

# Immunological memory: Understanding, regulation and medical innovation

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## Research and Development Objective

Immunological memory: Understanding, regulation and medical innovation

※ Immunological memory: a phenomenon that comprises perturbation of immune system by primary antigen exposure, and immediate and powerful immune response when exposed again by the same antigen

## Targets

This R&D objective aims to integratively understand immunological memory that is closely implicated in cancer, infectious disease, and allergy/autoimmune disease by using the latest, most-advanced research technologies, and to create medical innovations to predict and control these diseases. In particular, the following four targets are to be achieved:

- (1) a new and fundamental understanding of how human immunological memory is formed, maintained, and lost
- (2) clarification of novel mechanisms of cancer immunity mediated by human immunological memory
- (3) an understanding of human immunological memory against infectious diseases in societies living with COVID-19 and after the COVID-19 pandemic
- (4) development of novel methods controlling allergic and autoimmune diseases, based on an understanding of human immunological memory

# Program Supervisor (PS)



Toshinori Nakayama, M.D., Ph.D  
President, Chiba University

## Profile

1988, Obtained PhD, Graduate School of Medicine, The University of Tokyo. -1991, National Cancer Institute, USA. 2001, Professor, Graduate School of Medicine, Chiba University. 2015, Dean, Graduate School of Medicine, Chiba University. 2018, Adjunct professor, University of California, San Diego. 2021, President, Chiba University  
Councilor, Japanese Society for Immunology, IUIS Education committee member

## Recent Research Direction

Generation and maintenance of immune system  
Generation and maintenance of Pathogenic Immunological Memory and its regulation

# Program Officer (PO)



Kiyoshi Takeda, M.D., Ph.D  
Professor, Graduate School of Medicine, Osaka University

## Profile

1998, Obtained PhD, Graduate School of Medicine, Osaka University. 2003, Professor, Medical Institute of Bioregulation, Kyushu University. 2007, Professor, Graduate School of Medicine, Osaka University, 2019, Director, Immunology Frontier Research Center, Osaka University  
Councilor, Japanese Society for Immunology, Society for Mucosal Immunology

## Recent Research Direction

Study of the etiology and pathogenesis of intractable immune diseases

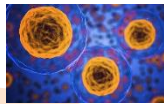
- Analysis of the intestinal immune system
- Analysis of intestinal environmental factors that influence the gut homeostasis
- Analysis of barrier function of the intestinal epithelial layer

# Immunological memory: Understanding, regulation and medical innovation

## Background

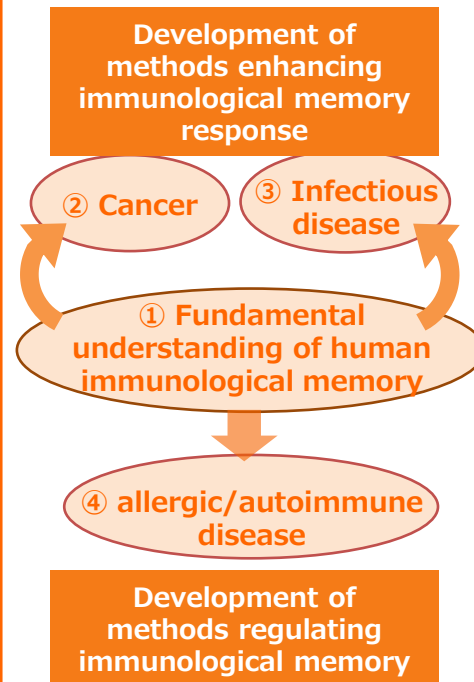
- SARS-CoV-2 pandemic has highlighted the importance of human immunological memory.
- Immunological memory is closely implicated in multiple disease pathologies, including cancer, infectious disease, and allergy/autoimmune disease, but it still remains unclear.

