Understanding Proteostasis and Discovering Innovative Medical Applications

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Program Officer (PO)

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Research and Development Objective

Understanding and medical application of proteostasis

*"proteostasis" means a series of processes that control the amount, quality, and localization of proteins in the homeostatic maintenance function of living organisms.

Targets

Focusing on the homeostasis of proteins inside and outside the cell (proteostasis), this research and development objective aims to clarify the mechanism of disease onset and create innovative medical technologies by analyzing the dynamics of degeneration, aggregation, decomposition, etc. from the cell to the individual level. In particular, the following three targets are to be achieved:

(1) Improved understanding of the environment surrounding proteins involved in proteostasis at the molecular level
(2) Elucidation of the mechanism of diseases onset resulting from disruption of proteostasis
(3) Development of seeds for therapeutic drugs and biomarkers targeting the mechanisms by which proteostasis disrupts

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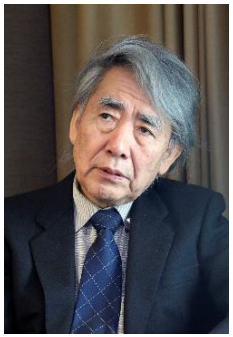


Kazuhiro Nagata, Ph.D
(Director General, JT Biohistory Research Hall; Professor Emeritus, Kyoto University; Professor Emeritus, Kyoto Sangyo University)

Profile

Dr. Kazuhiro Nagata graduated from the Department of Physics, Faculty of Science, Kyoto University in 1971. After working at Morinaga's Central Research Institute, he was appointed as Lecturer of the Chest Disease Research Institute, Kyoto University in 1979. In 1984 he took a post as Visiting Associate at the National Cancer Institute, NIH in the US. He was appointed as Professor of the Chest Disease Research Institute, Kyoto University, in 1986 and as Professor of the Institute for Frontier Medical Sciences, Kyoto University in 1998. He was appointed as Dean of the Faculty of Life Sciences, Kyoto Sangyo University, in 2010 and as Director of the Institute for Protein Dynamics, Kyoto Sangyo University, in 2016. He was appointed to his current position in 2020. Dr. Nagata has also served as President of the Japan Society for Cell Biology, President of the Cell Stress Society International, and in various other capacities. He won the Hans Neurath Award for protein research including discovery of the collagen-specific molecular chaperone Hsp47. He is a recipient of the Medal with Purple Ribbon.

Recent Research Direction

Regulation of cell functions by molecular chaperones
Basic research into proteostasis and endoplasmic reticulum (ER) homeostatic mechanisms involving the ER reductase ERdj5
Development of agents to treat fibrotic disease that target the collagen-specific molecular chaperone Hsp47

Program Officer (PO)

Tamao Endo, Ph.D
(Senior Fellow, Tokyo Metropolitan Institute of Gerontology)

