Elucidation of mechanisms for stress responses to disease development

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Research and Development Objective

Elucidation of stress responses and pathogenic mechanisms

Targets

Under this Research and Development Objective, the goals are to develop an integrated understanding of phenomena from the cellular to the individual level and a scientific assessment of stress responses at each level (from cellular to individual) caused by various types of stress, including emotional stress. Further goals are to develop measuring technologies capable of capturing subtle biological information in an accurate and detailed manner over long periods of time and to identify new stress markers for objective indicators of stress exposure. Specifically, this Objective aims to achieve the following:

(1) Elucidation of the mechanisms involved when the body comes under stress and systems for stress adaptation or avoidance break down and disease occurs, with a view to applications in prevention of disease onset
(2) Identification of predictive markers of disease due to stress exposure and elucidation of the biological significance and mechanism of action of these markers at a molecular and cellular level as a stress response
(3) Development of new measuring devices capable of detailed, long-term measurements of the subtle fluctuations in biological information in response to stress in humans

Program Supervisor (PS)

Hiroyasu Iso, M.D., Ph.D., MPH
Director of Institute for Global Health Policy Research (iGHP),
Bureau of International Health Cooperation,
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Profile

Dr. Hiroyasu Iso completed the Doctoral Program at the Graduate School of Medicine, University of Tsukuba in 1986, and after working at the Osaka Medical Center for Cancer and Cardiovascular Diseases he served as an Assistant Professor from 1990, later as Associate Professor, and from 2002 as Professor of Public Health, University of Tsukuba. From 2005 to 2022 Dr. Iso was Professor of Public Health at the Graduate School of Medicine, Osaka University, serving as its Vice Dean for two years from 2013. He was also responsible for the JSPS Inter-University Exchange Project, and Director of the Ministry of Environment's Japan Environment and Children's Study (JECS) Osaka Unit Center. Dr. Iso won the Medical Award of The Japan Medical Association in 2015. He was appointed as the Director, Institute for Global Health Policy Research (iGHP), National Center for Global Health and Medicine in 2019, and has been involved in research and policy recommendations concerning healthcare in Japan and overseas. Dr. Iso is currently the President of the Japanese Society of Public Health (JSPH), a Council Member of the Science Council of Japan (SCJ), and Vice President of the Japanese Medical Science Federation.

Recent Research Direction

The relationship between stress and disease is an old, yet new theme in the fields of the life sciences/basic medical science, clinical medicine, and social medicine. For example, various life science/basic medical science studies have shown that biochemical stress brings about changes at the molecular and cellular levels. For a long time, clinicians have suggested that physical stress (such as change in atmospheric pressure) plays a role in the worsening of symptoms of autoimmune or orthopedic diseases. Epidemiological research has clarified the relationship between emotional or psychological stress and the onset of hypertension, diabetes, and ischemic heart disease. However, there are almost no examples in Japan or overseas of research into the relationship between stress and disease that uses life science/basic medical research as the basic platform to develop an integrated understanding all the way through from the molecular/cellular level to the individual and societal levels. It would be very meaningful for Japan to take a leading role in this type of research.

Program Officer (PO)

Hidenori Ichijo, Ph.D.
Professor, Graduate School of Pharmaceutical Sciences/
Laboratory of Cell Signaling, the University of Tokyo

Profile

Dr. Hidenori Ichijo completed the Doctoral Program at the Graduate School of Dentistry, Tokyo Medical and Dental University in 1990, and after working at the Uppsala Branch of the Ludwig Institute for Cancer Research he became a Research Assistant in the Faculty of Dentistry, Tokyo Medical and Dental University in 1992. After serving as an Associate at the Cancer Institute, Japanese Foundation for Cancer Research (JFCR), in 1998 he became a Professor at the Faculty of Dentistry, Tokyo Medical and Dental University, and since 2002 he has been a Professor at the Graduate School of Pharmaceutical Sciences, The University of Tokyo. Since 2012 Dr. Ichijo has served as the Director of what is now the Drug Discovery Initiative (DDI), The University of Tokyo, and from 2018 to 2020 was Dean of the Graduate School of Pharmaceutical Sciences, The University of Tokyo. He also served as the President of the Japanese Biochemical Society for two years from 2021. Dr. Ichijo was awarded the Uehara Prize in 2016, was decorated with the Medal with Purple Ribbon in the Japanese Government's Autumn Awards 2019, and won the Takeda Prize for Medical Science in 2020. In 2021 he won the Japan Academy Prize for his research into the Elucidation of the Stress Response Mechanism based on the ASK Family.

