emergence of dynamic mechanobiology research.

Started in 2016

PRIME

Single molecule imaging; on the mechanism behind the tension sensing by actin filaments (*)

TATSUMI Hitoshi
Professor
Kanazawa Institute of Technology

Intracellular and extracellular mechanical forces affect the dynamics of actin cytoskeleton, however, the underlying biophysical mechanisms how forces are transduced into changes in the actin dynamics remain largely unknown. We propose a new hypothesis that actin filaments work as a tension sensor and will explore the mechanism behind the tension sensing.

Started in 2016

PRIME

Elucidation of mechanobiology of renal glomerular podocytes and development of innovative evaluation method of intraglomerular pressure (*)

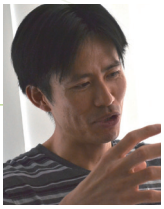
NAGASE Miki
Professor, Department of Anatomy, Kyorin University Faculty of Medicine

The renal glomerular podocytes line the outer aspect of the glomerular capillary tufts, and are involved in the production of primary urine. Podocytes have numerous cellular processes, undergo dynamic morphological and functional changes, and are impaired by excessive mechanical stress in diabetes and hypertension, causing proteinuria and glomerulosclerosis. In this project, we aim to investigate the molecular mechanisms of mechanosensing, mechanotransduction, and mechanoresponse in podocytes, focusing on Rho family small GTPases and actin cytoskeleton in in vitro and in vivo systems. We also aim to develop innovative evaluation method of intraglomerular pressure by searching for markers reflecting glomerular pressure.

Started in 2016

PRIME

Elucidating the mechanism of cellular force-sensing and -generating systems by using live-cell, low invasive imaging technique (*)



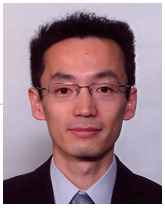
YOSHIMURA Shige H.
Associate Professor, Division of Integrated Life Science, Graduate School of Biostudies, Kyoto University

Cell contains a number of force-sensing, -generating, and -regulating molecules, which play critical roles in various cellular processes and homeostasis. In this project, we utilize low-invasive live-cell imaging technique which is based on high-speed atomic force microscopy, to visualize the dynamics of such force-related molecules in a living cell. Obtained images will be subjected to the image analysis to quantify and characterize the working force. Based on these information, we will try to elucidate the molecular mechanism of the entire force-maintenance system working in a cell.

Started in 2016

PRIME

The role of phospholipid flippase-mediated mechanosensing machinery in myotube formation (*)



HARA Yuji
Associate Professor, Graduate School of Engineering, Kyoto University

Myoblast fusion and subsequent elongation of multinucleated syncytia are fundamental steps to generate myotubes, the precursor of muscle fibers. Membrane tension is known to be crucial for myogenesis, but the underlying mechanisms remain to be elucidated. The aim of this project is to investigate the role of phospholipids, the components of lipid bilayers, in myotube formation. Especially, we are interested in the functional interplay between membrane-resident mechanosensing machineries and phospholipid flippases that catalyze translocation of phospholipids from the outer to the inner leaflets of the membrane. Our project may provide insights into therapeutic strategies for muscle disease.

Started in 2017

PRIME

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

I recently developed unique nano-bio device called “Nanospring” using DNA nanotechnology. This is a protein-sized coil-shape nanostructure with high brightness, high-resolution force sensing and tunable spring constant. Here, I aim at incorporating optimized nanospring into cardiomyocyte and observing the extension and retraction using super resolution imaging techniques to measure force in cells. Further, I’ll optically control nanospring and perturb the force-field. This experiment enables us to obtain data regarding not only force-field by cells but mechanical properties like force-velocity, power etc. at various points in a single cell. Our results will be useful for understanding a mechanism of heart disease like hypertrophic cardiomyopathy.

Started in 2016

PRIME

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

Osmolality and Na^+ level in body fluids are maintained within a specific physiological range. Dehydration causes an increase in body-fluid osmolality and Na^+ level, which is detected by some brain sensor molecules, leading to the generation of thirst and suppression of salt-appetite. Information about the Na^+ level in body fluids is also used by the body for blood pressure control. The purpose of this research project will be identify the molecular entity of the brain sensors involved in body-fluid homeostasis and blood-pressure control and to reveal the mechanism and physiology of the regulatory mechanism based on the information from the brain sensors.

Started in 2017

PRIME

Mechanobiology of stem cell tissues under adhesion-modulated microenvironment (*)

OKEYO Kennedy Omondi
Senior Lecturer, Institute for Frontier Life and Medical Sciences, Kyoto University

This research aims to employ a novel micromesh culture technique to realize an adhesion-modulated microenvironment in order to investigate how the balance between cell-cell adhesion and cell-substrate adhesion influences self-assembly mediated stem cell tissue formation and differentiation. The ultimate goal is to elucidate the mechanobiology of self-organization of stems cells for application to engineering functionally relevant biostructures such as organoids with potential application to drug screening, disease modeling and basic biological studies.

Started in 2017

PRIME

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

Temperature is an important mechanical stimulus that directly affects various biochemical reactions in animal. Variety of temperature sensor proteins such as TRP channel and heat shock protein are previously determined, however, unidentified temperature sensing mechanisms are thought to be remaining. In this study, we are planning to isolate novel temperature sensor proteins, by using original in vivo high throughput experimental system with nematode C. elegans. In addition, we are planning to manipulate a cell activity by using their novel temperature sensor proteins, after isolation of novel temperature receptor proteins.

Started in 2017

PRIME

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

We have reported that heat stress improves mitochondrial function in skeletal muscle. Mitochondrial dysfunction with age in skeletal muscle leads to sarcopenia, which causes systemic age-associated diseases. Hence, improving mitochondrial homeostasis in skeletal muscle by heat therapy can contribute to the extension of health span. Unfortunately, even if heat therapy was given to aged mice, the magnitude of mitochondrial adaptabilities was approximately 50% or less as compared with young mice. To establish an innovative heat therapy to extend health span in the elderly, the proposer will elucidate molecular mechanisms by which heat stress-induced mitochondrial adaptabilities are impaired by aging, and identify nutrients/drugs to rescue mitochondrial adaptabilities.

Started in 2017

PRIME

Quantification of stress/deformation/ signal fields and data assimilation to understand and predict mechanics of a growing epithelial tissue (*)

SUGIMURA Kaoru
Associate Professor, Institute for Integrated Cell-Material Sciences (WPI-iCeMS), Institute for Advanced Society, Kyoto University

How do cells push and pull each other to trigger precisely the deformations of a tissue when shaping the body? The answer to this fundamental question is crucial for understanding the development of animal forms including our body.
Over the next 3 years, we propose to extend our earlier research work and elucidate how tissue mechanics and biochemical signaling are orchestrated to control epithelial tissue morphogenesis. Specifically, by combining fly genetics, live imaging, quantitative data analysis, physical modeling, and data assimilation, we aim at understanding the emergence of different tissue shapes regulated by the multi-scale feedback mechanism.

Started in 2017

PRIME

The function and regulation of mechanosensors in skin metabolism (*)

TOYOSHIMA Fumiko
Professor, Institute for Frontier Life and Medical Science, Kyoto University

Skin is a barrier of the body that faces exogenous and endogenous mechanical stimuli. To accommodate mechanical stresses in homeostasis, the skin maintains a high metabolic rate by providing continually the tissues with fresh cells through proliferation and differentiation of epidermal stem cells. In this project, we elucidate the molecular mechanisms that link the mechanical stimuli and epidermal stem cell proliferation especially focusing on the function of mechanosensors. We aim to understand the pathogenesis of chronic skin diseases, such as diabetes-associated skin complaint, which are often developed on a pressure-facing body surface area.