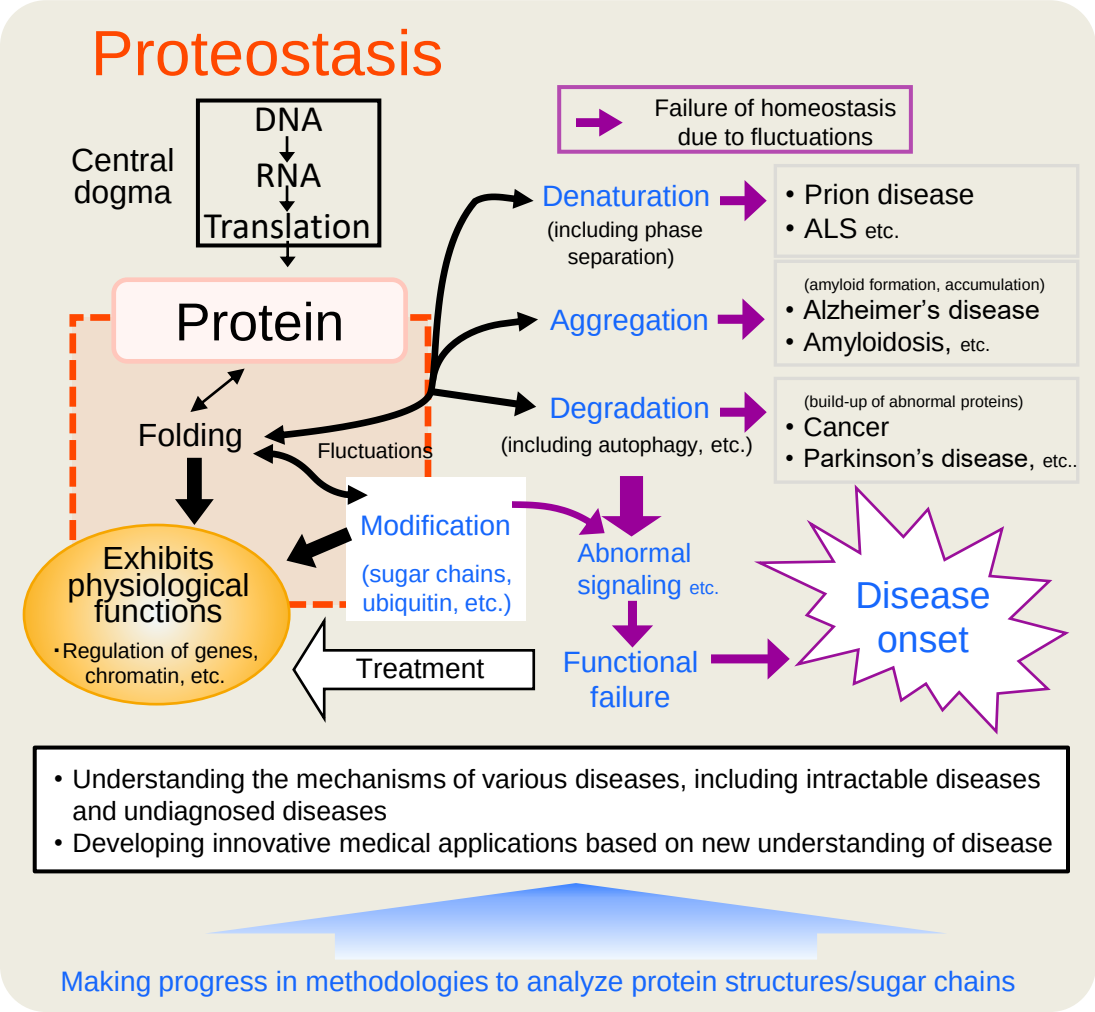
Profile

Dr. Tamao Endo completed the doctoral program at the Graduate School of Pharmaceutical Sciences, the University of Tokyo in 1982 (Ph.D in Pharmaceutical Sciences). After working at the Baylor College of Medicine in the US and the Institute of Medical Science, the University of Tokyo, in 1994 he was appointed as Laboratory Chief of the Tokyo Metropolitan Institute of Gerontology. He was appointed to his current position after serving as Vice-Director and Deputy Director of the Tokyo Metropolitan Institute of Gerontology. Dr. Endo has served as an officer of the Japanese Society of Carbohydrate Research and other associations related to medicine and biochemistry. He is the recipient of numerous awards, including the 2017 Japan Academy Prize for the discovery of novel glycans and a systematic understanding of glycan synthesis abnormalities including Fukuyama muscular dystrophy.

Recent Research Direction

Aims to understand aging processes and mechanisms of disease onset through research into post-translational modifications
Attempting to better understand biological phenomena by developing new analytical methods
Aims to develop therapeutic agents based on findings obtained through basic research

Image of the R&D area



Outline of solicitation

There are still many diseases of which the molecular mechanism leading to the onset is unknown.

In future disease studies, it is necessary to deepen the understanding of the process of posttranslational modification (glycosylation, oxidation, glycation, etc.) and control of translation, in addition to analysis of expression of gene and protein.

In particular, it is necessary to conduct protein-focused research that leads to medical treatments (keeping in mind that research is to be conducted by AMED).

(Proteins are difficult to handle and research into proteins has lagged behind that into nucleic acids)

Selection policy

(1) Improved understanding of the environment surrounding proteins involved in proteostasis at the molecular level
(2) Elucidation of the mechanism of diseases onset resulting from disruption of proteostasis
(3) Development of seeds for therapeutic drugs and biomarkers targeting the mechanisms by which proteostasis disrupts

【AMED-CREST】

World-class, innovative research proposals—that is to say, proposals that go beyond current frameworks and use new concepts to drive a paradigm shift in the fields of the life sciences and disease research—and research aimed at medical application that should be conducted by AMED

【PRIME】

We invite proposals particularly for highly innovative research.