Recent Research Direction

Stress responses are one of the most basic biological phenomena in cells. The breakdown of this system can play a role in the onset of various diseases, including cancer, neurodegenerative diseases, immune disorders, and metabolic diseases. We are focusing on various stress responses closely connected with homeostasis in the body (such as oxidative stress, osmotic stress, endoplasmic reticulum stress, and mitochondrial stress) and the "signature molecules" that play a key role in receiving and recognizing such stress, with the goal of elucidating stress signals and creating drug discovery platforms based on these signals.

Program Officer (PO)

Tsuyoshi Sekitani, Ph.D.
Professor, The Institute of Scientific and Industrial Research, Osaka University

Profile

Dr. Tsuyoshi Sekitani graduated from the School of Engineering Science, Osaka University in 1999, and in 2003 completed early the Doctoral Program at the Graduate School of Engineering, The University of Tokyo. After serving as an Assistant Professor and Lecturer, he became an Associate Professor at the Graduate School of Engineering, The University of Tokyo. Dr. Sekitani became an Associate Professor at the Institute of Scientific and Industrial Research (ISIR), Osaka University in 2014, and currently holds the posts of Executive Assistant to the President, Osaka University and Director, Co-Creative Incubation Center, Osaka University. He was made a Professor Emeritus, Osaka University in 2017. Currently he serves as a member of the Materials Strategy Experts Meeting, Cabinet Office; Expert Committee member, Council for Science and Technology, MEXT; editor of the American Chemical Society's journal ACS Nano (IF:18.027) and Director of the Engineering Academy of Japan Inc. (EAJ). He is the winner of 41 prizes including the Jan Rajchman Prize.

Recent Research Direction

It is extremely difficult to develop technologies capable of accurate and continuous measurements over long periods of time to monitor the ever-changing biological status. In our Laboratory, we conduct R&D using flexible electronic technologies to develop new ways to take measurements without placing a burden on the targets under investigation. Our research is wide ranging and includes investigations into materials, physical properties, processes, and systems, with the goal of applying our findings to medical devices.

Image of the R&D area

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AMED

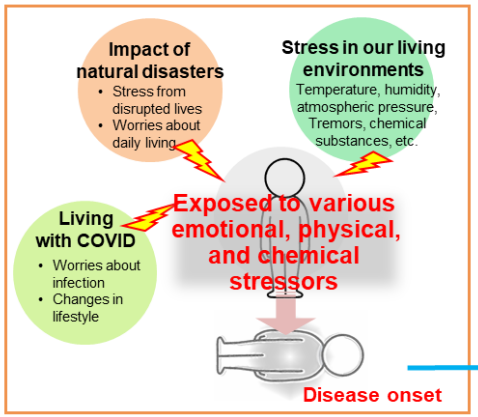
Targeting a scientific and integrated understanding from the "cellular level" to the "individual level" and elucidation of pathological mechanisms!

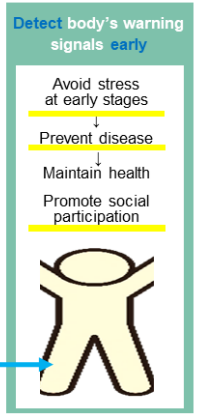
Basic researchers × Clinical researchers

Elucidation of mechanisms for stress responses to disease development

Background

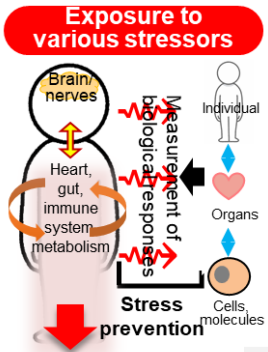
- **Prevention of disease** caused by stress is important for improved QOL etc.
- **Difficult to measure biological responses** to various types of stress
- **The mechanisms of onset** for many diseases caused by stress exposure have **yet to be identified**
- **Disease prevention based on an understanding of early warning signals** in response to stress not yet possible





Goals and Objectives

The goals are to develop an integrated understanding of phenomena from the cellular to the individual level and a scientific assessment of stress responses at each level (from cellular to individual) caused by various types of stress.



Research that links phenomena at cell level to individual level

1. Development of new measuring devices capable of detailed measurement of stress responses
2. Identification of predictive markers of diseases caused by stress exposure and elucidation of their biological significance and mechanisms
3. Elucidation of the mechanisms of disease onset caused by a breakdown in the body's systems to adapt to/avoid stress impacts and disease prevention

Development of measurement devices

Promotion of collaborations with basic researchers and clinical researchers

Expected scientific impacts

Enable disease prevention or early interventions through technological advances that allow the accurate, detailed measurement of fluctuations in biological information over long periods of time and identification of new markers that provide objective indicators of stress exposure

Future vision

Research allows us to gain an objective understanding of the effects of stress exposure from an early stage, thereby realizing a society where people can all enjoy healthier lives and participate in society with peace of mind

Outline of the research and development area

The goal is to develop a scientific understanding of stress responses at the individual level and the mechanisms leading to disease onset. The research will include integrated analyses of phenomena at the molecular/cellular level and at the individual level in response to stress and will be performed through a close collaboration between researchers engaged in basic life science fields and clinical medicine, as well as with researchers in other disciplines including epidemiology, measurement engineering, or computer sciences.