Started in 2017

PRIME

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

Elucidation of an invasion process of glioma, which is a brain tumor, is an urgent issue for the treatment of glioma. In this project, we recapitulate tumor microenvironments using a microfluidic device, and investigate an invasion mechanism of glioma stem cells (GSCs), which respond to the application of interstitial flow. In particular, we focus on the mechanism how GSCs respond to the flow and recognize surrounding environments, which may contribute to the development of a future therapeutic strategy as well as diagnostic devices.

Started in 2017

PRIME

Functional analysis of a transcriptional co-activator that senses mechanical stimulation and promotes tissue fibrosis for developing a new fibrotic treatment method (*)

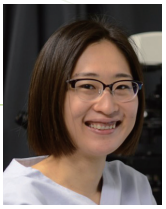
NAKAYA Michio
Associate Professor, Graduate School of Pharmaceutical Sciences, Kyushu University

When extracellular matrix (ECM) proteins such as collagen are upregulated, various tissues harden and undergo function decrements. This condition is called fibrosis and results from myofibroblasts, which produce ECM proteins such as collagen. I found a transcriptional co-activator that expresses in myofibroblasts, and promotes tissue fibrosis by sensing mechanical stimulation from ECM components. Therefore, in this study, I aim to clarify the mechanism underlying the promotion of tissue fibrosis by the transcriptional co-activator. Simultaneously, I also aim to establish a foundation for a novel method to treat fibrosis by targeting the pathway by which the transcriptional co-activator promotes fibrosis.

Started in 2017

PRIME

Elucidation of the role of mechanosensation for proper circulation of lymph (*)



NONOMURA Keiko

Assistant Professor, Division of Embryology, National Institute Basic Biology

The lymphatic vasculature is essential for the maintenance of fluid homeostasis, dissemination of immune cells, and lipid reabsorption. Compared to other parts of cardiovascular system, such as the heart and the blood vasculature, physiological importance of mechanosensation in the lymphatic vasculature is poorly understood. It is recently suggested by studies of human patients with familial lymphedema that mechanoactivated channel Piezo1 is required for proper circulation of lymph. In this research, I aim to elucidate physiological role of Piezo1-mediated mechanosensation in the lymphatic system.

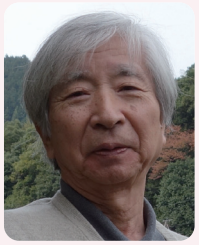
(*) indicates completed R&D projects.

Lipid Molecules

Lipid Molecules Studies on Specific Activities and Functions of Lipid Molecules to Develop Innovative Medical Technologies

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

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.

AMED-CREST
AMED-PRIME

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
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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

Started in 2015

Development of MULTUM-PALM and its application to cell membrane biology (*)

UEDA Masahiro

Professor, Graduate School of Frontier Biosciences, Osaka University

In this research project, we aim to reveal how membrane proteins and lipids interact in order to emerge signaling functions on plasma membrane. We attempt to develop a new correlative microscope (MULTUM-PALM) by which membrane proteins can be observed at single-molecule level with super resolution (PALM) and lipid molecules can be observed with mass spectroscopy (MULTUM). We will apply this MULTUM-PALM to various membrane proteins including GPCRs and components of phosphatidylinositol lipids signaling pathway on plasma membrane. Through the development of both statistical analysis methods for characterizing lipid/protein distributions and their mathematical modeling, we will try to reconstruct spatiotemporal dynamics of lipid/protein interactions in silico.

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

This project aims to create a novel technology “Optolipidomics” to identify, control and observe functional lipids using light; By improvement of the mass microscope in mass resolution and sensitivity, we will try to identify important lipids in human diseases using imaging mass spectrometry. Additionally, we will develop the optically controllable modules and florescent probes to regulate the candidate lipids spatiotemporally and to observe the results of control, respectively. This seamless system to study the functional lipids will be a basis of the lipidome editing technology, leading to a new concept of drug discovery by targeting lipids in the future.

Started in 2015

Elucidation of molecular mechanism of body surface barrier formation by lipids (*)

KIHARA Akio

Professor, Faculty of Pharmaceutical Sciences, Hokkaido University

Lipids form a barrier in the body surface (epidermis and eyes) and prevent invasion of pathogens and allergens. Barrier abnormality causes various cutaneous disorders (ichthyosis, atopic dermatitis etc.) and eye diseases (dry eye etc.). However, molecular mechanisms producing the barrier lipids are still largely unknown. In this research, we aim to elucidate these problems and create a foundation for drug discovery that enables cause treatment for the skin and eye diseases.

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

Although infectious diseases represent a major threat to humans, the repertoire of anti-viral therapeutic drugs available currently remains very limited. Recent studies, including our own, demonstrated that various intracellular pathogens hijack the lipid transport proteins (LTPs) of host cells in order to use host lipids for their own proliferation. Thus, in this research and development project, we aim to elucidate the molecular mechanisms by which a pathogen utilizes the lipids of host cells for its own proliferation, and to develop an inhibitor of this lipid-utilizing process.

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

In mammalian cells, fatty acid elongases and desaturases play critical roles in regulating the length and degree of unsaturation of fatty acids and thereby their functions and metabolic fates. We have shown that not only the quantity but also the quality of lipid is important for our health. Our goal is to elucidate the molecular mechanism of diseases such as metabolic syndrome and cancer and develop new strategies for the diagnosis and treatment of these diseases by focusing on the chain-length of fatty acids as a novel qualitative aspect of lipid.

Started in 2016

Understanding disease mechanisms based on glucosylated lipid functions

KAMIGUCHI Hiroyuki

Deputy Director, RIKEN Center for Brain Science

Novel glucosylated lipids present in small amounts in the human body have been discovered as intercellular signal messengers that regulate the formation of neural networks. It has also been suggested that glucosylated lipid signaling mediated by G protein-coupled receptor participates in pathological states not only of the nervous system but also of the blood and metabolic systems. In this project, we will elucidate structure-function relationship and disease-associated mechanisms of glucosylated lipids, with the aim of establishing new strategies for the development of disease biomarkers and therapeutics.

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

We have recently succeeded in developing antibodies against native GPCRs using this technology in combination with our improved immunization and screening methods. In this project, we have been trying to develop innovative technologies using a successful example of prostaglandin E2 receptor (one of the GPCRs) with an inhibitory antibody structure. To avoid several adverse effects of current therapeutics, it is essential to understand the molecular mechanism of GPCR signal transduction to selectively regulate GPCR signaling via functional antibodies, which are developed by our methods, and/or the designed small organic molecules depending on the GPCR structures.

Started in 2016

Development of novel anti-infective drugs targeting lipid metabolism

YAMASAKI Sho

Professor, Research Institute for Microbial Diseases, Osaka University

Infectious diseases are one of the leading causes of death. Successful control of global infectious diseases is therefore a common and critical issue worldwide. Immune receptors can recognize pathogens via their characteristic lipids to trigger host defense responses. However, some pathogens degrade/modify these lipids to evade host immune responses. In this project, we aim to identify novel immunostimulatory lipids and their metabolic pathways in pathogens, which will lead to the development of novel anti-infective drugs that confer 'immunological susceptibility' on pathogens by preventing their immune-evading strategies.

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

Metabolic disorder of cholesterol, a fundamental structural component of biological membranes, causes the onset of various diseases. Although the most potent regulatory factor of sterol metabolism is oxysterols, their synthetic mode, intracellular distribution, and function of their mediator molecules remain relatively unknown. In this study, we aim at analyzing the multi-layer regulatory system controlled by oxysterols and making a proposal for next-generation drug discovery together with elucidation of molecular disease mechanisms.