Proposals for ambitious projects that could overturn existing concepts, challenging projects that could generate unique research leading to new breakthroughs, or research to develop novel technologies that may contribute to basic research in this R&D area, with a particular focus on abnormal proteins and posttranslational modifications

Examples of R&D Proposals (1) *Excerpt from Application Guidelines

- Understand the early-stage processes occurring in vivo, including protein denaturation and aggregation, and the molecular mechanisms of the processes involved in progression (including environmental factors, positional information, and posttranslational modifications); also understand control mechanisms due to constituent elements in vivo (e.g., regeneration, disaggregation, and degradation).
- Identify the mechanisms involved in the recognition and response to denatured/aggregated proteins (abnormal proteins) and abnormal modifications in vivo or molecule species that exhibit cytotoxicity, and understand the mechanisms of disease onset, such as analysis of the molecular mechanisms that manifest as toxicity.
- Conduct biochemical and structural biological analyses of abnormal proteins and posttranslational modifications in human diseases and how they relate to location information, and use these findings to develop highly extrapolative experimental models.
- Develop technology to detect at a high sensitivity the presence and location of abnormal proteins and special posttranslational modifications in biological tissues.
- Create technologies to control the synthesis and spread of abnormal proteins (e.g., suppress toxicity, promote degradation).
- Create mathematical models using bioinformatics methodologies that can model and predict the molecular mechanisms leading to disease onset, in light of biochemical and molecular biological evidence on protein denaturation/aggregation and posttranslational modifications.

Examples of R&D Proposals (2) *Excerpt from Application Guidelines

- Understand the mechanisms behind abnormal protein synthesis based on abnormalities in the protein translation mechanism and understand the molecular mechanisms involved when these abnormal proteins affect cells and tissues in the body.
- For proteins in cell surface receptors and adhesion molecules, as well as in extracellular matrix, understand the mechanisms of disease onset based on proteome analysis and analysis of the correlation between structure and function, as well as control mechanisms regulating protein physiological functions that involve glycans or changes in site-specific glycosylation.
- Develop cell engineering and chemical technologies that enable control of site-specific glycan structures and control of the nonuniformity of glycosylation.
- Understand the environmental factors, biochemical structural changes, and molecular pathways involved in glycation, oxidation, and other modifications, and analyze functional changes in modified proteins.

[Important]
R&D Proposals Outside the Scope of the Program

1. Research into systems that use reversible protein modification to effect functional change, such as phosphorylation and lipid oxidation affecting protein localization with the objective of understanding signaling systems
2. Research that mainly concerns the development of functional molecules (e.g., membrane lipids, nucleic acids) other than those involved in the protein itself or posttranslational modifications

Points to Note When Submitting a Proposal

- Applicants are asked to hypothesize on at least one disease relevant to the target proteins or phenomena under research. When the application is submitted, proof of concept **does not necessarily need to be provided**.

- **There is no requirement** for a single team to investigate an understanding of all three items of protein denaturation, aggregation, and degradation. **There is also no requirement** for a single team to investigate both proteins and posttranslational modifications like glycosylation.

