Early Life Stage

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

Research and Development Objectives

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

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

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AMED-CREST Started in 2019 · 1st period

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

ARIMA Takahiro
Professor , Tohoku University
Graduate School of Medicine

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

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

UENO Hideki
Professor, Graduate School of Medicine,
Kyoto University

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

Innovative imaging platform for elucidating pathophysiology of neurodevelopmental disorders

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

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

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

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

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

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

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

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

AMED-CREST Started in 2020 · 2nd period

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

USHIJIMA Toshikazu
President,
Hoshi University

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

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

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

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

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

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

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

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

HASE Koji
Professor,
Faculty of Pharmacy, Keio University

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

AMED-CREST Started in 2021 — 3rd period

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

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

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

Creating innovative human embryology using stem cells

TAKASHIMA Yasuhiro
Associate Professor,
Kyoto University, CiRA,

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

Study on the dynamism of subplate neural activity during brain development

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

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

PRIME Started in 2019 — 1st period

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

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

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

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

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

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

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

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

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

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

SAWA Shinichiro
Professor, Medical Institute of Bioregulation,
Kyushu University

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

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

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

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

Is epigenome transgenerationally inherited or not? (*)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Regulatory mechanism of longevity through developmental environment (*)

OBATA Fumiaki
Team Leader,
RIKEN Center for Biosystems Dynamics Research

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

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

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

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

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

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

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

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

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

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

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

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

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

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

MASUDA Takahiro
Professor, Medical Institute of Bioregulation,
Kyushu University

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Study on reproductive life span using infertile model animals

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

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

Mechanisms of disease predisposition by transgenerational histone modifications

INOUE Azusa
Team Leader,
RIKEN Center for Integrative Medical Sciences

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

Identification of tolerogenic bacteria in the neonatal gut microbiota

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

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

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

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

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

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

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

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

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

KUBO Akiharu
Professor, Kobe University Graduate School of Medicine

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

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

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

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

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

TSUKASAKI Masayuki
Professor,
School of Dentistry, Showa University.

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

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

SHINOHARA Ryota
Associate Professor,
Kobe University Graduate School of Medicine

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

Unveiling novel roles for maternal bile acids in fetal organ development

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

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

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