Stress

Elucidation of mechanisms for stress responses to disease development

Research and Development Objectives

Elucidation of stress responses and pathogenic mechanisms

Under "Stress" R&D area, the goal is to scientifically elucidate the biological responses at various different levels, from molecular/cellular levels to individual levels, caused by physical, chemical, biological, or emotional/psychological stress, and to develop an integrated understanding of stress responses and the mechanisms involved from the molecular/cellular level to the individual level.

We are surrounded by various different stressors, and new stressors have also emerged because of the changes in our lifestyles and social environments during the recent COVID-19 pandemic. Prevention of diseases triggered by such stressors is important to improve our QOL.

Specific goals of this R&D area include (1) elucidation of stress adaptation or avoidance systems in humans with a focus on applications in disease prevention, and elucidation of the mechanisms involved between the breakdown of these systems and disease onset; (2) identification of markers that allow objective evaluation of stress status in humans or prediction of disease onset due to stress, and elucidation of their pathophysiological significance; and (3) research and development of new techniques or methods, new measuring devices, or signal processing technologies that allow accurate, detailed, and long-term capture of human biological information that fluctuates subtly with exposure to stress.

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Stress

Aging

Immunological Memory

Multi-Sensing

Anti-infectives

Proteostasis

Early Life Stage

Adaptation / repair

Functional Impairment

Microbiome

FORCE

LEAP

Completed

Started in 2023 ● ● ● **1st period** AMED-CREST

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

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

Started in 2023 ● ● ● **1st period** AMED-CREST

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

MURAKAMI Masaaki
Professor, Institute for Genetic Medicine,
Hokkaido University

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

Started in 2023 ● ● ● **1st period** AMED-CREST

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

KENGAKU Mineko
Professor,
Institute for Advanced Study, Kyoto University

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

Started in 2023 ● ● ● **1st period** PRIME

Study of regulation of metabolic stress–induced cell death and chronic inflammation in the liver and adipose tissue
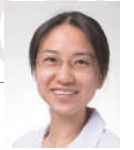
INABA Yuka
Associate Professor,
Institute for Frontier Science Initiative, Kanazawa University

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

Started in 2023 ● ● ● **1st period** AMED-CREST

Study of mechanisms of mental stress-induced cardiovascular pathogenesis using stress response control technology
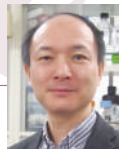
NAKAMURA Kazuhiro
Professor,
Nagoya University Graduate School of Medicine

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

Started in 2023 ● ● ● **1st period** PRIME

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

INO Daisuke
Lecturer,
Graduate School of Medicine Osaka University

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

Started in 2023 ● ● ● **1st period** AMED-CREST

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

MASUDA Takahiro
Professor, Medical Institute of Bioregulation,
Kyushu University

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

Started in 2023 ● ● ● **1st period** PRIME

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

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

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

Started in 2023 • • • 1st period — PRIME

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

SAKAMAKI Jun-ichi
Project assistant professor, Graduate School and Faculty of Medicine, The University of Tokyo

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

Started in 2023 • • • 1st period — PRIME

Investigating Crohn's disease pathogenesis focusing on Paneth cells

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

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

Started in 2023 • • • 1st period — PRIME

DNA damage response by the RNA spatiotemporal regulation via membrane-less organelles
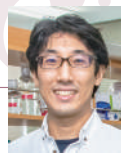
SHICHINO Yuichi
RIKEN Cluster for Pioneering Research Research Scientist

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

Started in 2023 • • • 1st period — PRIME

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

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

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

Started in 2023 • • • 1st period — PRIME

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

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

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

Started in 2023 • • • 1st period — PRIME

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

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

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

Started in 2023 • • • 1st period — PRIME

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

Toshiaki Teratani
Associate Professor, Keio University, School of medicine

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