Immunological Memory

Immunological memory:
Understanding, regulation and medical innovation

Research and Development Objectives

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Understanding, regulation and medical innovation**

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.
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. However, the importance of the understanding of the human immune system is rapidly becoming clear as a countermeasure against the COVID-19 pandemic, and basic research to understand human immunological memory is now seen as even more important. A better understanding of how immunological memory in humans is formed and maintained, how it is activated according to the environmental situation, and how it becomes weaker and disappears, will help us to develop new perspectives on the management of the numerous diseases in which the immune system is closely involved.
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.

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AMED-CREST Started in 2022 · 1st period

Establishing renovative autoimmune therapies targeting novel types of self-reactive memory T cells

OKAZAKI Taku
Professor, Institute for Quantitative Biosciences, The University of Tokyo

Self-reactive memory T cells play pathogenic roles in many autoimmune diseases, while their phenotypic and functional properties remain ill-defined. In this project, we aim to identify novel types of self-reactive memory T cells by focusing on immune-checkpoint molecules and elucidate how each type of self-reactive memory T cells escapes immune tolerance to induce persistent immune responses and tissue damage under disease conditions. Based on these findings, we try to establish novel and effective autoimmune therapies that target disease-relevant types of self-reactive memory T cells.

Elucidation of immunological memory underlying human immunotherapy by single-cell analysis of multi-timepoint and multi-region samples

KATAOKA Keisuke
Professor, Keio University School of Medicine

We have collected multi-timepoint and/or multi-region samples from patients receiving immunotherapies, such as allogeneic hematopoietic stem cell transplantation and immune checkpoint inhibitors against malignancies. In addition, we have established cutting-edge single-cell and immune repertoire analysis technologies, which enable immunological analysis in a comprehensive manner. Therefore, here we will examine cellular and molecular dynamics underlying the efficacy and complications of immunotherapies by applying our cutting-edge analytical techniques to these human samples. In addition, we plan to perform in-depth characterization of the related protective and/or pathogenic memory using functional assays and mouse models.

Study of innate immune memory control via neuro-immune linkage

KUMANOGOH Atsushi
Professor and chair, Graduate School of Medicine, Osaka University

Immune memory has been thought to be a property unique to the acquired immunity. However, it has been shown that immune memory exists in the innate immune system as well. It has also been reported that the central nervous system regulates the innate immunity, pointing to the importance of innate immune memory control in humans from the perspectives of both disease control and enhancing and maintaining vaccine efficacy. From the unique perspective of "human innate immune memory regulation by neuro–immune coupling," this study aims to elucidate the mechanisms of immune memory induction, maintenance, and regulation in the human innate immune system with the goals of enhancing vaccine efficacy and controlling autoimmune diseases.

Evolution of humoral immune memory for resisting viral escape

TAKAHASHI Yoshimasa
Director,Research Center for Drug and Vaccine Development, National Institute of Infectious Diseases

Humoral immune memory is pivotal for durable protection provided by SARS-CoV-2 vaccines. Repeated vaccination accelerates an evolution of antibody presenrved in humoral immune memory; the phenomenon is an immunological basis for combating Omicron variants by the vaccination. We aim to understand the evolution by introducing novel immune profiling approach. The findings may guide the development of next-generation of vaccines that are effective to viral escapes.

Study of T cell subsets associated with immune memory for both cytotoxic and adaptive immune responses in autoimmune diseases

FUJIO Keishi
Professor, Graduate School of Medicine, The University of Tokyo

The mechanisms of organ inflammation important in autoimmune diseases are still unknown. We have found that highly proliferating CD4-positive T cells expressing cytotoxic and B-cell function-promoting molecules infiltrate the inflamed organs of autoimmune diseases. This cell population, which increases with age in the peripheral blood of healthy individuals, has been named as age-associated T (ThA) cells. This study aims to elucidate the function of ThA cells and to develop new therapeutic strategies and stratification of autoimmune diseases.

AMED-CREST Started in 2023 · 2nd period

Elucidation of the pathogenesis and development of therapeutic strategies for autoimmune diseases by targeting neo-self-responsive memory T cells.