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)

Cellular membranes contain several classes of glycero- phospholipids, which have functional roles in cells. Glycerophospholipids contain two fatty acids and one polar head group, and the compositions vary across cell and tissue types. Little is known about how the phospholipid compositions impact their cellular functions; therefore, we utilize lysophospholipid acyltransferase knock-out mice to control membrane phospholipid compositions and uncover novel lipid functions. Additionally, we will observe phospholipids spatiotemporally at the subcellular level to gain new understanding about physiological roles of phospholipids. This project will contribute to finding novel lipid functions and establishing novel therapeutic strategies.

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

Sphingosine 1-phosphate (S1P) is an intercellular signaling molecule that is produced inside the cells by phosphorylation of sphingosine and is exported outside the cells by its specific transporters.
In this experiment, we are trying to understand the pharmacokinetics of S1P comprehensively through identifying all S1P transporters in mammalians and to clarify the role of the S1P transporters in various diseases. Based on these findings we will establish a strategy to develop a novel transporter oriented drugs.

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

Stress due to social environments and lifestyle habits can promote the onset and pathophysiology of various mental and physical illnesses. Recent studies have suggested that the regulation of inflammation by multiple bioactive lipids is involved in stress-induced changes in mental and physical functions. In this research, we will identify bioactive lipids underlying stress-related dysfunctions and elucidate their roles, regulations and actions, and will develop tools for measuring and visualizing these bioactive lipids. Through this strategy, we aim to develop novel technology platforms targeting bioactive lipids for preventing and curing stress-related dysfunctions.

Started in 2017

AMED-CREST

Elucidation of disease mechanism and study of drug discovery targeted for oxidized lipids

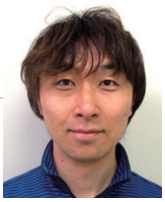
YAMADA Kenichi
Professor, Faculty of Pharmaceutical Sciences, Kyushu University

Lipids are easily oxidized by reactive oxygen species (ROS), resulting in lipid peroxidation and metabolic products such as lipid-derived electrophiles. Lipid peroxidation products and lipid-derived electrophiles have been reported to bind to protein or DNA and induce inflammation and apoptosis. However, such oxidized lipids have high reactivity, appropriate detection technologies is limited. Here, in this study, we aim to develop the detection technique, elucidate disease mechanism, and study drug discovery targeted for oxidized lipids

Started in 2015

PRIME

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

Dendritic spines in neurons play important roles in synapse plasticity underling learning and memory. Mental diseases such as Autism Spectrum Disorder, Fragile X syndrome, and Cowden syndrome often exhibit abnormal spine morphology. My previous study shows that a functional lipid, phosphatidylinositol 3,4,5-trisphosphate (PIP3) regulates spine morphology. Therefore, I would like to reveal that PIP3 can be a key target for drug development for the mental diseases using a brand new technology, lipid optogenetics.

Started in 2015

PRIME

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)

Lipid metabolites consist of a wide variety of hydrophobic molecular species. Some of them are metabolized by intestinal bacteria, and function to regulate host immune response and intestinal homeostasis. Mass spectrometry-based metabolomics is an effective method to grasp metabolic interplay between intestinal bacteria and host metabolism. However, it remains insufficient to measure these metabolites comprehensively because conventional analytical methods are focused on the host metabolites with a limited search range.
In this study, we designed a new non-targeted lipidomics, namely milieu-lipidomics, to search lipid metabolites derived from the symbiotic relationship using LC/Q-TOF MS and in-house lipid screening software “Lipidiscovery”. Our advanced lipidomics platform has a strong potential that help to understand the interplay between intestinal bacteria and host metabolism unbiasedly. Also this system could lead to the identification of bioactive metabolites that control intestinal tissue homeostasis.

Started in 2015

PRIME

The role of lipid in the exosome derived from the inflammatory cancer (*)

KOTANI Ai
Professor, Institute of Medical Science, Tokai University

Exosome is a kind of vesicles which work as intercellular communicator. It has been recently reported that several lipids are enriched in exosome. Exosome contains nucleic acid whose functions we found to be enhanced in the macrophages specifically taking it in the EBV related lymphoma. Accordingly we hypothesized that lipids amplify the function of nucleic acid in the exosome. We will test the hypothesis and try to find the novel lipid therapeutic target for the EBV related lymphoma.

Started in 2015

PRIME

Elucidation of roles of lipids in the epithelial-mesenchymal transition (*)

IKENOUCHI Junichi
Professor, Faculty of Sciences, Kyushu University

Epithelial cells adhere between adjacent cells and form a cell sheet that covers the surface of organs such as the digestive tract. Epithelial cells play an essential role in maintaining life, such as absorption of nutrients from the outside world. On the other hand, epithelial cells lose adhesion and convert to mesenchymal cells in pathological conditions such as invasive cancer and fibrosis. I aim to develop innovative medicines by clarifying the roles of lipids in the pathological conditions associated with the epithelial-mesenchymal transition.

Started in 2015

PRIME

Development of basic technologies for medical application based on oxidized phospholipid-derived bioactive fatty acids (*)

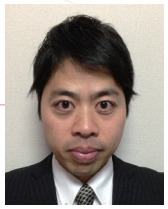
KONO Nozomu
Associate Professor, Graduate School of Pharmaceutical Sciences, The University of Tokyo

Membrane phospholipids abundantly contain polyunsaturated fatty acids such as arachidonic acid and docosahexaenoic acid. These polyunsaturated fatty acyl chains in membrane phospholipids are easily oxidized to form oxidized phospholipids. Although oxidized phospholipids have been suggested to be associated with various pathological conditions, its molecular mechanisms remain to be clarified. The aim of this project is to elucidate the mechanism of production and action of oxidized phospholipid-derived bioactive fatty acids and the role of the bioactive fatty acids in metabolic diseases.

Started in 2015

PRIME

Mechanisms of lipid dynamics on plasma membranes and their application (*)



SUZUKI Jun
Professor, Institute for Integrated Cell-Material Sciences (iCeMS), Kyoto University

Phospholipids on plasma membranes are asymmetrically distributed. Among the lipids, Phosphatidylserine (PS) is maintained to the inner side of the membranes. However, this asymmetry is collapsed by the action of scramblases and exposed PS functions as a signaling molecule. In this study, I will investigate how scramblases are activated and how they function in vivo.

Started in 2015

PRIME

Palmitoylation-dependent regulations of membrane receptors in synapses (*)

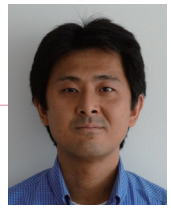
HAYASHI Takashi
Section Chief, National Institute of Neuroscience, National Center of Neurology and Psychiatry (NCNP)

Glutamate is the major excitatory neurotransmitter in the vertebrate central nervous system. Our projects focus on palmitoylation-dependent regulation of ionotropic glutamate receptors (iGluRs) on the synaptic membrane. Post-translational protein palmitoylation is the reversible addition of the lipid palmitate to intracellular cysteine residues that can direct many channels and receptors to specific regions of the cell membrane. We will reveal the molecular and cellular mechanisms in impaired behavior including mental disorder-like symptoms, using iGluR palmitoylation-deficient mice, which our group has already generated. Furthermore, we attempt to develop a novel imaging method to detect single membrane receptor movement with a TIRF microscopy, especially in synapses of cultured cortical neurons.

Started in 2015

PRIME

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

We identified a novel metabolic system orchestrated by a metabolite sensor. The system governs global metabolism including lipid, glucose and inflammation by sensing multiple metabolic intermediates and could play a critical role in the pathogenesis of metabolic diseases. The sensor molecule accommodates metabolic intermediates in its pocket which can be targeted by small molecules. We will unravel molecular basis of the system toward development of novel therapeutics.