Powerful and world-class immunology researches in Japan



New technologies: Single cell/repertoire analyses and structural analyses, etc

## Examples of R&D



### ① Fundamental understanding of how human immunological memory is formed, maintained, and lost

Comprehensive understanding of the mechanisms underlying the establishment of memory in lymphocytes and innate immune cells, and the regulatory mechanisms of immunological memory by Treg cells, tissue-resident immune cells, and even non-immune cells

### ② Clarification of new mechanisms of cancer immunity mediated by human immunological memory

Clarification of novel mechanisms of cancer immunity from the perspective of immunological memory

### ③ Infectious diseases and human immunological memory in societies living with COVID-19 or after the COVID-19 pandemic

Understanding of immunological memory response against various pathogens, and development of innovations for new diagnostic, preventive, and therapeutic methods, based on immunological memory with a particular focus on personalized medicine for infectious diseases

### ④ Development of novel therapeutics for allergic and autoimmune diseases, based on an understanding of human immunological memory

Identification of pathogenic memory cells in allergic and autoimmune diseases and development of innovations for new therapeutic methods.

※ Immunological memory: a phenomenon that comprises perturbation of immune system by primary antigen exposure, and immediate and powerful immune response when exposed again by the same antigen

## Future

- Realizing personalized preventive and therapeutic care for cancer, infectious disease, etc. where the immune system is closely involved
- Complete recovery from allergic and autoimmune diseases without relapse
- Development of safe, effective, and fast-acting vaccines

Extending healthy life expectancy by regulating diseases, based on the understanding of human immunological memory system

# Outline of the Research and Development Area

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Immunological memory is an important host defense system that functions against infectious microorganisms, but is also closely implicated in the pathogenesis of various diseases, including cancer and allergy/autoimmune disease.

Immunological memory is a potential target for the development of clinical methods to predict, prevent, and treat such diseases, so a better understanding of the mechanisms will be vital to lay the foundations for medical advances in the management of these diseases.

Creation of new concepts of immunological memory will be expected by investigating the mechanism on the establishment of memory based on recognition of self and non-self, memory against pathogenic and symbiotic microorganisms, and pathogenic memory vs. beneficial memory.

# Outline of the Research and Development Area

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The goal of this R&D area is to create medical innovations that will contribute to predicting and regulating diseases like cancer, infectious disease, and allergy/autoimmune disease, through a hierarchical and multifaceted understanding of immunological memory in humans by applying advanced research technologies such as the recently developed single-cell/repertoire analyses and structural analyses using cryo-electron microscopy.

We have specified cancer, infectious disease, and allergic and autoimmune diseases as the targets, but immunological memory is deeply involved in other diseases as well, so we also look forward to R&D plans aiming the elucidation of mechanisms that point to new concepts for the onset, prevention, and regulation of those diseases.

# Human Immunology

Basic research on immunology to date has mostly been performed using mice and has focused on investigating short-term immune responses. The difference in the immune system between humans and animal models such as mice has been a barrier to the application of basic research achievements to the clinical setting.

Research to understand human immunological memory will progress effectively if performed with a correct understanding of the similarities and differences between mouse and human immune systems and pursued through an efficient interaction between mouse and human researches. We strongly recommend that your proposal not be restricted to investigations in animal models, but should involve close collaboration with clinical researchers with expertise in human diseases.



Your proposal needs to include plans for proof of concept (POC) research in humans/patients, to verify the findings obtained from experiments in mouse and other animal models.



# R&D costs and R&D period



In order to select a wide variety of R&D projects to this R&D area, 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)	300 million yen or less (entire direct costs)	Up to 5.5 years	Around 4-6 projects

# Team construction



Research on human immunological memory is a field that is becoming increasingly competitive around the world. To discover novel medical innovations or scientific concepts, it is necessary to involve collaborations not only between immunologists and clinical researchers, but also with researchers in other fields (e.g., bioinformatics, structural biology, metabolomics, mathematical modelling, chemical biology, imaging, or microbiology) who possess original analytical technologies or cutting-edge methods. We look forward to applications by powerful and very active research teams who will be able to lead immunological memory research in global levels over the next 10–15 years.

The goal is to create new concepts in immunological memory, and to use these concepts as the basis for innovation to develop futuristic preventive and therapeutic methods. We expect to see the research teams that mainly comprise young and mid-career researchers from not only immunology but also various research fields.