Further goals are the discovery and development of drugs that target stress, as well as the identification of new stress markers that provide objective indicators of biological responses to stress exposure and the development of new measuring devices or signal processing technologies that allow accurate, detailed, and long-term capture of biological information that fluctuates subtly in response to stress.

R&D costs and R&D period

In this R&D area, we will select a diverse range of research themes relevant to the elucidation of mechanisms for stress responses leading to disease development, and invite research proposals that satisfy the conditions below.

Type of proposal	R&D funds	R&D period	No. of projects to be selected
AMED-CREST (unit-type)	300 million yen or less (entire direct costs)	Up to 5.5 years	Around 4–6 projects
PRIME (solo-type)	40 million yen or less (entire direct costs)	Up to 3.5 years	Around 8–12 projects

Selection policy AMED-CREST

(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
(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

【AMED-CREST】

We invite proposals for research that will involve the formation of an R&D unit to facilitate close collaboration between researchers in basic life science research fields and in clinical medicine, as well as with researchers in other disciplines including epidemiology, measurement engineering, or computer sciences, with the goal of combining research at the molecular/cellular level with the individual level and developing an understanding and establishing evaluation methods for the human body's response to stress.

We expect basic researchers to take the findings from R&D at the molecular or cellular level and to collaborate with clinical medicine researchers to investigate and develop an understanding at the individual level in humans. We look for epidemiologists to work with basic researchers on stress markers or mechanisms as predicted from cohort research and other types of investigations in order to investigate and develop an understanding at the molecular or cellular level, or to work with clinical medicine researchers to investigate and develop an understanding at the individual level in humans. For measurement engineering or computer science researchers, we look for the invention of technologies needed by basic researchers in the life sciences, clinical medicine researchers, or epidemiology researchers to allow the establishment of technologies to objectively evaluate stress.

Examples of R&D Proposals (1)

*Excerpt from Application Guidelines

- Research to clarify the sensitivity, vulnerability, tolerance, and resilience to stress of healthy individuals and to understand individual differences in these responses, based on defined molecular entities, or to elucidate molecular entities using robust methodologies, with the goal of understanding normal biological responses to stress
- Research to develop methodologies to objectively assess at the individual level the biological responses to stress, understanding quantitative factors over time in physiological or pathophysiological changes due to stress (e.g., qualitative or quantitative changes in biological factors)
- Research to elucidate stress level thresholds relevant to disease onset (including acute, chronic, or cumulative perspectives)
- Investigations at the individual level to explore new stress markers for objective evaluation of stress status in humans, elucidate their pathophysiological significance, and determine whether these markers are objective indicators

Examples of R&D Proposals (2)

*Excerpt from Application Guidelines

- Research and development of new measurement methods, new optical devices, or non-invasive wearable devices to measure changes in stress markers, such as physicochemical factors on the body surface or biological factors in sweat, blood, or urine that are triggered by stress
- Research to elucidate the complex and multidimensional biological responses triggered at various life stages by the build-up or sum total of the various types of stress we are exposed to in our daily living environments (including use of data technologies or AI)
- Data-driven research through existing or new cohort research or using biobanks in order to identify stress markers
- New cohort research aimed at exploring new stress markers and investigating their utility

Points to note when submitting a proposal

Under AMED-CREST, our focus is on understanding stress responses at the individual level and evaluation of stress levels, so we will give precedence to the following selection criteria:

(A) Research involving the formation of an R&D unit, with close collaboration between researchers in basic life science research fields and in clinical medicine, as well as with researchers in other disciplines including epidemiology, measurement engineering, or computer sciences.

(B) Research plans that include work in individual humans or animals. However, research plans that only include work in individual animals need to include a reasonable explanation of how this links to research at the individual human level.

(C) Research proposals at the molecular or cellular level that do not include plans for research at the individual level need to include a reasonable explanation of how this links to research to promote health or prevent disease in humans.

Selection policy PRIME

(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
(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

【PRIME】

We invite proposals for highly innovative research, including in the R&D areas described in the AMED-CREST program, particularly for the items described below.