Started in 2015

PRIME

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

Recurrent implantation failure is one of the major clinical issues in the field of reproductive medicine. Previous studies indicate that the enzymes associated with polyunsaturated fatty acid metabolism have key roles in embryo implantation, but it remains unclear which lipid metabolites are critical for this event. The aim of this project is to elucidate the mechanism of embryo implantation and the pathogenesis of recurrent implantation failure by using lipidomics analysis and mice lacking enzymes involved in polyunsaturated fatty acid metabolism. The ultimate goal of the project is to discover novel therapeutic approach to recurrent implantation failure by focusing on lipid metabolites and their metabolizing enzymes.

Started in 2015

PRIME

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

It has been difficult to determine individual lipid species in live tissues or iPS cells derived from patients, because the conventional lipid labeling techniques usually disrupted the physiological condition and it could not keep spatial distributions of lipids in tissues untouched. In this study, we measure intrinsic molecular vibrations in order to identify lipid species. Vibrational spectroscopy provides vibrational information characteristic of chemical groups in a molecule without any labeling procedures. Using this technique, we develop a new vibrational microspectroscopy which locates and quantitates specific lipid species in molecular specific manner. In addition, we aim to propose an application strategy which benefits researchers working on diagnosis and treatment of lipid metabolism disorders.

Started in 2015

PRIME

Physiological and pathological roles of cholesterol in primary cilia (*)

MIYAMOTO Tatsuo
Associate Professor, Research Institute for Radiation Biology and Medicine, Hiroshima University

The primary cilium formed on the surface of quiescent human cells functions as a sensor for receiving the extracellular signals. Ciliary dysfunction is causally linked to the group of human hereditary disorders and cancers.
The goals of this study are to elucidate the physiological roles of cholesterol in the ciliary membrane, and to establish the pathological concept of cilia-related diseases from the aspect of impaired cholesterol metabolism. This study also attempts to create the pharmaceutical seeds of ciliary cholesterol regulation.

Started in 2015

PRIME

Functional elucidation of bioactive alkenyl-type lysophospholipids (*)

YAMAMOTO Kei
Associate Professor, Graduate School of Technology, Industrial and Social Science, Tokushima University

Recently, lipid metabolomics analyses using mice gene-manipulated for lipid metabolism-related enzymes have revealed that they display diverse functions by driving unique diseases pathways. In this research, we elucidate the possible mechanism of metabolic and dynamic action of alkenyl-type lysophospholipids (P-LPEs) as a novel bioactive lipid for exacerbation of epidermal hyperplastic diseases. Based on the knowledge, this project is aiming to contribute to improvement of healthy longevity society through development of new biomarkers and drug discovery.

Started in 2016

PRIME

Functional analysis on cholesterol metabolizing enzyme that defines a novel T cell subset and the clinical application for disease control (*)

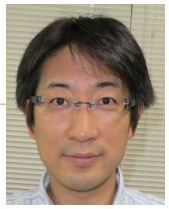
TAKAHASHI Hayato
Assistant Professor, Department of Dermatology, Keio University School of Medicine

$CD4^+$ T cell is a crucial immune cell that is involved in various infections and allergic diseases. The aim of this project is to identify the T cell with new functions. We assumed that the T cells might be armed with a sort of cholesterol metabolizing enzyme based on our data. That nature has not been seen in the known helper T cell subsets. The metabolite produced by the enzyme is estimated to regulate immune reaction. Intensive investigation on the mechanism of the metabolite action would be helpful to develop new therapeutic strategies and drugs in the future.

Started in 2016

PRIME

Understanding lipid-related orphan G protein-coupled receptors using activating GPCR mutations (*)



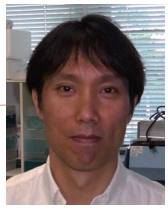
INOUE Asuka
Associate Professor, Graduate School of Pharmaceutical Sciences, Tohoku University

G protein-coupled receptors (GPCRs) represent the most promising targets for drug development. Currently, there are approximately 20 orphan (ligand-unknown) GPCRs that are phylogenetically located near lipid-recognizing receptors. In general, orphan GPCRs are poorly characterized and thus excluded from drug development because of lack of pharmacological methods to activate these receptors. In this project, the PI will develop a strategy to analyze orphan GPCRs by introducing an activating amino acid mutation. Expression of such an activating GPCR is expected to mimic ligand-induced activation of the native GPCR. The project will enable a genetic approach to induce orphan GPCR signaling and possibly expand orphan GPCR as next-generation drug targets.

Started in 2016

PRIME

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

Lipids exert their function properly only when transported correctly in cells. A variety of human diseases involve malfunction of cellular lipid transport systems, whose underlying mechanisms are still largely unknown. Our study is focused on to clarify how cellular lipids are specifically recognized and exchanged at a region (termed “membrane contact sites”) where two cellular membranes come close each other. Understanding the regulation and dysregulation of the lipid countertransport systems will help developing new strategies to treat and prevent human diseases.

Started in 2016

PRIME

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

Pulmonary artery hypertension (PAH) characterized by stenosis of pulmonary blood vessels and right heart failure is one of the intractable diseases whose pathology and pathogenic mechanisms are still unclear. Bioactive lipids that control cardiovascular function positively or negatively in vivo are drawing attention as a therapeutic target for PAH. In this study, we aim to create new therapeutic strategies via appropriate quantitative and qualitative control of the lipids by clarifying the role of various functional lipids in PAH and changes in lipid metabolism in failure hearts.

Started in 2016

PRIME

Understanding pathogenic mechanisms of skin diseases by focusing on polyphosphoinositide metabolism (*)

NAKAMURA Yoshikazu
Associate Professor, Faculty of Science and Technology, Tokyo University of Science

Some inflammatory skin diseases, including atopic dermatitis and psoriasis have a significant negative impact on quality of life of patients by chronic itch and changes in skin appearance. The aim of this project is to contribute to understanding the mechanisms of pathogenesis and exacerbation of these inflammatory skin diseases through clarification of the relationship between inflammatory skin diseases and abnormal phospholipid metabolism.

Started in 2016

PRIME

Development of molecular tools for the clarification of metabolism and molecular interaction of glycolipids (*)

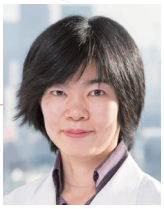
HIRAI Go
Professor, Graduate School of Pharmaceutical Science, Kyushu University

We aim to develop molecular tools contributing to functional analysis of glycolipids, which control several cellular events at plasma membrane and so on. Function of glycolipids is considered to differ by carbohydrate structures and length of lipid chains, and degradation of carbohydrate structure by glycohydrolases also causes change of glycolipids structure. We address the design and development of molecules capable of analyzing “binding partners” and “metabolism” of “particular glycolipids in interest”, based on the knowledge of organic chemistry and bioorganic chemistry.

Started in 2017

PRIME

Elucidation of the immune-metabolic-regeneration systems network linked by fatty acids (*)



OISHI Yumiko
Professor, Department of Biochemistry & Molecular Biology, Nippon Medical School

Obesity, physical inactivity, and aging are the leading causes of the noncommunicable diseases (NCDs), such as cardiovascular disease, diabetes and cancer. Recent studies indicate that chronic inflammation crucially underlies NCDs, alterations in systemic metabolism due to obesity also greatly contribute to the progression of NCDs, suggesting the link between chronic inflammation and metabolic dysfunction. Moreover, insufficient regeneration prolongs inflammation, further accelerating tissue remodeling. In this study, I will elucidate the immune-metabolic-regeneration systems network linked by unsaturated fatty acids and signal-epigenome regulatory pathways in the maintenance of tissue homeostasis and development of NCDs.