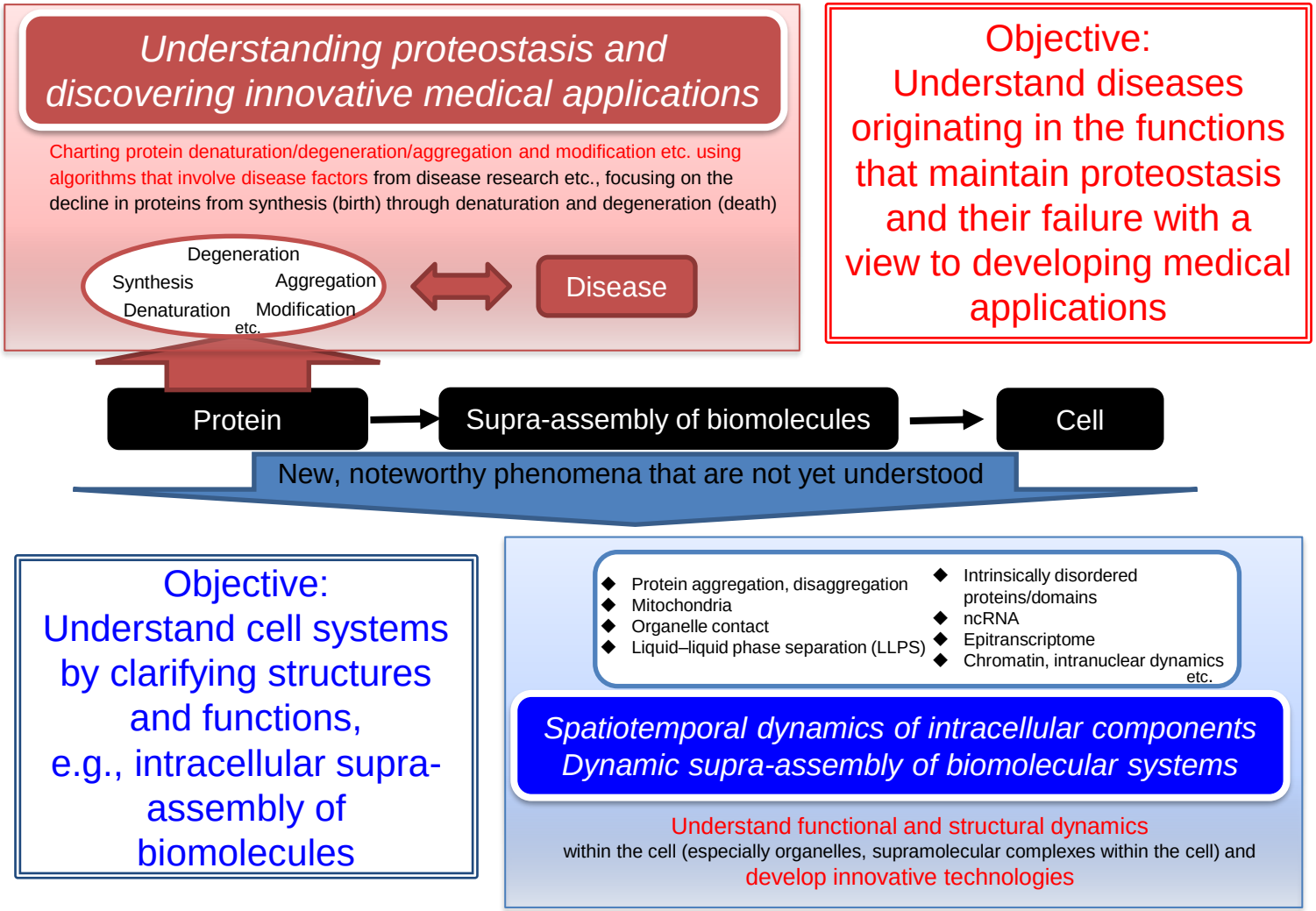
- When submitting the proposal**, there is no need** to include participation by multiple researchers from different fields in a single team. The applicant should consider building the essential team needed to prove a new concept. In terms of a multidisciplinary approach, during the research implementation phase, intra- and interdisciplinary interactions should be factored in as necessary, alongside a proactive approach to information sharing and exchange of opinions.

R&D costs and R&D period

In order to select a wide variety of R&D projects to understand proteostasis and discover innovative medical applications, AMED is soliciting research proposals according to the following conditions.

Type of proposal	R&D funds	R&D period	No. of projects to be selected
AMED-CREST (unit-type)	250 million yen or less (entire direct costs)	Up to 5.5 years	Around 3–5 projects
PRIME (solo-type)	40 million yen or less (entire direct costs)	Up to 3.5 years	Around 8–12 projects

Relationship to New JST Research Areas



Message from PS and PO (1)

- For the target area of proteostasis, AMED welcomes proposals for projects that could lead to new breakthroughs or develop novel technologies that may contribute to basic research (e.g., technology development for highly sensitive detection of abnormal proteins or abnormal modifications).
- AMED is looking for appealing and ambitious hypotheses and proposals for strategic processes to verify these hypotheses that could raise the level of all life sciences in Japan and have an enormous impact in other fields as well.
- AMED hopes to see challenging proposals that could prompt a paradigm shift in our understanding of biological phenomena and the basic principles of post-translational modifications, where research has lagged.
- Under AMED-CREST in particular, AMED will conduct a rigorous review of proposals focused solely on understanding proteostasis with limited discussion of healthcare applications. We think such proposals can be improved by including research and investigation using human specimens.

Message from PS and PO (2)

- Although PRIME is a research program under which research is performed by an individual researcher, it seeks motivated researchers capable of actively developing networks through exchange with other research groups in the same or different R&D areas with an eye on future R&D development rather that focusing solely on their own field of specialization.
- AMED aims to provide full support to young researchers* selected for the PRIME program to become cornerstones of the next generation in their respective R&D areas, so please be proactive in submitting proposals.

*AMED definition of “young researchers”

Young researchers in the AMED programs are defined as those males who are under 40 years old as of April 1, 2022 (i.e. who were born on or after April 2, 1982); females who are under 43 years old as of April 1, 2022 (i.e. who were born on or after April 2, 1979); or those who acquired their doctorate less than 10 years ago. However, for those who have taken pre- or post-natal leave or child-rearing leave, the age restriction (under 40 years old for males and 43 years old for females) may be extended by the number of days they took the leave.

AMED awaits innovative and creative proposals.

We particularly welcome newcomers in this long-established R&D area.

We are looking forward to your application.