- Elucidation of molecular and cellular mechanisms of stress responses using model cells or model animals
- Early-stage research and development aimed at exploring and identifying new stress markers
- Elucidation of the mechanisms of responses to stress using human samples
- Challenging research and development aimed at measuring biological information that fluctuates according to exposure to various types of stress

We also call for challenging R&D proposals beyond the items listed above.
We welcome proposals in the life sciences that can connect in the future to medical sciences and healthcare. However, for engineering proposals, there is no need to provide at the proposal stage the specific details of how the research connects to the medical sciences and healthcare. We look for proposals for unique measurement methods or devices based on new perspectives.

Message from the Program Supervisor (PS) Hiroyasu Iso

The mission behind this call for proposals is comprehensive research to investigate the relationship between stress and disease all the way through from the molecular/cellular level to individual and societal levels, using life science and basic medical science as a platform and developing collaborations with researchers in clinical medicine, social medicine, measurement engineering, computer sciences, and other disciplines. Through this, we expect to build up transdisciplinary scientific evidence, develop methods for effective stress interventions, prevent onset and worsening of the various diseases where stress plays a role, and contribute to longer healthy life expectancies.

There is a long history of research into the relationship between stress and disease, but we have not made significant progress because most studies thus far have involved investigations in a specific research field and attempts to understand the overall picture have involved different study populations and methodologies. However, we now see greater potential for joint research due to the rapid advances in research into molecular and cellular mechanisms in the life sciences; progress in the discovery of various biomarkers in clinical medicine, as well as methods for their application and monitoring; developments in large-scale epidemiological cohort research; and rapid advances in the technologies used in measurement engineering and computer sciences. Obviously, such research is new in global terms and we expect researchers to encounter difficulties, but it would be valuable for Japan to take a leading role in this research theme.

This call for proposals is aimed at selecting a large number of unit-type (AMED) and solo-type (PRIME) research programs, and we want to promote information exchange and collaborative work between the various researchers selected as they progress their investigations in order to contribute to real progress in this field of research. We hope to see a large number of submissions from researchers with experience in this field as well as enthusiastic young researchers who bring fresh perspectives to this field of research.

Message from the Program Officer (PO) Hidenori Ichijo

I am mostly responsible for the basic life sciences part of this CREST/PRIME program. I hope to contribute to dramatic developments in this field through fair and impartial evaluation and interactive discussions.

To achieve this, I would like applicants to refer to the following **instructions on how to complete the written application**. Of the many evaluation points that we look at, published research achievements are extremely important, both for measuring the applicant's actual abilities and predicting the feasibility of research plans. As evaluators, we are responsible for developing an accurate understanding of the value of each research paper and reflecting this understanding fairly in the evaluation results. We agree with the idea of not relying too much on impact factors when evaluating individual research papers, but it is extremely important for us to understand the standing of the journals where the applicant's research has been published and how much the applicant has contributed to the published research. Therefore, we ask that the applicants **highlight information to facilitate our understanding, including the journal name and other information such as the applicant's position as the author, making equal contributions, or acting as the corresponding author** (see the figure below).。

We hope to receive submissions that are based on defined molecular entities and research achievements, but are also challenging proposals that involve novel methodologies and will open up entirely new possibilities for research in the future.

☆ Show Journal name, applicant position (in bold, underlined text), equal contributions, corresponding authors, etc.

Good example: Watanabe, K., Morishita, K., Zhou, X., Shiizaki, S., Uchiyma, Y., Koike, M., Naguro, I.***** and **Ichijo, H.*** Cells recognize osmotic stress through liquid–liquid phase separation lubricated with poly(ADP-ribose). ***Nat. Commun.***, 12,1353 (2021) ***:** corresponding author

Bad example: Watanabe, K., Morishita, K., Zhou, X., Shiizaki, S., Uchiyma, Y., Koike, M., Naguro, I. and Ichijo, H. Cells recognize osmotic stress through liquid–liquid phase separation lubricated with poly(ADP-ribose). Nat. Commun., 12,1353 (2021).

Message from the Program Officer (PO) Tsuyoshi Sekitani

Digital, communication, big data, and artificial intelligence (AI) technologies are maturing and we are now starting to use them in our everyday lives.

We are now in an era when we can use such scientific technologies to tackle what was previously considered a very challenging field, namely the elucidation of mechanisms for stress responses leading to disease development.

This is an important research theme that is relevant to all, so we hope to gather together expertise from a wide range of fields to tackle this difficult question.

I want to work collaboratively to create good medical and healthcare technologies. I look for everyone to give their best to this goal.

We await innovative and creative research proposals that aim to develop a scientific understanding of stress responses and allow objective measurement of stress levels. Please send us your submissions!