Started in 2016

PRIME

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

Vesicular nucleotide transporter (VNUT) is responsible for vesicular storage of ATP, and is essential for purinergic chemical transmission. Recently, we demonstrated that VNUT-mediated ATP transport is allosterically activated by Cl^-, and this activation is inhibited by lipid metabolites. Regulation of the metabolic anion switch improved the major factors of lifestyle-related disease without side effects. In this study, we aim to identify functional lipid metabolites to selectively inhibit VNUT, develop the preventive drug of lifestyle-related disease, and establish the molecular mechanism-based drug discovery platform.

Started in 2017

PRIME

Characterization of the early steps of high-density lipoprotein (HDL) formation (*)

KIMURA Yasuhisa
Assistant Professor, Graduate School of Agriculture, Kyoto University

High-density lipoprotein (HDL) is thought to play important roles in prevention of atherosclerosis by removing excess cholesterol from peripheral tissues and transporting it to the liver. It is widely accepted that HDL is formed by an ATP-dependent lipid transporter (ABCA1), however, the detailed mechanisms are still controversial. The aim of this research is a clarification of the early steps of ABCA1-mediated HDL formation in molecular level to provide the useful information for the development of novel antiatherogenic drugs.

Started in 2016

PRIME

Development of novel microsystems for highly sensitive analysis of lipid transport proteins (*)

WATANABE Rikiya
Chief Scientist, Molecular Physiology Laboratory, RIKEN

The asymmetric phospholipid distribution on biological-membrane is a key feature of living cells. The disruption of lipid asymmetry, involved in physiological processes, is mediated by phospholipid scramblases, promoting bidirectional lipid transport across membranes. In this study, we attempt to analyze at the single-molecule level the phospholipid transport of scramblases by developing a microsystem equipped with asymmetric lipid membrane arrays. The findings from single molecule analysis will provide a molecular insight into how scramblases transport phospholipids, and moreover a versatile strategy for single-molecule analysis of other phospholipid-transport proteins, e.g. flippase and floppase.

Started in 2017

PRIME

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

Recently, the number of stroke or dementia patients is increasing in Japan; however, the therapeutic agents which improve the neurological deficits of these patients has not been developed. We have clarified that retinoids enhance the expression of scavenger receptors in infiltrating microglia and macrophages after ischemic stroke, and this leads to the acceleration of the resolution of cerebral post-ischemic inflammation. Based on these findings, this research aims at developing novel therapeutic agents which improve the functional prognosis of stroke and dementia patients through the identification of specific lipids which regulate the inflammatory and repairing process after stroke.

Started in 2017

PRIME

Development and application of the phosphatidylinositol-specific nucleic acid drug (*)

SUIZU Futoshi
Associate Professor, Institute for Genetic Medicine, Hokkaido University

This project aims at the development of the simple chase technology as well as manipulating technology of cellular phosphoinositide that was relative difficulty until now. I am planning to isolate nucleic acid drugs harboring three character with a small, stable, and high cell membrane permeability, and finally apply to develop drugs for an early diagnosis or a novel treatment of diseases that phosphoinositide abnormality is concerned with, such as cancer or neurodegenerative diseases.

Started in 2017

PRIME

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

Phospholipids, sphingolipids and acylglycerols act as cell membrane components, energy sources and signaling molecules, and are associated with various diseases including coronary heart disease, neurodegenerative diseases and cancers. However, there are no sensitive and simple methods for measuring these lipids. In this study, by using specific enzymes and fluorescent compounds, I develop new simple assays for quantifying phospholipids, sphingolipids and acylglycerols and for evaluating asymmetrical distribution of membrane lipids. These enzymatic fluorometric assays will be helpful for understanding of the pathogenesis of various diseases and for early detection of diseases.

Started in 2017

PRIME

The molecular mechanism that regulates cellular signaling pathways through organelle-specific lipid domains (*)

TAGUCHI Tomohiko
Professor, Graduate School of Life Sciences, Tohoku University

Intracellular organelles of eukaryotic cells have distinct lipid compositions, however, its significance has not been well understood. In this study, by exploiting the proximity-dependent biotinylation method with phospholipid-specific probes in living cells, proteins that are in close proximity to specific phospholipids will be identified. I expect that, through this approach, the novel function of organelle membranes and phospholipids will be revealed. Diseases that are caused by dysregulated function of organelle membranes will also be identified.

Started in 2017

PRIME

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

Although there are many reports on the relationship between diets and infertility, detailed mechanisms of the diet-induced infertility remains largely unknown. In this research project, focusing on an interesting finding that female mice genetically deficient in an intestinal lipid transporter exhibit diet-induced infertility, we will identify dietary lipids causing female infertility and clarify their clinical relevance and molecular mechanisms of the lipids-induced reproductive dysfunction. The outcome of this research project will lead to the development of new therapeutic strategies, drugs, and biomarkers for female infertility.

Started in 2017

PRIME

Dissecting intracellular phospholipid traffic for understanding mitochondrial functional integrity (*)

TAMURA Yasushi
Professor, Faculty of Science, Yamagata University

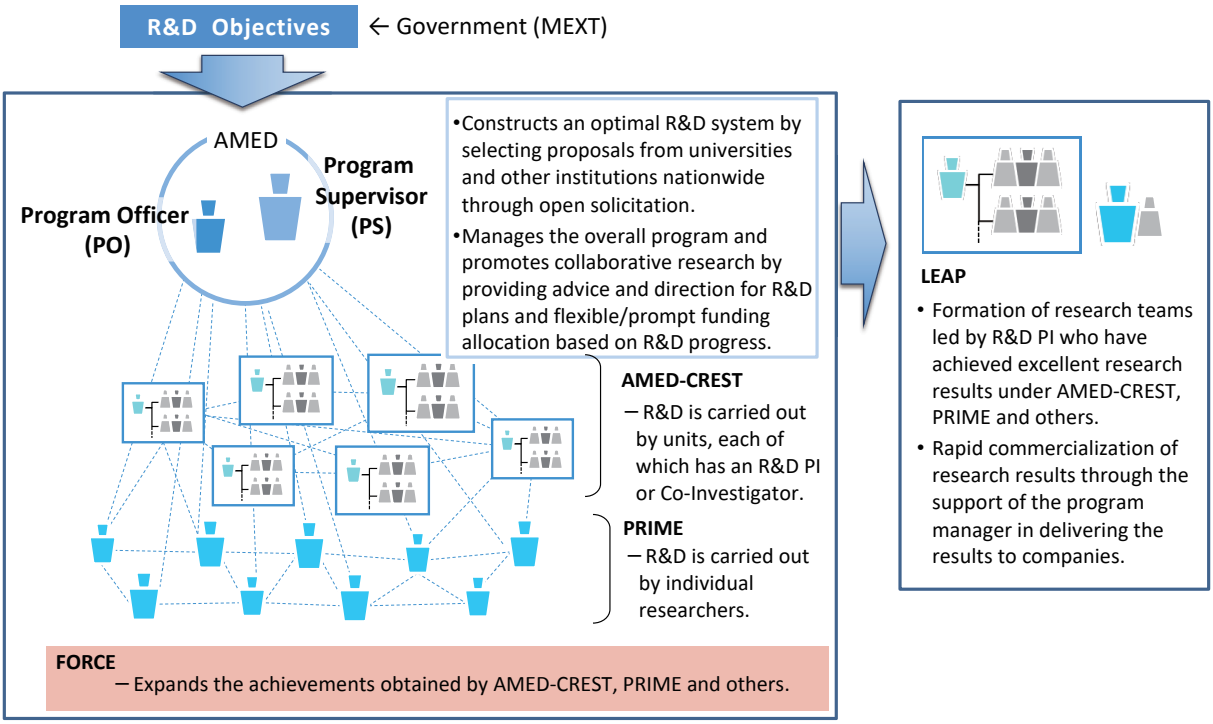
In order to understand functional integrity of mitochondria, it is essential to elucidate phospholipid traffic via mitochondria since phospholipids are major constituents of mitochondrial membranes. However, it is still largely unknown how phospholipids travel among cellular membranes. In addition, how cardiolipin, the mitochondria-specific phospholipid, is synthesized in mitochondria is still enigmatic. In this research, we will elucidate these mysteries and aim to develop innovative drugs to overcome diseases causing compromised phospholipid metabolism.