# Examples of R&D proposals (1)

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- (1) Fundamental understanding of how human immunological memory is formed, maintained, and lost
- Comprehensive understanding of the mechanisms underlying the establishment of memory in lymphocytes and innate immune cells, and the regulatory mechanisms of immunological memory by Treg cells, tissue-resident immune cells, and even non-immune cells
  - Development of animal models or analytical technologies that contribute to our understanding of human immunological memory
  - Changes in immunological memory over the course of life and clarification of their regulatory mechanisms
  - Understanding of the impact of environmental factors including microbiota on immunological memory
  - Clarification of the mechanisms how memory is established and regulated in the mucosal immune system

# Examples of R&D proposals (2)

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## (2) Clarification of novel mechanisms of cancer immunity mediated by human immunological memory

- Clarification of novel mechanisms of cancer immunity from the perspective of immunological memory
- Clarification of mechanisms how genetically engineered immune cells control immunological memory by in ex-vivo gene therapy

## (3) Infectious diseases and human immunological memory in societies living with COVID-19 or after the COVID-19 pandemic

- Understanding of immunological memory against various pathogens
- Clarification of mechanisms for immune activation and immune escape based on an understanding of immunological memory in emerging and re-emerging infectious diseases
- Development of innovations for new diagnostic, preventive, and therapeutic methods by the latest wet and dry research approaches, based on immunological memory with a particular focus on personalized medicine for infectious diseases

# Examples of R&D proposals (3)



(4) Development of novel therapeutics for allergic and autoimmune diseases, based on an understanding of human immunological memory

- Identification of pathogenic memory cells in allergic and autoimmune diseases, and clarification of the functional role of those cells in the pathogenesis of these diseases
- Development of innovations for new therapeutic methods for allergic and autoimmune diseases through the elimination of immunological memory

(5) Other target diseases, etc.

- Clarification of the mechanisms by which immunological memory is involved in the pathogenesis of cardiovascular, metabolic, and neurological diseases, etc
- Clarification of the mechanisms by which immunological memory is involved in chronic rejection reactions following organ transplantation

We also welcome proposals on other types of R&D based on original ideas.

# Points to note when submitting a proposal (1)

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- This R&D area aims to understand the mechanisms of immunological memory in humans, so your research plan needs to use human clinical samples. Research plans that use only animal models will not be recommended. Ideally, ethical approval for the use of human samples will have already been given at the time of application, but if more time is needed for approval, please ensure that the plan includes details on how ethical approval will be obtained and how much number of samples will be analyzed, etc. If the proposal is selected, please implement the next steps to apply for and obtain ethical approval without delay.

## Points to note when submitting a proposal (2)

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- Please formulate a hypothesis that will be proved during the research period, and clearly specify the milestones to be achieved at the interim and end points of the project, as well as plans for obtaining intellectual property rights. Please include alternative plans if results are not obtained as expected. Rather than investigations on an extension of existing research, we expect innovative proposals that may create new concepts in the field of immunology.
- Please include preliminary information that can support assessment of whether the research plan is feasible and the hypothesis is rational.

# Management plans for this program



## In Japan:

- We will collaborate actively with AMED's Strategic Center of Biomedical Advanced Vaccine Research and Development for Preparedness and Response (SCARDA).
- We encourage the participation of new researchers and the dissemination of research results through collaboration with the Japanese Society for Immunology (JSI) and other relevant academic societies.

## Worldwide:

- We will plan to promote immunological memory research in Japan to be world-wide through the use of international platforms that allow interactions with overseas researchers (e.g., the United States-Japan Cooperative Medical Sciences Program and the International Immunological Memory and Vaccine Forum (IIMVF)).



# Messages from PS and PO

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- We look forward to applications by powerful and very active research teams who will be able to lead immunological memory research in global levels over the next 10–15 years.
- Rather than the investigation such as an extension of existing research, we expect innovative proposals that may create new concepts in the field of immunology.
- We expect to see the research teams that mainly comprise young and mid-career researchers from not only Immunology but also various research fields. In particular, we expect aggressive proposals from young scientists who will lead future immunology in Japan.
- We strongly recommend that your proposal not be restricted to investigations in animal models, but should involve close collaboration with clinical researchers with expertise in human diseases.

**We are looking forward to your original  
and exiting proposals.**