ARASE Hisashi
Professor, Research Institute for Microbial Diseases, Osaka University

Neoself antigens, which is different from normal self antigens, has been shown to be involved in autoimmune responses in autoimmune diseases. Therefore, this study aims to elucidate the mechanisms of neoself generation and recognition, to understand how neoself-reactive memory T cells are involved in the pathogenesis of autoimmune diseases, and to develop new methods for the treatment and prevention of autoimmune diseases by targeting neoself-reactive memory T cells.

Study on regulation of generation, maintenance, and activation of protective or pathogenic memory helper T cell repertoire and development of novel immune therapy

ISE Wataru
Professor, Center for Infectious Disease Education and Research, Osaka University

The humoral immune memory is essential for defense against infection and is also strongly involved in the onset and relapse of allergies and autoimmune diseases. Thus, it could be possible that various immunological diseases can be controlled by regulating the development or activation of humoral immune memory cells. This study aims to understand molecular mechanisms underlying differentiation, long-term survival, and re-activation of follicular helper T cells that function as drivers of humoral immune memory response. We will also develop highly accurate immunoregulatory methods that target antigen-specific, pathogenic memory helper T cells.

Understanding of autoimmune response mechanism and disease pathology by pathogenic memory B cells

BABA Yoshihiro
Professor, Medical Institute of Bioregulation, Kyushu University

Autoreactive B cells are censored to avoid autoimmune diseases by immune tolerance. Autoreactive memory B cells are presumed to be key in the pathology of autoimmune diseases, but their pathological significance is unknown. The aim of this research is to identify key memory B cell subtypes associated with autoimmune pathology and establish the molecular mechanism underpinning the generation, maintenance, and activation of pathogenic memory B cell subtype in autoimmune disease in mice and humans, and define the target pathways/molecules to prevent it. Through this research, we hope to contribute to understanding autoimmune disease pathology and developing a new therapeutic strategy.

Elucidation of the pathophysiology of tissue inflammatory memory formation by external environmental stimuli: Toward the development of a new strategy for treating intractable allergic diseases

HIRAHARA Kiyoshi
Professor, Graduate School of Medicine, Chiba University

The formation of “tissue inflammatory memory” including CD4+ tissue resident memory T (TRM) cells and tertiary lymphoid structures (TLSs) plays a crucial role in the pathophysiology of intractable allergic diseases. However, precisely how the external environmental stimuli, such as hypoxia and changes in airway pressure under chronic inflammatory conditions, are involved in the formation and maintenance of tissue inflammatory memory is still unclear. Therefore, we plan to comprehensively analyze the regulatory mechanisms of tissue inflammatory memory at the molecular, cellular, and biological levels to establish a basis for developing new therapeutic strategies to successfully treat intractable allergic diseases in humans.

AMED-CREST Started in 2024 ····· 3rd period

Deciphering Human Liver Immune Responses and Unveiling Novel Therapeutic Targets

UENO Hideki
Professor,
Graduate School of Medicine, Kyoto University

The liver has a specialized immune system to handle substances and pathogens from the intestinal tract and portal vein. Despite its importance, the global understanding of human liver resident immune cells is limited, especially regarding immune responses in human liver diseases. Our research will focus on the human liver immune system using liver specimens, including liver tissues and perfusate. We aim to elucidate mechanisms associated with immune tolerance, immunological memory, breakdown of homeostasis, and pathogenesis of hepatobiliary diseases.

Population, individual, and single cell level omics elucidates how immune memory can be acquired, accumulated, and lost.

OKADA Yukinori
Professor,
Graduate School of Medicine, the University of Tokyo

By interpreting human omics information in a multilayered manner from population, individual, and single-cell resolution, we aim to understand immune memory along life stages and elucidate the mysteries of human immune memory “introduction, accumulation, and loss” through integrated cross-sectional omics analysis. We would like to challenge to elucidate the long-standing riddle of clinical immunology, “why, when, and how immune memory can be introduced, accumulated, and lost”.

Understanding Age-Related Characteristics and Individual Differences in Human Immunological Memory

HAMAZAKI Yoko
Professor, Center for iPS Cell Research and Application, Kyoto University

The immune status in humans significantly changes with age. This study aims to elucidate the transitions, age-related differences, and individual variations in immunological memory across a wide range of age groups, from childhood to old age, using multi-layered omics analysis. Based on this knowledge, we intend to scientifically define immune capability and immune age, and to establish a molecular basis and develop technologies that enable the efficient induction and maintenance of memory responses based on individual immune status.