(*) indicates completed R&D projects.

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

FORCE Program Supervisor (PS)/Program Officer (PO)

PS

OHSHIMA Etsuo Senior Fellow, KYOWA HAKKO BIO Co., Ltd.

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, Institute of Development, Aging and Cancer, Tohoku University

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

Started in 2019

FORCE

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

In PRIME study, we investigated how lipid dynamics on plasma membranes were regulated at molecular level and what kind of phenotype was shown by knockout mice, defective in regulation of lipid dynamics. Based on the data obtained in these analysis, in this study, we are going to examined the correlation between mice analysis and human diseases.

Started in 2019

FORCE

Protein modification at excitatory synapses in brain diseases (*)

HAYASHI Takashi
Researcher, National Institute of Neuroscience, National Center of Neurology and Psychiatry (NCNP)

Post-translational protein S-palmitoylation is the covalent attachment of the lipid palmitate to proteins. Most excitatory synaptic transmission is mediated by glutamate receptors in the mammalian brain. As previously shown, deficiency of glutamate receptor–palmitoylation aggravates seizure susceptibility in mutant mice. In the FORCE project, we aim to confirm modifications of glutamatergic synapses in surgically resected specimens from epilepsy patients. Furthermore, we will establish an animal model for assessment of drugs for epileptic seizure and PTSD.

Started in 2019

FORCE

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

Chronic inflammation causes various diseases such as autoimmune diseases. RNA binding proteins including Regnase-1 and Roquin function as the brake of inflammation by degrading RNAs encoding inflammatory mediators. In this study, we aim to uncover relationship between RNA binding proteins and human chronic inflammatory diseases, as well as to develop novel strategies regulating immunity targeting these RNA binding proteins.

Started in 2019

FORCE

Exploration of disease-associated lipid maps by PLA2 metabolome and their human relevance (*)

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

In this study, we will use a series of PLA2-deficient mouse strains in combination with lipidomics to identify novel lipid-metabolic pathways related to diseases. We will perform a bench-to-clinic approach, in which human relevance of the particular PLA2-driven lipid pathways found to be associated with mouse disease models will be evaluated using clinical samples obtained from patients, and a clinic-to-bench approach, in which we will extract particular PLA2-lipid pathways that show correlation with human diseases from clinical specimens, evaluate the pathophysiological roles of these pathways using mouse models, and verify the validity as drug targets or biomarkers.

Started in 2019

FORCE

Development of cancer navigation strategy based on RNA pathophysiology in endocrine therapy-resistant breast cancer (*)

NAKAO Mitsuyoshi
Professor, Kumamoto University, Institute of Molecular Embryology and Genetics

About 70% of breast cancers are positive for hormone receptor (mainly estrogen receptor-α (ER)). Endocrine therapy effectively inhibits estrogen action that promotes tumor formation, but disease recurrence often occurs after acquiring resistance to treatment. This project aims to perform basic research and clinical application for endocrine therapy-resistant ER-positive breast cancer, through the development of a diagnostic way using RNA characteristics and a regulatory method based on cancer navigation strategy that combines endocrine therapy and other treatments including estrogen re-administration.

Started in 2020

FORCE

Elucidation of disease-specific microbiota and personalized medicine by metagenome-wide association studies

OKADA Yukinori
Professor, Osaka University Graduate School of Medicine

This project aims integration of microbiome omics data – metagenome, human genome, and metabolome – to elucidate disease biology and identify novel drug targets. In addition to construction of the population-specific database of metagenome, human genome, and metabolome, we will conduct the metagenome-wide association study (MWAS) for a variety of diseases, and identify microbiome features specific to the diseases. Considering technical and visionary advantage of our MWAS strategy, our group should achieve the proposed goals of elucidation of disease biology and microbiome-based personalized medicine.

Started in 2020

FORCE

Investigating the relationship between detrimental neutrophil activation and anti-tumor immunity by using lung cancer patient samples.

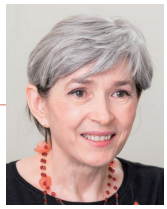
KUMANOGOH Atsushi
Professor, Department of Respiratory Medicine and Clinical Immunology, Osaka University Graduate School of Medicine

Semaphorins regulate the differentiation, metabolism, migration and stress response in immune cells. However, it is unknown how semaphorins in neutrophils modulate anti-tumor $CD8^+$ T cell response in lung cancer patients. In this study, we will investigate the role of semaphorins to regulate detrimental neutrophil activation, which contribute $CD8^+$ T cell suppression and reduce the sensitivity for anti-PD-1 immunotherapies, using lung cancer patient samples.

Started in 2020

FORCE

Psychiatric symptoms associated with autoimmune diseases: The metabolic link



FAGARASANSidonia
Team Leader, RIKEN Center for Integrative Medical Sciences

So far, the psychiatric symptoms associated with autoimmune diseases are thought to result from immune cell infiltrating the brain and their local production of proinflammatory cytokines or autoantibodies. In this project, we aim to clarify whether the autoimmune-related psychiatric symptoms are mechanistically caused by systemic metabolome shift associated with immune activation as previously discovered during the CREST project. In addition, we attempt to identify novel metabolites associated with psychiatric symptoms that have a potential to be therapeutic targets of the autoimmune diseases.

Started in 2020

FORCE

Identification of cell clusters exerting EP2/EP4-dependent immune-evasion in human tumors

NARUMIYA Shuh
Professor, Kyoto University Graduate School of Medicine

Tumor microenvironment (TME) is the site of chronic inflammation, where various types of cells and their products accumulate and active inflammation and immune evasion occur simultaneously. Prostaglandin (PG) has been suggested as one of the factors shaping TME. We have used several mouse tumor models and found that the PGE2-EP2 signaling and PGE2-EP4 signaling additively or synergistically facilitate inflammation and immune evasion in TME to promote tumor growth. In this study, we will identify cell clusters mediating EP2 and EP4-dependent immune evasion and inflammation amplification in human tumors by sorting of EP2 and EP4-epressing cells from human tumors and clarifying their gene expression signature by single cell RNA sequencing. By this achievement, we will be able to stratify patients for EP2 antagonists or EP4 antagonists and promote clinical application of these drugs.

Started in 2021

FORCE

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

We previously elucidated that "qualitative changes in cell membranes," such as changes in membrane lipid composition and association of the actin cortex, define the mode of invasion in malignant cancer cells. In this research project, we focus on kidney and prostate cancers, for which effective treatments are not well established. We will examine the qualitative changes in the cell membrane of malignant kidney and prostate cancers with the aim to develop new diagnostic tool and treatment method for these cancers.

Started in 2020

FORCE

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

Recurrent implantation failure (RIF) is one of major issues in reproductive medicine. In the treatment of in vitro fertilization and embryo transfer (IVF-ET), the patients with RIF are difficult to conceive even after the repeated transfer of good-quality embryos into the uterus. However, appropriate diagnostic methods of RIF remain to be established. In this project, we perform comprehensive lipidomic, transcriptome and genomic analyses using human endometrial tissues in the implantation period. We will elucidate fundamental mechanisms of RIF and contribute to the establishment of novel methods for the diagnosis and treatment of RIF.

Started in 2021

FORCE

Polyclonal metastasis mechanism of human colon cancer

OSHIMA Masanobu
Professor, Cancer Research Institute, Kanazawa University

A novel concept of polyclonal metastasis has been proposed, wherein tumor cell clusters break off from the primary site, and are disseminated and colonized in the distant organ, leading to development of metastatic tumors. We have examined polyclonal metastasis of intestinal tumors using mouse models, and found that non-metastatic tumor cells can form chimeric metastatic lesions when co-disseminated with metastatic cells. In this research project, we will establish metastatic human colon cancer-derived organoids and investigate how genetically and phenotypically heterogenous cells generate clusters and interact with surrounding cells to develop polyclonal metastatic foci in the liver.

Started in 2021

FORCE

Comprehensive evaluation of pseudo exonic splicing mutations for drug development

HAGIWARA Masatoshi
Professor, Department of Anatomy and Developmental Biology, Kyoto University

In this proposal, we will challenge elucidation of splicing code using artificial intelligence-driven novel strategy and conduct a genome-wide functional annotation for deep-intronic variant of unknown significance of more than 10,000 whole genome sequence data. Then, an in-house panel of splice-manipulating small molecule compounds are applied for validated pseudo exonic splicing regulations. Resulting compound response profiles with surrounding sequence information will be analyzed by deep-learning to establish prediction system to identify the best compound for each splicing mutation. We will construct an original data base to accumulate above data to realize precision medicine of genetic diseases.

Started in 2021

FORCE

Development of Treatment Targeting NFIA for Obesity in Humans

YAMAUCHI Toshimasa
Professor, Graduate School of Medicine, the University of Tokyo

Brown adipose tissue dissipates energy in the form of heat and can counteract the development of obesity. We previously conducted epigenomic analyses on brown adipose tissue and identified NFIA as a critical factor that regulates brown-adipocyte-specific gene transcription. In this project, we establish the role of NFIA in human adipocytes and adipose tissues to create base technology that will contribute to the development of novel strategy for the treatment of obesity.

Started in 2021

FORCE

Molecular Mechanism and Therapy in AHR and NRF2-mediated Atopic Dermatitis

YAMAMOTO Masayuki
Professor, Department of Medical Biochemistry, Graduate School of Medicine, Tohoku University

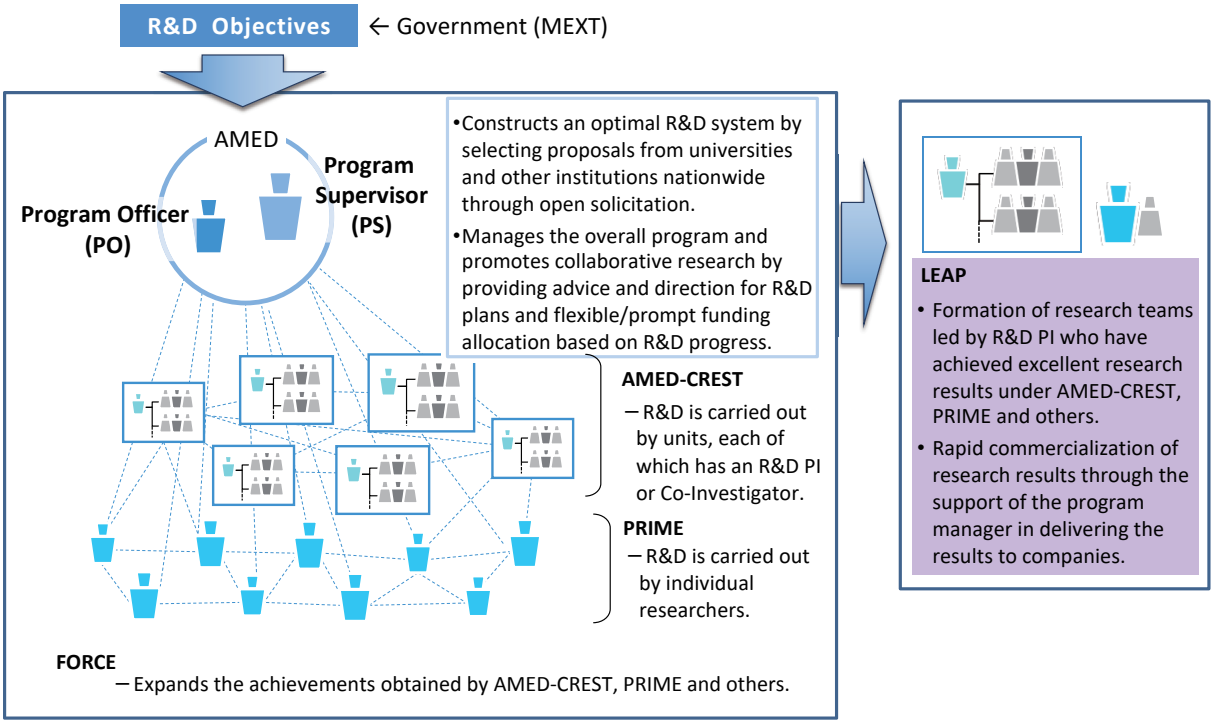
AHR and NRF2 are key transcription factors that response to environmental chemicals and oxidative stress and regulate gene expressions in xenobiotic detoxification and antioxidant response. Based on the studies that constitutive activation of AHR and/or NRF2 causes atopic dermatitis, we hypothesized that susceptibilities to the environmental stress are associated with the development of atopic dermatitis. In this study, we will elucidate the involvement of AHR and NRF2 in the pathogenesis of atopic dermatitis and challenge to the development of innovative drugs targeting the environmental stress response.

(＊) indicates completed R&D projects.

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

LEAP Program Supervisor (PS)/Program Officer (PO)

PS

TAKIMOTO-KAMIMURA Midori Distinguished research scientist, Teijin Institute for Biomedical research

PO

UCHIDA Takahiro President and CEO, Kyowa Pharma Chemical Co., Ltd.

KAWAKAMI Koji Professor, Graduate School of Medicine and Public Health, Kyoto University

R&D Period and R&D Costs

The R&D period and costs for a single R&D project are basically as follows

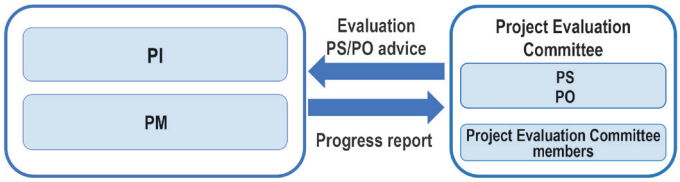
Program	R&D Period	Annual R&D Costs (direct cost)
LEAP	Up to five years	Up to 300 million yen

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.

- The PM and R&D PI organize an appropriate R&D system that is necessary and sufficient for proving and presenting technical feasibility.
- 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.
- 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.
- 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.
- R&D is implemented by the R&D PI.



Started in 2017

LEAP

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

In this study, we focus on the pathophysiological roles of lysophospholipids which have only one acyl chain. These lysophospholipids function as lipid mediators through GPCR. We aim to develop drugs for lysophosphoipids and biomarkers by determining the level of lysophospholipids and their producing enzyme in clinical samples, and their pathological roles.

Started in 2018

LEAP

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

Regulatory T (Treg) cells naturally present in every individual are a population of T cells specialized for suppressing excessive or abnormal immune responses, thereby preventing a variety of immunological diseases. This project aims at deciphering the transcriptional and epigenetic basis of Treg cell development and function, and thereby developing the technology to convert conventional T cells mediating inflammation into functionally stable Treg cells in vivo and in vitro. Such de novo induced Treg cells will be used in humans for the treatment of immunological diseases such as autoimmune disease and allergy, and also for controlling graft rejection in organ transplantation.

Started in 2019

LEAP

Mechnikov-based Drug Development by AIM

MIYAZAKI Toru
Professor,
Faculty of Medicine, The University of Tokyo

Program Manager **KUROKAWA Kiyoshi**
Professor Emeritus, The University of Tokyo

Accumulation of various self-pathogens such as dead cells, inflammatory elements, toxic metabolites, and abnormal proteins, causes types of chronic diseases including kidney disease and dementia, for which no effective therapies have reached clinic. Due to the ageing society and the modern life-style, the number of patients of those diseases are remarkably increasing, resulting in a huge medical burden. In this project, we will challenge to such incurable modern diseases by employing a circulation protein AIM, which profoundly enhances phagocytic elimination of self-pathogens, thereby promoting the repair of various diseases. This trial is the first clinical application of the phagocytic system, one of our fundamental defense mechanisms, which was discovered by Mechnikov more than hundred years ago.

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.

Advanced Research and Development Programs for Medical Innovation Completed R&D Areas and Projects

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

※ The names of the position, institution and organization are as of the end of the R&D pursuit area year.

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

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

※ The names of the position, institution and organization are as of the end of the R&D pursuit area year.

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

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

※ The names of the position, institution and organization are as of the end of the R&D pursuit area year.

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

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

※ The names of the position, institution and organization are as of the end of the R&D pursuit area year.

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

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

※ The names of the position, institution and organization are as of the end of the R&D pursuit area year.

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

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

※ The names of the position, institution and organization are as of the end of the R&D pursuit area year.

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

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

※ The names of the position, institution and organization are as of the end of the R&D pursuit area year.

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

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
PM :	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
PM :	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
PM :	KOBAYASHI Masakazu	Medical Institute of Bioregulation, Kyushu University

Started in 2015

Generation of functional organs using developmental niche

	NAKAUCHI Hiromitsu	Distinguished Professor, IMSUT Distinguished Professor Unit, Division of Stem Cell Therapy, The University of Tokyo
PM :	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
PM :	SHIOTA Atsushi	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.

【革新的先端研究開発支援事業の由来】

本事業は、国立研究開発法人科学技術振興機構（JST）の、戦略的創造研究推進事業の一部として誕生しました。

健康・医療戦略推進本部の総合的な予算配分調整の下で取りまとめられた各省連携プロジェクトのひとつである「オールジャパンでの医薬品創出」を目的とする事業として、「医療分野研究開発推進計画（平成26年7月22日健康・医療戦略推進本部決定）」における「基礎研究から医薬品としての実用化につなげるまでの切れ目のない支援を推進する」ことが決定されました。その一環として、画期的な医薬品等を切れ目なく創出することを目的に、JST戦略的創造研究推進事業（新技術シーズ創出）で実施した基礎研究の成果のうち、特に医療応用に向けた特筆すべき進展があったものを支援する事業として、「革新的先端研究開発支援事業」が開始され、平成26年には2課題が選定されました。

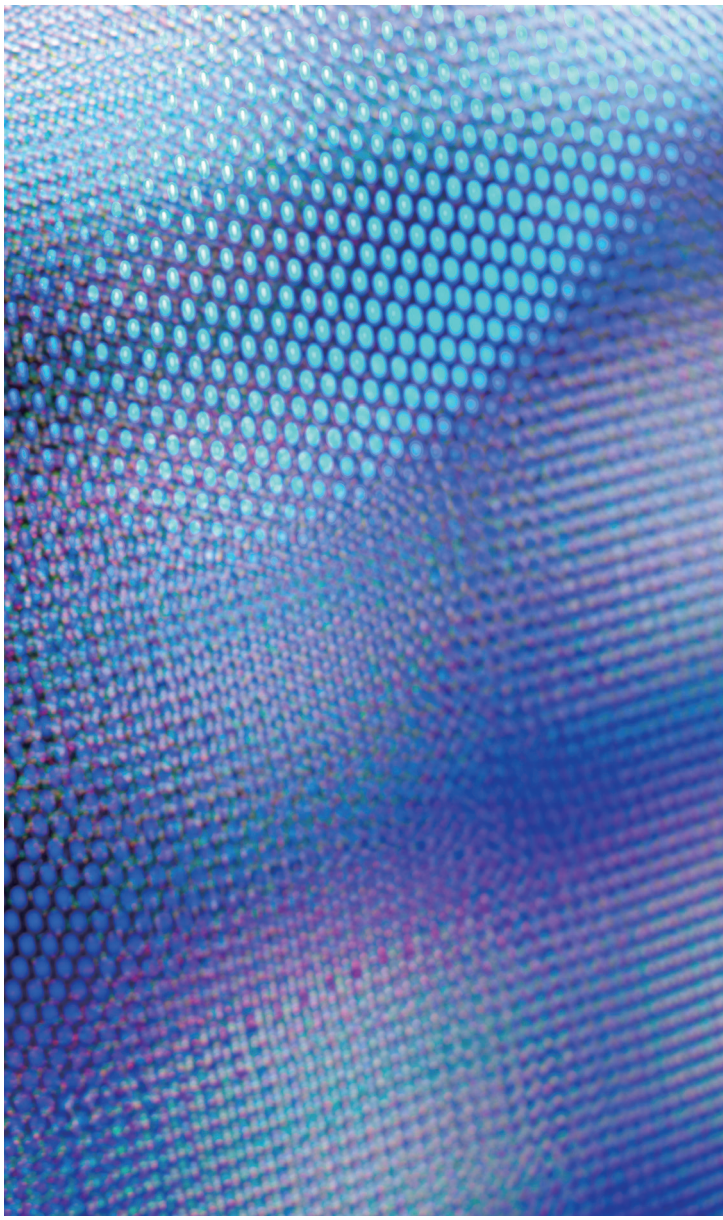
平成27年4月1日、国立研究開発法人日本医療研究開発機構（AMED）の設立に伴い、JSTから革新的先端研究開発支援事業2課題が移管され、同時に移管されたJSTのCREST課題の一部を組み込んで現在の事業の形となりました。移管された2課題についてはAMED創薬戦略部医薬品研究課が事業運営を担当しましたが、以降のLEAPは、AMEDシーズ開発・研究基盤事業部 革新的先端研究開発課が担当しています。

参考 web サイト

JSTの革新的先端研究開発支援事業紹介：
https://www.jst.go.jp/kisoken/archives/kakushin/index.html

AMED創薬戦略部医薬品研究課 革新的先端研究開発支援事業
（インキュベートタイプ）：
https://www.amed.go.jp/program/list/06/01/003.html

AMEDシーズ開発・研究基盤事業部 革新的先端研究開発課
革新的先端研究開発支援事業
（AMED-CREST、PRIME、LEAP、FORCE）：
https://www.amed.go.jp/program/list/16/02/001.html



CREST PRIME LEAP FORCE

Japan Agency for Medical Research and Development

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Tokyo 100-0004, Japan
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E-mail : kenkyuk-ask@amed.go.jp
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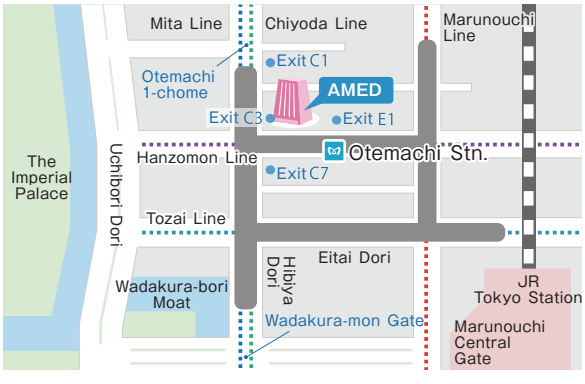

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